

Short-term exposure to air pollutant mixtures and seasonal acute exacerbations of chronic obstructive pulmonary disease: A time-stratified case-crossover study

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ABSTRACT

Although ambient air pollution triggers acute exacerbation of chronic obstructive pulmonary disease (AECOPD), pollutants are commonly evaluated individually and mixture and lagged effects are often overlooked. Using the Korean National Health Insurance Service–National Sample Cohort (2006–2019), the short-term effects of air pollution on AECOPD incidence were investigated. A time-stratified case-crossover design matched each case day to control days from the same year, season, and weekday. Conditional Poisson regression with distributed lag nonlinear models (DLNMs) estimated lag-specific and cumulative relative risks for single pollutants, while quantile g-computation (Qgcomp) evaluated mixture effects. Lag structures up to 7 d were analyzed, adjusting for meteorological factors and public holidays. Stratified analyses were conducted by age, sex, income level, smoking status, and body mass index (BMI). In total, 5981 AECOPD events were identified. Short-term ambient pollutant exposure increased AECOPD risk, especially during winter and spring. In season-stratified DLNMs, pollutant effects strengthened across longer lags and moving-average windows, whereas O₃ showed opposite patterns in winter. Multiple pollutants exerted combined effects on AECOPD, with early peaks in spring (lags 0–2), the highest estimate at lag 0 (odds ratio [OR] = 1.19, 95% CI: 1.04–1.34), and persistent associations across lag structures in winter (ORs: 1.20–1.28). Stronger effects were observed among men, adults aged ≥ 65 years, current smokers, and individuals with BMI ≥ 25. Short-term ambient air pollutant exposure increased AECOPD risk during winter and spring, especially in men and the elderly, underscoring the importance of targeted measures to reduce pollution exposure among vulnerable populations.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of mortality and morbidity (2024) and places a remarkable economic burden on healthcare systems worldwide (Chen et al., 2023). Acute exacerbation of COPD (AECOPD) is an acutely worsening state caused by increased airway inflammation in patients with COPD (Celli et al.,

2021; Oh, 2023). It can decrease the quality of life (Spencer et al., 2004), worsen symptoms and lung function (Seemungal et al., 2000), lead to a more rapid decline in lung function (Donaldson et al., 2002; Dransfield et al., 2017), and eventually increase mortality rates (Soler-Cataluña et al., 2005). Therefore, the prevention of acute exacerbation (AE) is important in COPD treatment (Agustí et al., 2023).

While respiratory infections are well-known precipitants of AECOPD

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(Celli et al., 2021), increasingly more evidence is indicating that ambient air pollution also plays a significant role. In recent meta-analysis and multi-city time-series studies, short-term particulate matter (PM_{2.5} and PM₁₀) exposure was found to increase the risk of AECOPD-related hospital admissions, emergency visits, and mortality (Li et al., 2022; López et al., 2024). Positive associations were also reported for NO₂, whereas results for O₃ have been inconsistent across studies (López et al., 2024; Ross et al., 2023). Other studies found that these associations varied by season, likely reflecting differences in pollutant concentrations and meteorological conditions such as temperature and humidity (Jenkins et al., 2012; Kim et al., 2023; Niu et al., 2024).

Despite the increasing recognition of air pollution as a trigger for AECOPD, most analyses have assessed the effect of pollutants individually, ignoring the strongly correlated and interactive nature of air pollutant mixtures. Given that real-world exposure involves the simultaneous inhalation of multiple pollutants, single-pollutant models may yield biased or incomplete risk estimates. Additionally, the effects of air pollution on AECOPD may follow lagged or cumulative patterns, emphasizing the need for analytical approaches that can capture such temporal dynamics to fully elucidate the short-term impacts of air pollution on AECOPD.

To address these issues, the present study evaluated the delayed and cumulative effects of air pollution on AECOPD and applied a mixture approach to assess the combined effects of multiple pollutants. Furthermore, to determine whether the susceptibility to effects from air pollution differs across population subgroups, stratified analyses were conducted by season, sex, and age group. This approach provides a more nuanced explanation of how complex and time-dependent air pollution exposure contributes to AECOPD, offering valuable evidence for targeted prevention and environmental health policy.

2. Methods

2.1. Study population and design

This study used data from the Korean National Health Insurance Service–National Sample Cohort (KNHIS-NSC), which contains health insurance claims recorded from January 2002 to December 2019 (Lee et al., 2017). The KNHIS-NSC, a population-based cohort, was established by the National Health Insurance Service. It was designed to provide representative and comprehensive information on healthcare utilization and health screening for public-health research and policy-making. Constructed in 2002 by randomly selecting 1025,340 individuals, the cohort represents approximately 2.2% of the total Korean population, with all participants having been monitored for 18 years until 2019 unless they lost eligibility owing to death or emigration (Kyoung and Kim, 2022). Individuals aged ≥ 40 who had been diagnosed with COPD and had experienced AE between January 8, 2006, and December 31, 2019, were included. To evaluate the short-term effects of air pollution on AECOPD, a time-stratified case-crossover design was applied. Each AECOPD incidence (case day) was matched with control days from the same year, same season (spring: March–May; summer: June–August; autumn: September–November; winter: December–February), and same week day, with control days being at least 28 d from the case day.

The Institutional Review Board of Chung-Ang University (1041078–20231121-HR-313) approved the study's protocol, and informed consent was waived because the data analyses were performed retrospectively using anonymized data from the KNHIS database.

2.2. Acute exacerbation chronic obstructive pulmonary disease (AECOPD)

COPD was defined as the presence of at least two claims yearly that included International Classification of Diseases, 10th Revision, COPD

diagnosis codes (J42–J44, except J43.0) as well as COPD prescriptions (Crisafulli et al., 2018; Huh et al., 2022). Meanwhile, AECOPD was defined as hospitalization with prescriptions for systemic corticosteroids and/or antibiotics (Joo et al., 2024; Kim et al., 2022). To avoid multiple admissions being counted for one event, a 30-d wash-out period was applied; if the interval between consecutive AECOPD events for an individual exceeded 30 d, each subsequent event was considered a new and independent event and was also analyzed (Guerrero et al., 2016).

2.3. Ambient air pollution

Nationwide air pollution and meteorological data for the period 2006–2019 were utilized, with air pollutant concentrations estimated using the U.S. Environmental Protection Agency Community Multiscale Air Quality model (version 4.7.1) and calibrated using data fusion techniques with observational monitoring data (Oh et al., 2021). The final dataset yielded daily air pollution and meteorological information on 9- × 9-km grid cells. Meteorological data were obtained from the Korea Meteorological Administration (KMA) Data Portal (<https://data.kma.go.kr>). These data were originally measured at an hourly resolution from Automated Synoptic Observing System and Automatic Weather Station monitoring networks operated by the KMA. For this study, hourly measurements were aggregated to daily averages. Moreover, individual-level exposure was estimated by linking residential administrative area codes from the KNHIS eligibility database with daily city- and district-level air pollution and meteorological data. Air pollution and meteorological data were aggregated to the district level and assigned to individuals based on their residential administrative codes. For districts without a meteorological monitoring station, missing values were imputed using the average of the three nearest neighboring districts.

Exposure metrics were calculated using the corresponding date of AECOPD incidence or matched control days. In addition, single-day lags (lag0–lag7) and cumulative moving averages (lag01–lag07) were generated. The air pollutants analyzed in this study included PM₁₀, PM_{2.5}, NO₂, SO₂, CO, and O₃, while the meteorological variables included mean temperature (°C), relative humidity (%), and wind speed (m/s). For PM₁₀ and PM_{2.5}, concentrations were measured in micrograms per cubic meter (µg/m³), while for NO₂, SO₂, CO, and O₃, they were measured in parts per billion (ppb). All effect estimates obtained from regression models were interpreted per 1 µg/m³ or 1 ppb increase in pollutant concentration.

