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ORIGINAL RESEARCH

COPD Exacerbations, Air Pollutant Fluctuations, and Individual-Level Factors in the Pandemic Era

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Purpose: Pandemic-era associations between air pollutant exposures and exacerbations of chronic obstructive pulmonary disease (COPD) are under-explored. Given the considerable observed pandemic-era pollutant fluctuations, these associations were investigated along with possible individual-level risk factors.

Patients and Methods: Participants with spirometry-confirmed COPD from Canadian Cohort Obstructive Lung Disease (CanCOLD) were included, with data collected before ("pre-pandemic") and during ("pandemic") the COVID-19 pandemic. Nitrogen dioxide (NO_2), fine particulate matter ($PM_{2.5}$), ground-level ozone (O_3), total oxidant (O_x) and weather data were obtained from national databases. Associations between each air pollutant and "symptom-based" exacerbations (increased dyspnea or sputum volume/purulence ≥48hrs) and "event-based" exacerbations ("symptom-based" plus requiring antibiotics, corticosteroids, or unscheduled healthcare use) were estimated in separate models. Generalized estimating equations (GEE) models were reported as rate ratios (RRs) per interquartile range (IQR) increment in pollutant concentration with 95% confidence intervals (95% CIs).

Results: NO_2, $PM_{2.5}$, and O_x (NO_2+O_3) concentrations (but not O_3) fell significantly during the pandemic. In the 673 participants with COPD included, both symptom-based and event-based exacerbation rates were likewise significantly higher during the pre-pandemic period. During the pre-pandemic period, O_x was positively associated with symptom-based exacerbations (RR: 1.21 [1.08,1.36]). During the pandemic period, O_x was positively associated with symptom-based (1.46 [1.13,1.89]) and event-based (1.43 [1.00,2.05]) exacerbations. Fewer self-reported pandemic protective behaviors, and higher viral infectious symptoms, were also associated with exacerbations. In stepwise multivariable risk-factor analyses, female gender (1.23 [1.04,1.45] and 1.41 [1.13,1.76]) and co-morbid asthma (1.65 [1.34,2.03] and 1.54 [1.19,2.00]) were associated with symptom-based and event-based exacerbations, respectively, blood eosinophils (1.42 [1.10,1.84]) were associated with event-based exacerbations, and each IQR increment in O_x was associated with symptom-based exacerbations (1.31 [1.06,1.61]).

Conclusion: O_x exposure was consistently associated with symptom-based COPD exacerbations, and female gender, co-morbid asthma, and blood eosinophilia were found to be relevant risk factors.

Plain language summary: Previous research has identified air pollution as a relevant non-infectious trigger for episodic 'lung attacks', referred to as exacerbations, in patients living with chronic obstructive pulmonary disease (COPD). Very few studies,

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however, have studied this relationship during the COVID-19 pandemic. During that time, there were large fluctuations in key forms of air pollution (air pollutants). The few studies available used population-level approaches and relied on hospital administrative coding of visits to classify the disease and to identify exacerbation events. This approach may lead to potentially missing clinically important non-severe events and may limit individual-level risk factor assessment around this period.

This study was conducted in participants with COPD as confirmed by the gold-standard test, spirometry, who were living in 9 Canadian cities across 6 provinces. The results showed that while the air pollutants nitrogen dioxide (NO_2), fine particulate matter ($PM_{2.5}$), and total oxidant (O_x) concentrations were all notably higher before the pandemic (pre-pandemic), only ambient O_x concentration was consistently associated with exacerbations. This relationship was seen across both pre-pandemic and pandemic periods. Female gender, co-morbid asthma, and eosinophilia were identified as notable risk factors for exacerbations and were effect modifiers for the association between O_x exposure and exacerbations. This study adds to a very limited existing literature on the relationship between air pollutant fluctuations and exacerbations of COPD around the pandemic era and highlights important risk factors to guide targeted public health and exposure response interventions.