2.4. Statistical analysis

The characteristics of the studied participants were examined using descriptive statistical analyses, with categorical variables presented as counts and percentages. The associations between each air pollutant and the AECOPD risk were evaluated using a time-stratified case-crossover design. Specifically, the exposure levels on case days were compared with those on the corresponding control days. To estimate relative risk (RR) while considering time-varying factors, conditional Poisson regression models with a log link function were applied (Armstrong et al., 2014). This allowed for direct RR estimation from count data, an improvement in computational efficiency, and the appropriate handling of overdispersion and autocorrelation. To assess the delayed (lagged) and nonlinear effects of air pollutants on AECOPD incidence, distributed lag nonlinear models (DLNMs) were incorporated into the conditional Poisson framework. For each pollutant, a cross-basis function was constructed based on the previously defined single-day (lag0–lag7) and cumulative moving-average (lag01–lag07) exposure metrics to simultaneously model the exposure–response and lag–response relationships. Furthermore, a third-degree polynomial function was applied to the lag dimension, with the maximum lag set at 7 d according to previous findings that the acute effects of air pollution typically occurred within a week of exposure (Chen et al., 2010; Jiang et al., 2023). To evaluate the

cumulative exposure–response relationships across different lag windows, all lag-specific and moving-average concentrations were simultaneously included in extended DLNM models. Effect estimates were expressed as the RRs of AECOPD incidence associated with an inter-quartile range (IQR) increase in pollutant concentrations or by comparing specific percentiles (e.g., 25th and 95th percentiles) with the median (50th percentile, used as a reference).

To further assess the combined impact of multiple air pollutants, the quantile g-computation (Qgcomp) model was applied to estimate the overall effect of pollutant mixtures on AECOPD incidence. PM₁₀, PM_{2.5}, NO₂, SO₂, CO, and O₃ were included in the analysis, and both single-day lag exposures (lag0–lag7) and cumulative moving averages (lag01–lag07) were used. By employing the Qgcomp approach, joint mixture effects were quantified by assigning data-driven weights to each pollutant according to its relative contribution, without assuming a common association direction (Keil et al., 2020). This flexible method accommodates nonlinear relationships and interactions among multiple exposures. Before modeling, all exposure variables were converted into quantiles, and both positive and negative weights were estimated to capture bidirectional influences. The overall effect was interpreted as the expected change in AECOPD incidence associated with a simultaneous one-quantile increase in all pollutants.

Meteorological factors, such as mean temperature, relative humidity, and wind speed, were incorporated into the model and adjusted to correspond to the same lag days as those of the air pollutant exposures. Meanwhile, public holidays were adjusted to consider potential influences on traffic volume, air pollutant emissions and concentrations, health-related behavior, and healthcare service availability. As sensitivity analyses, stratified analyses were conducted according to sex, age, income level, smoking status, and body mass index (BMI) to determine whether the associations between air pollutant mixtures and AECOPD risk differed across population subgroups. Statistical analyses were performed using the R software (version 4.3.0, R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Online supplementary Figure 1 shows the process used to select study participants and identify AECOPD cases. In total, 5981 independent incident cases for AECOPD were identified after a 30-d washout period was applied (Table 1). Of these, 80.9% and 19.1% occurred among individuals aged ≥ 65 years and ≤ 64 years, respectively. In addition, men and women accounted for 75.3% and 24.7% of the cases, respectively. Regarding season, incidences were most frequent in spring (28.0%) and winter (27.4%), followed by summer (22.5%) and then

autumn (22.1%). The distributions of air pollutants and meteorological variables on case (lag 0) and matched control days are presented in online supplementary Table 1.

Fig. 1 presents the seasonally stratified RRs of AECOPD incidence associated with IQR (75th vs 25th percentile) increases in air pollutant concentrations across single-day lag and moving-average exposures. Overall, most significant associations were found in winter. For PM₁₀ and PM_{2.5}, the risks were most pronounced during winter, with relatively consistent effects across single-day lags, and progressively stronger associations over longer moving-average windows. NO₂, CO, and SO₂ showed similar seasonal patterns, with risk increases becoming more evident after lag day 3, and statistical significance observed both at later single-day lags and at extended moving averages (lags 0–6 and 0–7), where the effect sizes were the largest. Contrastingly, O₃ showed the opposite trend in winter, demonstrating decreasing risks with increases in the lag period.

Fig. 2 presents the cumulative exposure–response relationships between air pollutant concentrations and AECOPD incidence estimated using a DLNM incorporating all single-day lags up to 7 d. For PM₁₀, PM_{2.5}, and O₃, statistically significant linear increasing trends existed when pollutant concentrations exceeded the median level, with RRs increasing with concentration. NO₂ showed an increasing pattern, although the association was not statistically significant. In contrast, CO and SO₂ showed decreasing trends throughout the concentration range, but the associations were similarly nonsignificant.

Fig. 3 shows the seasonally stratified associations between the co-exposure to air pollutants and AECOPD risk across single-day lag and moving-average exposures. In the season-stratified analyses, spring and winter demonstrated increased risks overall. In spring, the effect became evident from lag 0 and remained relatively stable during the first 2 d, followed by gradual attenuation. The largest single-day effect occurred at lag 2 (odds ratio [OR] = 1.17; 95% confidence interval [CI], 1.05–1.30). Moreover, the cumulative effects across short moving-average windows (up to 0–5 d, ORs: 1.13–1.18) remained significant, with the highest association being at the moving average of lags 0–2 (OR = 1.19; 95% CI, 1.06–1.34). In winter, the estimated risks remain high across single-day lags, with only minor temporal fluctuations. All moving-average windows demonstrated statistically significant associations, with the effect magnitudes remaining nearly constant and the highest being at the moving average of lags 0–1 (OR = 1.30; 95% CI, 1.12–1.49).

The relationships between the co-exposure to air pollutants and AECOPD risk, stratified by sex within each season, across single-day lag and moving-average exposures are shown in Fig. 4. Overall, the associations were stronger and statistically significant among men. Specifically, in spring, the highest risk increase among men occurred at lag 0 (RR = 1.18, 95% CI: 1.04–1.34). This effect remained relatively stable for approximately the first 2 d, after which it gradually attenuated, resembling the overall pattern shown in Fig. 3. The cumulative effects across short moving-average windows (up to 0–5 d ORs: 1.16–1.18) also remained significant, suggesting that the short-term accumulation of exposure during this season contributed to a risk increase. In winter, the risk remained high across nearly all lags and moving-average windows, indicating sustained cumulative effects of co-exposure. However, among women, the effect directions were generally similar, showing modest risk increases, particularly in spring and winter, though most estimates did not reach statistical significance.

Fig. 5 shows the associations between the co-exposure to air pollutants and AECOPD risk, seasonally stratified by age group, across single-day lag and moving-average exposures. Overall, associations among younger adults (≤ 64 years) were nonsignificant, whereas among older adults (≥ 65 years), clearer and statistically significant increases in risk were found, particularly in spring and winter. Among older adults, effects in spring were evident from lag 0 and remained relatively stable through lag 3, followed by gradual attenuation (ORs: 1.13–1.17). The largest single-day association occurred at lag 1 (OR = 1.17; 95% CI,

Table 1
Characteristics of independent AECOPD events (n = 5981).

Characteristics	N (%)
Age (years)	
≤ 64	1141 (19.1)
≥ 65	4840 (80.9)
Sex	
Male	4501 (75.3)
Female	1480 (24.7)
Season	
Spring	1672 (28.0)
Summer	1345 (22.5)
Autumn	1325 (22.1)
Winter	1639 (27.4)

AECOPD, acute exacerbation of chronic obstructive pulmonary disease.

Each AECOPD case was considered an independent AECOPD event if the interval between consecutive admissions for the same individual exceeded 30 d (washout period = 30 d)

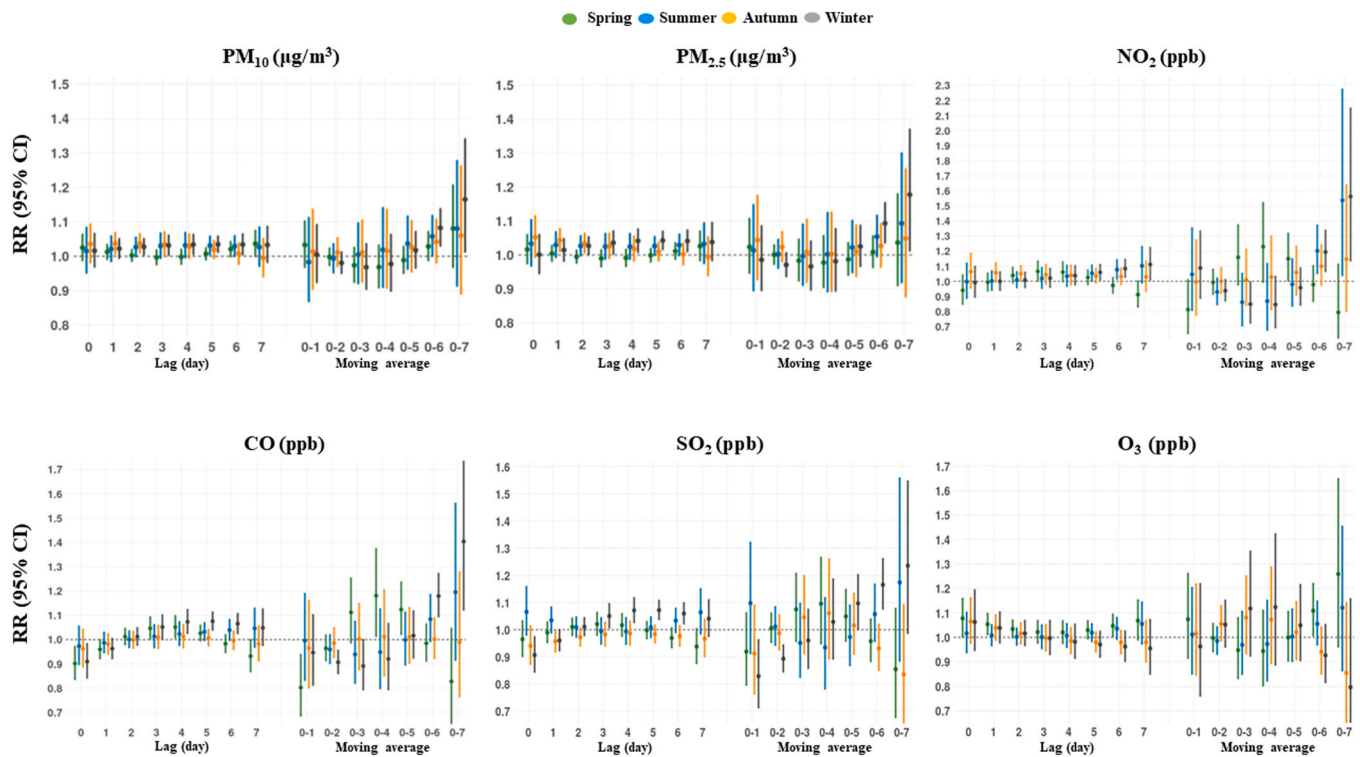


Fig. 1. Seasonally stratified relative risks of AECOPD associated with interquartile range (75th vs 25th percentile) increases in air pollutant concentrations across single-day lag and moving-average exposures, estimated using DLNM. All models were adjusted for holidays, relative humidity, and temperature at each time point. Abbreviations: RR, relative risk; CI, confidence interval; PM₁₀, particulate matter $\leq 10 \mu\text{m}$; PM_{2.5}, particulate matter $\leq 2.5 \mu\text{m}$; CO, carbon monoxide; NO₂, nitrogen dioxide; SO₂, sulfur dioxide; O₃, ozone.

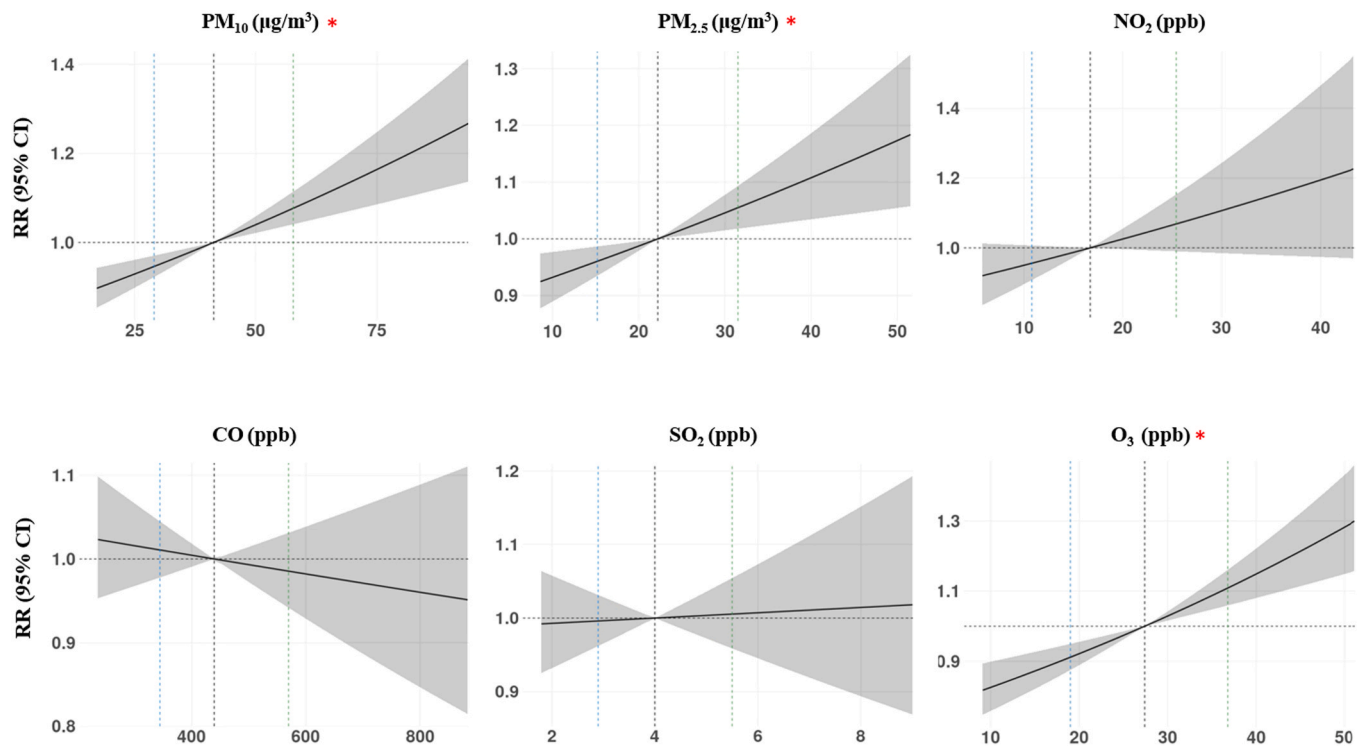


Fig. 2. Seasonally stratified cumulative exposure–response relationships between air pollutant concentrations and AECOPD incidence estimated using DLNM incorporating all single-day lags (0–7 days). The x-axis represents pollutant concentrations. Vertical dashed lines indicate concentration percentiles: black, blue, and green for the median (50th percentile, used as a reference), 25th percentile, and 95th percentile, respectively. All models were adjusted for holidays, relative humidity, and temperature. * $p < 0.05$. Abbreviations: RR, relative risk; CI, confidence interval; PM₁₀, particulate matter $\leq 10 \mu\text{m}$; PM_{2.5}, particulate matter $\leq 2.5 \mu\text{m}$; CO, carbon monoxide; NO₂, nitrogen dioxide; SO₂, sulfur dioxide; O₃, ozone.