Keywords: Chronic obstructive pulmonary disease, acute exacerbations of chronic obstructive pulmonary disease, ambient air pollution, COVID-19 pandemic, total oxidant concentration

Introduction

Chronic obstructive pulmonary disease (COPD) is the third-leading cause of global morbidity and mortality worldwide,[1,2] and exacerbations of COPD (ECOPDs) represent a major burden to patients and health systems. The modern exacerbation framework recognizes air pollution as a relevant non-infectious precipitant.[3]

The COVID-19 pandemic resulted in considerable global fluctuations in air pollutant concentrations. During recurrent lockdowns across Europe, North America, and Asia,[4,5] the ambient concentrations of most air pollutants including nitrogen dioxide (NO_2) and fine particulate matter ($PM_{2.5}$) decreased, while an increase in ozone (O_3) concentrations was observed.[6,7] Total oxidant (O_x), the arithmetic sum of NO_2 and O_3 concentrations and an indicator of ambient oxidative capacity,[8] varied regionally during the pandemic, increasing in some areas due to elevated O_3 despite reduced NO_2, and were influenced by complex atmospheric dynamics and regional factors that were not uniform across various geographic regions.[9–14]

Within the limited literature focused strictly on these pandemic-era phenomena and associations, some reported an observed reduction in COPD exacerbation rates and COPD-related admissions,[15–18] though few actually explored air pollution-ECOPD associations.[18] Studies that did estimate these pandemic era associations mainly pursued an ecological approach, with reliance on International Classification of Disease (ICD) codes for disease diagnosis,[16–19] which may risk disease and outcome misclassification and tend to neglect non-severe events that are still clinically relevant.[20,21] More detailed information of study participants, had they been available in those ecological studies, may have allowed for investigation into individual-level risk factors in the observed pandemic-era "pollutant-exacerbation" associations.

The present study sought first to characterize the fluctuations in ambient air pollution during and preceding the COVID-19 pandemic in 9 Canadian cities, and to determine COPD exacerbation rates over these same periods. The main objective was to determine the relationship between each air pollutant and COPD exacerbation rates with consideration of relevant confounders. The secondary objective was to identify individual-level risk factors in relation to these associations. We hypothesized a positive association between ambient air pollutant concentration fluctuations and COPD exacerbation rates, and that certain risk factors may emerge in these relationships. Some of the results of this study have been previously reported in the form of an abstract.[22]

Material and Methods

Population and Study Periods

Data from Canadian Cohort Obstructive Lung Disease (CanCOLD), a prospective longitudinal cohort study described previously (see online data Supplement), were utilized. The present study included participants diagnosed with COPD by spirometry (post-bronchodilator $FEV_1/FVC<0.7$) with telephone interview exacerbation data available. Two distinct

periods of observation were included: the "pre-pandemic" period (July 2012-December 2019, inclusive) and the "COVID-19 pandemic" period (January 2020-December 2022, inclusive). Institutional review board approval was obtained, and all participants provided written informed consent.

Study Outcomes, Air Pollution Exposure, and Covariates

Exacerbations were collected prospectively via structured telephone interview at three-month intervals throughout both study periods. Exacerbations were defined as either "symptom-based" (increase in dyspnea, sputum volume or sputum purulence lasting ≥48 hours) or "event-based" (meeting "symptom-based" criteria plus requiring either antibiotic or systemic corticosteroid treatment or unscheduled visit/hospitalization).[20,21,23,24] Exacerbation rates were calculated for each of the two study periods.

Collection and aggregation of daily air pollutant concentrations and weather covariates were performed as reported previously[25] (see Supplement). Air pollution exposure data were obtained from the federal National Air Pollution Surveillance (NAPS) monitoring network using fixed-location monitoring stations within each of the nine CanCOLD cities.

Additional Pandemic-Specific Covariates

From May 2020 onwards, a monthly "COVID-19 Questionnaire" was administered to collect relevant behaviors, symptoms, and events directly or indirectly related to the COVID-19 pandemic (see Supplement text, and Supplement Figure S1, for details).

Statistical Analysis

Differences between the pre-pandemic and COVID-19 pandemic periods were compared using generalized estimating equations (GEE) with normal distribution, adjusted for season and for temperature and humidity (restricted cubic splines). Differences in symptom-based and event-based exacerbation rates between the two study periods were compared using unadjusted and adjusted GEE models with negative binomial distribution (see Supplement).