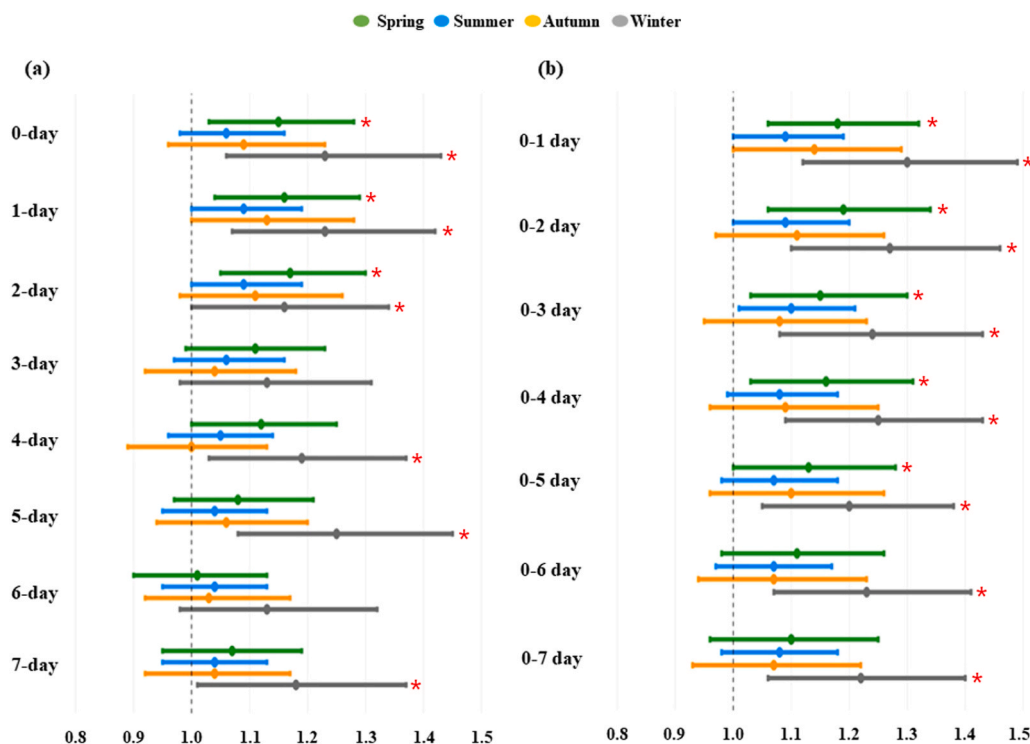


Fig. 3. Seasonally stratified associations between the co-exposure to air pollutants and risk of AECOPD estimated using the Qgcomp model. Panel (a) shows results for single-day lag exposures; panel (b) presents results for moving-average exposures. The x-axis represents the overall ORs. All models were adjusted for temperature, wind speed, relative humidity, and holidays. * $p < 0.05$.

1.04–1.31). Meanwhile, the cumulative effects across short moving-average windows (up to 0–5 d) remained significant, with the highest occurring at the moving average of lags 0–4 (OR = 1.18; 95% CI, 1.03–1.35), suggesting a short-term accumulation of exposure. In winter, risks remained high across all single-day lags and moving-average windows, with the effect magnitudes remaining relatively stable throughout the lag period. In addition, all associations were statistically significant, indicating sustained cumulative effects of co-exposure among older adults.

The results obtained from analyses stratified by income level, smoking status, and BMI are presented in [Supplementary Tables 2](#) and [Supplementary Figures 2–4](#). The proportion of AECOPD cases was similar across income groups (Q1–Q4: 15.5%, 15.4%, 15.7%, and 15.5%, respectively), smoking categories (never, former, and current smokers: 15.4%, 15.6%, and 15.4%, respectively), and BMI categories (BMI <23, 23–24.9, and ≥ 25 : 15.5%, 15.4%, and 15.2%, respectively). Under stratification by income level ([Supplementary Figure 2](#)), the overall pattern generally resembled that observed in the total population. Significant associations mainly occurred during spring and winter in Q3 and Q4, whereas in Q1, they were observed during autumn and winter. In the smoking-stratified analyses ([Supplementary Figure 3](#)), the air pollution mixture had a more pronounced effect during winter among smokers, with larger effect sizes than those observed in the overall population. The largest effect was observed among current smokers during winter at single-day lag0 (OR = 1.85, 95% CI: 1.28–2.67). Contrastingly, seasonal patterns differed among never and former smokers; associations appeared mainly in autumn among never smokers and in summer among former smokers. In the BMI-stratified analyses ([Supplementary Figure 4](#)), no significant association was found in the group with BMI < 23. In contrast, significant associations existed across multiple lag structures in the groups with BMI 23–24.9 and BMI ≥ 25 . Unlike the results obtained in the overall analysis, significant associations also existed during summer among overweight and obese participants.

4. Discussion

In this study, short-term exposure to ambient air pollutants was associated with an increased AECOPD risk, with significant relationships observed mainly in winter and spring. In the season-stratified single-pollutant DLNM, positive associations occurred, generally increasing with the lag period and over extended moving-average windows; however, the results for O₃ showed the opposite trend. The Qgcomp model, used to evaluate the combined effects of multiple pollutants, again revealed that significant mixture effects mainly occurred in winter and spring. Specifically, in spring, mixture effects peaked at early windows (lags 0–2) and attenuated thereafter, whereas in winter, significant associations persisted across all single-day lags and all moving averages from lag 0–1 through lag 0–7 days; however, this interpretation was based on window-to-window comparisons rather than an explicit distributed-lag model. Stratified analyses indicated stronger and statistically significant associations among men, older adults (≥ 65 years), current smokers, and individuals with higher BMIs, which suggested greater susceptibility to the adverse effects of air pollution in these subgroups.

Previous epidemiologic studies have likewise found positive relationships between the short-term exposure to air pollution and AECOPD, along with seasonal variations in these associations, with stronger effects occurring during colder months. Meanwhile, in meta-analysis and multi-city studies, short-term PM (PM_{2.5}/PM₁₀) exposure was associated with increased AECOPD-related hospital use—and, in pooled analyses, mortality ([Li et al., 2022](#); [López et al., 2024](#)). Meanwhile, time-series analyses conducted in Bogotá revealed positive short-term associations for PM and O₃, with the effect sizes differing depending on the meteorological conditions ([López et al., 2024](#)), whereas in the Canadian CanCOLD case-crossover study, NO₂ and PM_{2.5} showed positive associations but O₃ was inversely associated during the warm season ([Ross et al., 2023](#)).

These findings are consistent with exposure contexts, as the ambient

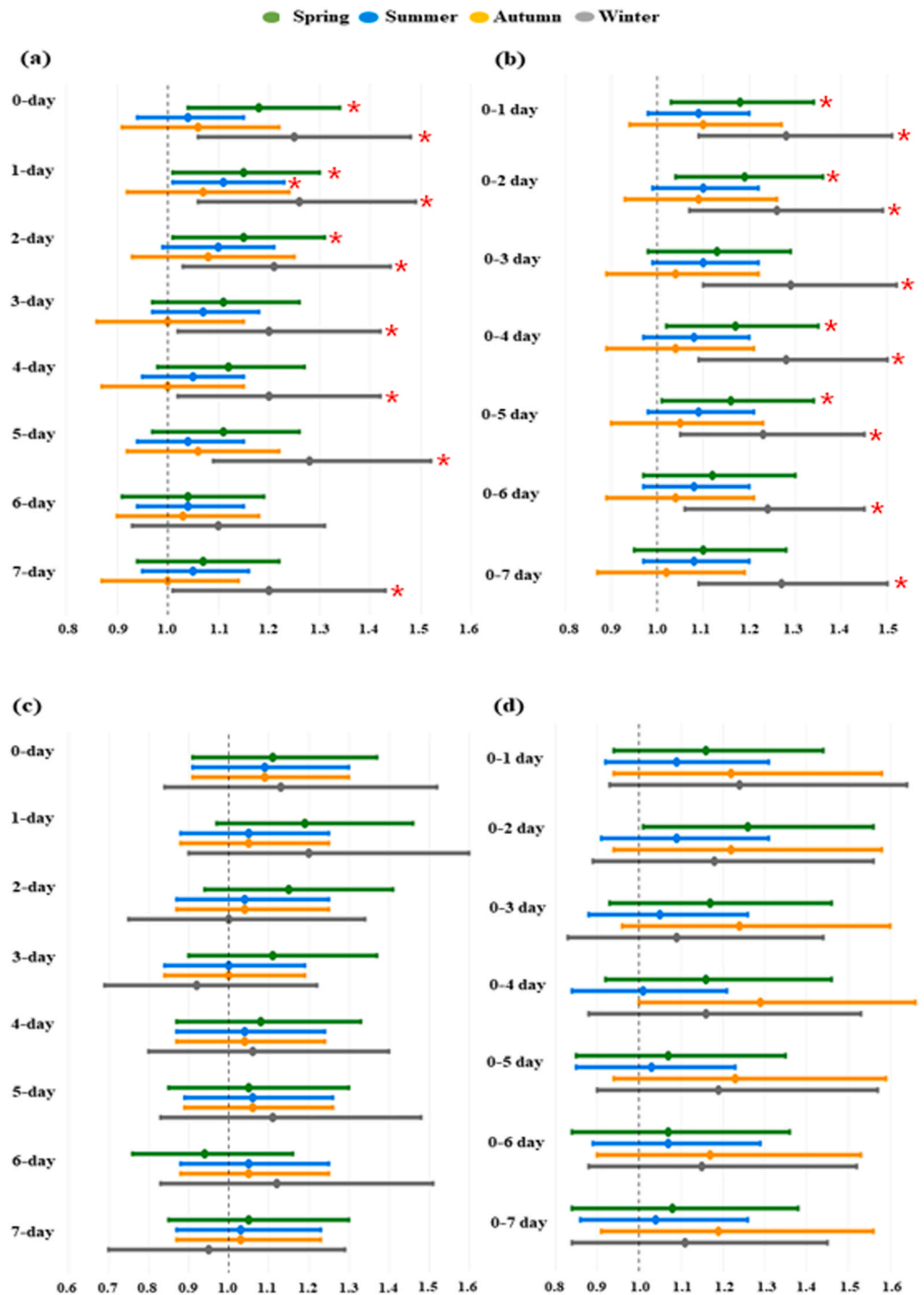


Fig. 4. Associations between air pollution mixture exposure and AECOPD risk estimated using the Qgcomp model, stratified by sex and season. Panels (a) and (b) show results for men, and panels (c) and (d) show results for women. The left column [(a) and (c)] presents single-day lag exposures, while the right column [(b) and (d)] shows moving-average exposures. The x-axis represents the overall ORs. All models were adjusted for temperature, wind speed, relative humidity, and holidays. * $p < 0.05$.

PM_{2.5} levels in winter and spring generally exceed those in summer or autumn (Kim et al., 2023), and both temperature and humidity influence the associations between air pollutants and AECOPD (Jenkins et al., 2012; López et al., 2024; Niu et al., 2024). Consistent with this evidence, our data revealed a distinct seasonal pattern of AECOPD and the air pollutant concentration. The number of AECOPD cases peaked in winter and spring and was lowest in late summer and early autumn (online supplementary Figure 5 and Figure 6). Furthermore, the concentrations of PM₁₀ and PM_{2.5} remained higher in spring and winter, and that of O₃

was the highest in spring and summer and the lowest in winter. Meanwhile, the highest NO₂, CO, and SO₂ concentrations occurred in winter (online supplementary Figure 7). These patterns indicate that both pollutant concentrations and AECOPD incidence were elevated during colder or transitional seasons.

This seasonal pattern may be due to the combined influences of meteorological and biological factors. Lower temperatures and low humidity can impair mucociliary clearance, increase airway reactivity, and promote viral circulation, thereby intensifying the impact of air

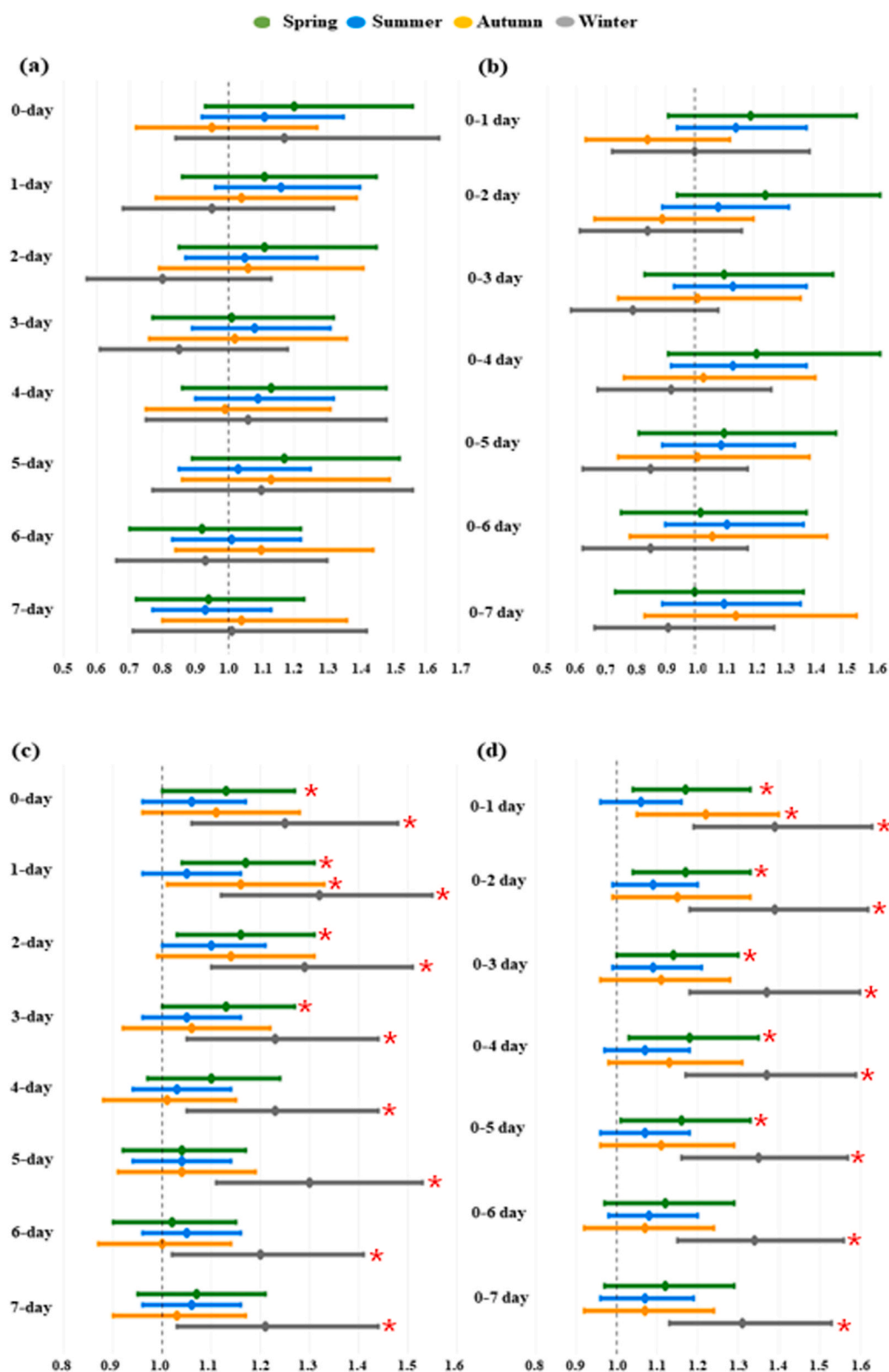


Fig. 5. Associations between air pollution mixture exposure and AECOPD risk estimated using the Qgcomp model, stratified by age group and season. Panels (a) and (b) show results for individuals aged ≤ 64 years, and panels (c) and (d) show results for those aged ≥ 65 years. The left column [(a) and (c)] presents single-day lag exposures, while the right column [(b) and (d)] presents moving-average exposures. The x-axis represents the overall ORs. All models were adjusted for temperature, wind speed, relative humidity, and holidays. * $p < 0.05$.

pollution on COPD exacerbations (Jenkins et al., 2012; Kim et al., 2023; Romaszko-Wojtowicz et al., 2025). Moreover, short-term exposure to particulate and gaseous pollutants can trigger airway inflammation, oxidative stress, and epithelial damage, which can, in turn, precipitate AEs and exacerbate underlying respiratory impairments (Guarnieri and Balmes, 2014).

Studies on air pollution and AECOPD have largely relied on single-pollutant models. Contrastingly, a mixture-based approach using the Qgcomp model was applied in our study to estimate the overall impact of the concurrent exposure to multiple pollutants. In real-world environments, individuals are simultaneously exposed to multiple correlated pollutants rather than a single pollutant alone (Yu et al., 2022). Therefore, single-pollutant models may underestimate or obscure the overall impact of air pollution owing to collinearity among pollutants and the inability to capture joint exposure effects. Mixture-based approaches, by contrast, estimate the combined effect of multiple pollutants and may better reflect cumulative environmental burdens (Keil et al., 2019). When evaluating the combined effects of multiple pollutants, mixture effects were generally more consistent and often larger than those reflected by single-pollutant estimates, particularly during winter and spring. In spring, mixture effects peaked at early exposure windows (lags 0–2), after which they attenuated, whereas in winter, significant relationships persisted across all single-day lags and all moving averages from lag 0–1 through lag 0–7 days. This seasonal difference may indicate earlier effects in spring and more sustained short-term exposure effects in winter. Because air pollutant concentrations and compositions vary substantially by season, mixture-based approaches that account for simultaneous exposure to multiple pollutants may better capture seasonal variations in the overall pollution burden, thereby better highlighting seasonal patterns in AECOPD risk.

In the subgroup analysis, men and adults aged ≥ 65 years exhibited stronger and statistically significant seasonality between air pollutants and AECOPD when compared to women and adults aged < 65 years. However, evidence on sex-specific vulnerability remains inconsistent across studies. In the Canadian CanCOLD case-crossover study, women showed stronger associations for short-term PM_{2.5} and NO₂ exposure with AECOPD, potentially reflecting smaller airway calibers and increased particle deposition, the hormonal modulation of oxidative stress, and differences in exposure profiles (Ross et al., 2023). Contrastingly, a retrospective cohort from China reported stronger effects among men and older adults, implicating context-specific factors such as higher cumulative or occupational exposures, more-extensive smoking history, or phenotypic differences as potential contributors (Lian et al., 2025). However, our study included patients hospitalized owing to worsening symptoms, whereas the CanCOLD study defined AE based on increased dyspnea or sputum purulence, which resulted in a more sensitive definition of exacerbation than that used in the present study. Furthermore, the CanCOLD study enrolled only patients with mild to moderate COPD, which made drawing definitive conclusions regarding sex-specific effects difficult. Regarding age, short-term air pollutant exposure has been reported to correlate with poorer outcomes in elderly patients with COPD (Chen et al., 2021; Di et al., 2017; Lian et al., 2025; Liu et al., 2023). In patients with COPD, age-related declines in lung function (Kim et al., 2016), as well as the presence of multiple comorbidities, may increase the susceptibility to effects from air-pollution-related AEs during the cooling-down season (Lian et al., 2025). Accordingly, we found that, during winter or spring, susceptibility to COPD exacerbation due to exposure to air pollution may be higher in older patients with COPD. Further research is warranted to clarify sex- or age-specific vulnerabilities to air-pollution-related AECOPD.

Previous studies reported that individuals with lower socioeconomic status experienced worse COPD outcomes, including higher risks of exacerbation, hospitalization, and mortality (Lee et al., 2025). These disparities have been linked to factors such as higher exposure to environmental pollutants, poorer housing conditions, unhealthy-lifestyle

factors, and limited access to healthcare resources. However, the present study found that the overall patterns of association between co-exposure to air pollutant mixtures and AECOPD risk were broadly similar across income groups, with no clear socioeconomic gradient observed. This was possibly because the studied population consisted entirely of patients with COPD, among whom disease-related susceptibility may be shared across income groups. In addition, Korea's universal healthcare system may reduce disparities in healthcare utilization across socioeconomic strata (Kim et al., 2017). In contrast, differences existed according to smoking status and BMI. The strongest association occurred among current smokers, particularly during winter. Smoking induces chronic airway inflammation, increases oxidative stress, and impairs mucociliary clearance, thereby weakening airway defense mechanisms and amplifying the harmful effects of inhaled pollutants (Strzelak et al., 2018). These mechanisms may partly account for the stronger association observed among current smokers in this study, although smoking status was based on self-reported questionnaire data and may have been subject to some degree of misclassification. Similarly, the largest effects occurred among individuals with higher BMIs. Obesity has been suggested to increase susceptibility to the respiratory effects of PM exposure in patients with COPD, with obese individuals showing greater increases in respiratory symptoms and rescue-medication use following PM exposure compared with non-obese individuals (McCormack et al., 2015). These findings may, in part, explain the stronger associations observed among individuals with higher BMIs in the present study.

This study had several limitations. First, because a case-crossover design inherently controls for time-invariant individual factors such as sex, smoking status, and baseline disease severity through within-person comparisons, adjustments were not required for these variables. However, the lack of detailed clinical information, including lung-function data, hindered the evaluation of effect modification by COPD severity. Second, both indoor and outdoor pollutants may contribute to AECOPD; however, obtaining specific data on indoor exposure is difficult. Indoor pollutant levels may vary by activity level, occupation, housing characteristics, sex, and age. Third, because air pollution exposure was assigned based on registered residential addresses, discrepancies between the actual and registered addresses may have led to exposure misclassification. Individuals who worked far from their place of residence may have had different exposure profiles. Finally, seasonal factors such as respiratory infections and seasonal allergens may also influence AECOPD. Because of data limitations, these factors could not be directly considered in the analysis, representing a limitation of this study. However, to partially address the temporal variability related to these conditions, season-stratified analyses were conducted.

Nevertheless, this study had several notable strengths. Using a large, nationwide dataset, the short-term effects of ambient air pollutants on AECOPD risk were comprehensively evaluated by applying DLNMs, so as to capture delayed and cumulative effects across multiple lag structures moving averages from lag 0–1 through lag 0–7 days. We also employed a Qgcomp approach to assess the combined effects of multiple pollutants. Additionally, analyses stratified by season, sex, and age were used to identify vulnerable subgroups and revealed seasonal heterogeneity in the air-pollution–AECOPD association. Understanding vulnerable subgroup differences is crucial for developing targeted public-health interventions and adaptive strategies under varying seasonal and environmental conditions.

In conclusion, the seasonality of AEs of COPD was associated with ambient air pollution. Short-term exposure to air pollutants increased the risk of AECOPD, particularly during winter and spring. This seasonal pattern was more clearly observed in the analysis of air pollutant mixtures, suggesting earlier effects in spring and more persistent effects throughout the winter lag period. This seasonal increase in AECOPD risk was generally more pronounced among men, older adults, current smokers, and obese individuals, indicating that these groups may be particularly vulnerable. These findings highlight the importance of

implementing targeted strategies to reduce exposure to air pollution during seasons when the risk of AECOPD is elevated, especially among susceptible populations.

Ethical approval

The study protocol was approved by the Institutional Review Board of Chung-Ang University (1041078–20231121-HR-313). Informed consent was waived because the data analyses were performed retrospectively using anonymized data from the KNHIS database.

CRediT authorship contribution statement

Yoon-Hee Kang: Resources, Investigation, Data curation. **Changhyun Jun:** Resources, Investigation, Formal analysis, Data curation. **Bomi Park:** Writing – review & editing, Writing – original draft, Supervision, Formal analysis, Data curation, Conceptualization. **Soontae Kim:** Validation, Software, Resources, Investigation, Data curation. **Moon Seong Baek:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization. **Chung Ho Kim:** Writing – original draft, Methodology, Formal analysis, Data curation.

Declaration of Competing Interest

The authors 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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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.ecoenv.2026.120090](https://doi.org/10.1016/j.ecoenv.2026.120090).

Data availability

Data used in this study are not publicly available due to KNHIS data use restrictions. Access to the data requires approval from the Korea National Health Insurance Service.

References

- Agustí, A., Celli, B.R., Criner, G.J., Halpin, D., Anzueto, A., Barnes, P., Bourbeau, J., Han, M.K., Martinez, F.J., Montes de Oca, M., Mortimer, K., Papi, A., Pavord, I., Roche, N., Salvi, S., Sin, D.D., Singh, D., Stockley, R., López Varela, M.V., Wedzicha, J.A., Vogelmeier, C.F., 2023. Global Initiative for Chronic Obstructive Lung Disease 2023 Report: GOLD Executive Summary. *Am. J. Respir. Crit. Care Med* 207, 819–837.
- Armstrong, B.G., Gasparrini, A., Tobias, A., 2014. Conditional Poisson models: a flexible alternative to conditional logistic case cross-over analysis. *BMC Med Res Method.* 14, 122.
- Celli, B.R., Fabbri, L.M., Aaron, S.D., Agustí, A., Brook, R., Criner, G.J., Franssen, F.M.E., Humbert, M., Hurst, J.R., O'Donnell, D., Pantoni, L., Papi, A., Rodríguez-Roisin, R., Sethi, S., Torres, A., Vogelmeier, C.F., Wedzicha, J.A., 2021. An Updated Definition and Severity Classification of Chronic Obstructive Pulmonary Disease Exacerbations: The Rome Proposal. *Am. J. Respir. Crit. Care Med* 204, 1251–1258.
- Chen, J., Shi, C., Li, Y., Ni, H., Zeng, J., Lu, R., Zhang, L., 2021. Effects of short-term exposure to ambient airborne pollutants on COPD-related mortality among the elderly residents of Chengdu city in Southwest China. *Environ. Health Prev. Med* 26, 7.
- Chen, R., Pan, G., Kan, H., Tan, J., Song, W., Wu, Z., Xu, X., Xu, Q., Jiang, C., Chen, B., 2010. Ambient air pollution and daily mortality in Anshan, China: a time-stratified case-crossover analysis. *Sci. Total Environ.* 408, 6086–6091.
- Chen, S., Kuhn, M., Prettnner, K., Yu, F., Yang, T., Bärnighausen, T., Bloom, D.E., Wang, C., 2023. The global economic burden of chronic obstructive pulmonary disease for 204 countries and territories in 2020–50: a health-augmented macroeconomic modelling study. *Lancet Glob. Health* 11, e1183–e1193.
- Crisafulli, E., Barbata, E., Ielpo, A., Torres, A., 2018. Management of severe acute exacerbations of COPD: an updated narrative review. *Multidiscip. Respir. Med* 13, 36.
- Di, Q., Dai, L., Wang, Y., Zanobetti, A., Choirat, C., Schwartz, J.D., Dominici, F., 2017. Association of Short-term Exposure to Air Pollution With Mortality in Older Adults. *Jama* 318, 2446–2456.
- Donaldson, G.C., Seemungal, T.A., Bhowmik, A., Wedzicha, J.A., 2002. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 57, 847–852.
- Dransfield, M.T., Kunisaki, K.M., Strand, M.J., Anzueto, A., Bhatt, S.P., Bowler, R.P., Criner, G.J., Curtis, J.L., Hanania, N.A., Nath, H., Putcha, N., Roark, S.E., Wan, E.S., Washko, G.R., Wells, J.M., Wendt, C.H., Make, B.J., 2017. Acute Exacerbations and Lung Function Loss in Smokers with and without Chronic Obstructive Pulmonary Disease. *Am. J. Respir. Crit. Care Med* 195, 324–330.
- Guarnieri, M., Balmes, J.R., 2014. Outdoor air pollution and asthma. *Lancet* 383, 1581–1592.
- Guerrero, M., Crisafulli, E., Liapikou, A., Huerta, A., Gabarrús, A., Chetta, A., Soler, N., Torres, A., 2016. Readmission for Acute Exacerbation within 30 Days of Discharge Is Associated with a Subsequent Progressive Increase in Mortality Risk in COPD Patients: A Long-Term Observational Study. *PLoS One* 11, e0150737.
- Huh, J.Y., Hong, J., Han, D.W., Park, Y.J., Jung, J., Lee, S.W., 2022. The Impact of Air Pollutants and Meteorological Factors on Chronic Obstructive Pulmonary Disease Exacerbations: A Nationwide Study. *Ann. Am. Thorac. Soc.* 19, 214–226.
- Jenkins, C.R., Celli, B., Anderson, J.A., Ferguson, G.T., Jones, P.W., Vestbo, J., Yates, J. C., Calverley, P.M., 2012. Seasonality and determinants of moderate and severe COPD exacerbations in the TORCH study. *Eur. Respir. J.* 39, 38–45.
- Jiang, Y., Yi, S., Gao, C., Chen, Y., Chen, J., Fu, X., Yang, L., Kong, X., Chen, M., Kan, H., Xiang, D., Su, X., Chen, R., 2023. Cold Spells and the Onset of Acute Myocardial Infarction: A Nationwide Case-Crossover Study in 323 Chinese Cities. *Environ. Health Perspect.* 131, 87016.
- Joo, H., Yoon, H.K., Hwang, Y.I., Kim, S.H., Um, S.J., Lee, W.Y., Jung, K.S., Yoo, K.H., Kim, W.J., Rhee, C.K., 2024. Application of the Lancet Commission COPD classification to COPD Cohort Population in South Korea. *Respir. Med* 230, 107679.
- Keil, A., Buckley, J., O'Brien, K., Ferguson, K., Zhao, S., White, A., 2019. A quantile-based g-computation approach to addressing the effects of exposure mixtures. *Environ. Epidemiol.* 3, 44.
- Keil, A.P., Buckley, J.P., O'Brien, K.M., Ferguson, K.K., Zhao, S., White, A.J., 2020. A Quantile-Based G-Computation Approach to Addressing the Effects of Exposure Mixtures. *Environ. Health Perspect.* 128, 47004.
- Kim, H., Huh, J.Y., Na, G., Park, S., Ra, S.W., Kang, S.Y., Kim, H.C., Kim, H.C., Lee, S.W., 2023. Lifestyle practices that reduce seasonal PM(2.5) exposure and their impact on COPD. *Sci. Rep.* 13, 11822.
- Kim, J.-A., Yoon, S., Kim, L.-Y., Kim, D.-S., 2017. Towards actualizing the value potential of Korea Health Insurance Review and Assessment (HIRA) data as a resource for health research: strengths, limitations, applications, and strategies for optimal use of HIRA data. *J. Korean Med. Sci.* 32, 718.
- Kim, S.J., Lee, J., Park, Y.S., Lee, C.-H., Yoon, H.I., Lee, S.-M., Yim, J.-J., Kim, Y.W., Han, S.K., Yoo, C.-G., 2016. Age-related annual decline of lung function in patients with COPD. *Int. J. Chronic Obstr. Pulm. Dis.* 51–60.
- Kim, Y., Kim, S.H., Rhee, C.K., Lee, J.S., Lee, C.Y., Kim, D.K., Shin, K.C., Jung, K.S., Yoo, K.H., Park, Y.B., 2022. Air Trapping and the Risk of COPD Exacerbation: Analysis From Prospective KOCSS Cohort. *Front Med (Lausanne)* 9, 835069.
- Kyoung, D.S., Kim, H.S., 2022. Understanding and Utilizing Claim Data from the Korean National Health Insurance Service (NHIS) and Health Insurance Review & Assessment (HIRA) Database for Research. *J. Lipid Atheroscler.* 11, 103–110.
- Lee, H., Lee, B.Y., Jung, J., Seok, J., Kim, J.H., Koo, S.M., Yoon, H.Y., 2025. Association of socioeconomic status with respiratory mortality and hospitalisations in COPD: a nationwide cohort study. *BMJ Open Respir. Res* 12.
- Lee, J., Lee, J.S., Park, S.H., Shin, S.A., Kim, K., 2017. Cohort Profile: The National Health Insurance Service-National Sample Cohort (NHIS-NSC), South Korea. *Int. J. Epidemiol.* 46, e15.
- Li, N., Ma, J., Ji, K., Wang, L., 2022. Association of PM2.5 and PM10 with Acute Exacerbation of Chronic Obstructive Pulmonary Disease at lag0 to lag7: A Systematic Review and Meta-Analysis. *Copd* 19, 243–254.
- Lian, Z., Cui, M., Liu, C., Chen, Y., Zhang, L., Wang, B., Yakufu, N., Xu, J., Li, L., Wei, X., Kelimu, J., 2025. Long-term exposure to ambient air pollutant and acute exacerbations of chronic obstructive pulmonary disease: a retrospective cohort study in Xinjiang, China. *Front Public Health* 13, 1658252.
- Liu, C., Jia, F., Ji, M., Qu, G., Ye, C., Cheng, J., Schwingel, A., Gao, R., 2023. The effect of short-term air pollutants exposure on daily mortality among elderly individuals in China: a systematic review and meta-analysis. *Water Air & Soil Pollut.* 234, 541.
- López, A.B.H., Torres-Duque, C.A., Arbeláez, M.P., Roa, N.Y.R., Ríos-Rodríguez, H., Sangrador, J.L.T., Herrera, V., Rodríguez-Villamizar, L.A., 2024. Short-term effect of air pollution exposure on COPD exacerbations: a time series study in Bogotá, Colombia. *Air Qual. Atmosphere & Health* 17, 2775–2787.
- McCormack, M.C., Belli, A.J., Kaji, D.A., Matsui, E.C., Brigham, E.P., Peng, R.D., Sellers, C., Williams, D.A.L., Diette, G.B., Breyse, P.N., 2015. Obesity as a susceptibility factor to indoor particulate matter health effects in COPD. *Eur. Respir. J.* 45, 1248–1257.
- Niu, Y., Niu, H., Meng, X., Zhu, Y., Ren, X., He, R., Wu, H., Yu, T., Zhang, Y., Kan, H., Chen, R., Yang, T., Wang, C., 2024. Associations Between Air Pollution and the Onset of Acute Exacerbations of COPD: A Time-Stratified Case-Crossover Study in China. *Chest* 166, 998–1009.

- Oh, J., Lee, J.H., Kim, E., Kim, S., Kim, H.S., Ha, E., 2021. Is Short-Term Exposure to PM (2.5) Relevant to Childhood Kawasaki Disease? *Int J. Environ. Res Public Health* 18.
- Oh, Y.M., 2023. Definition of Chronic Obstructive Pulmonary Disease Exacerbation: The Essentials of the Rome Proposal. *Tube Respir. Dis. (Seoul.)* 86, 61–62.
- Romaszko-Wojtowicz, A., Dragańska, E., Doboszyńska, A., Glińska-Lewczuk, K., 2025. Impact of seasonal biometeorological conditions and particulate matter on asthma and COPD hospital admissions. *Sci. Rep.* 15, 450.
- Ross, B.A., Doiron, D., Benedetti, A., Aaron, S.D., Chapman, K., Hernandez, P., Maltais, F., Marciniuk, D., O'Donnell, D.E., Sin, D.D., Walker, B.L., Tan, W., Bourbeau, J., 2023. Short-term air pollution exposure and exacerbation events in mild to moderate COPD: a case-crossover study within the CanCOLD cohort. *Thorax* 78, 974–982.
- Seemungal, T.A., Donaldson, G.C., Bhowmik, A., Jeffries, D.J., Wedzicha, J.A., 2000. Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med* 161, 1608–1613.
- Soler-Cataluña, J.J., Martínez-García, M.A., Román Sánchez, P., Salcedo, E., Navarro, M., Ochando, R., 2005. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax* 60, 925–931.
- Spencer, S., Calverley, P.M., Burge, P.S., Jones, P.W., 2004. Impact of preventing exacerbations on deterioration of health status in COPD. *Eur. Respir. J.* 23, 698–702.
- Strzelak, A., Ratajczak, A., Adamiec, A., Feleszko, W., 2018. Tobacco Smoke Induces and Alters Immune Responses in the Lung Triggering Inflammation, Allergy, Asthma and Other Lung Diseases: A Mechanistic Review. *Int J. Environ. Res Public Health* 15.
- Yu, L., Liu, W., Wang, X., Ye, Z., Tan, Q., Qiu, W., Nie, X., Li, M., Wang, B., Chen, W., 2022. A review of practical statistical methods used in epidemiological studies to estimate the health effects of multi-pollutant mixture. *Environ. Pollut.* 306, 119356.