The association between air pollutant concentrations and exacerbation rates across both study periods were estimated by fitting GEE models, first by period only and secondly following adjustment for period as well as age, gender, season, and temperature and humidity (spline terms). Within-period models were also fitted. Offset was used to account for differing period follow-up durations.

Sensitivity analyses were conducted in the subgroup of participants with COVID-19 Questionnaire responses available, in order to estimate the association between behavioral "protective" measures and markers of viral infection status with exacerbations. These two variables were inserted into the within-COVID-19 pandemic period models, to retest the associations between each air pollutant and exacerbation rates within this period.

Finally, the determination of relevant individual-level susceptibilities or 'risk factors' was investigated using multivariable analyses with a stepwise approach (see Supplement). Subgroup differences by self-reported gender, self-reported presence or absence of physician-diagnosed co-morbid asthma, and blood eosinophil count (Eos: <300 versus ≥300 counts/microliter and <3% versus ≥3%) were analyzed using of the Wald test for effect modification.

All GEE models used an exchangeable correlation structure. Results are presented as point estimates, or as rate ratios (RRs), as appropriate, with 95% confidence intervals (95% CIs). Adjustments for multiple comparisons were not made. All statistical analyses were conducted using SAS statistical software, version 9.4 (SAS Institute, Cary, North Carolina, USA).

Results

Study Population and Baseline Characteristics

In total, 673 of 1,561 CanCOLD study participants met all eligibility criteria and were included (Figure 1). Of these, 413 participants had COVID-19 Questionnaire data available for inclusion in within-COVID-19 pandemic period sub-analyses with behavioral and viral infection factors.

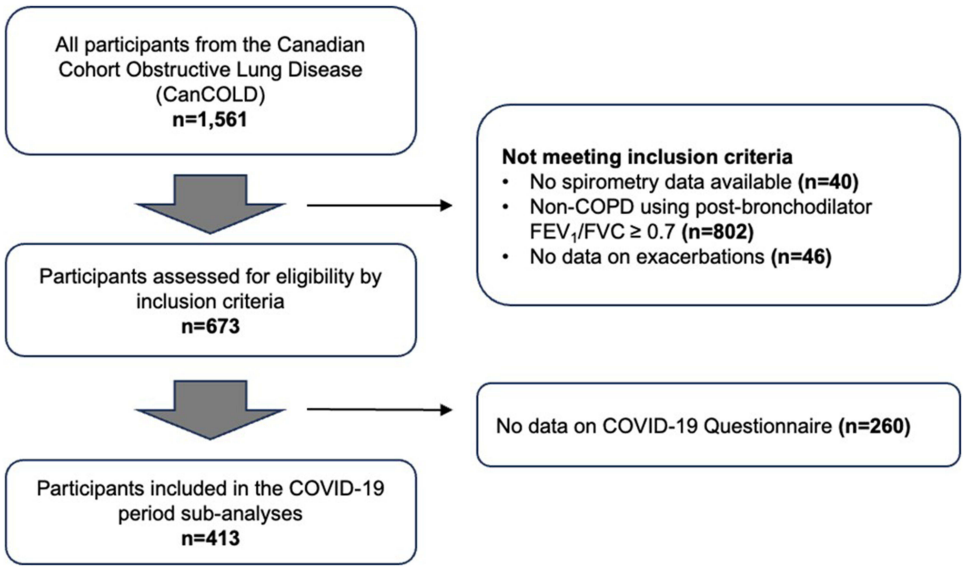

Figure 1 Flow diagram of study participants.
Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity. Symbols: n, number.

Baseline characteristics and missingness by variable are presented in Table 1. Participants were older adults with a slight preponderance of males, and just over half with mild (GOLD 1) COPD. Co-morbid self-reported physician-diagnosed asthma was present in 32.1% of participants, and among participants with blood eosinophil data available, 151 (25.5%) had Eos ≥300 counts/microliter.

Table 1 Characteristics of Study Participants

	All Participants (n=673)	
	N	**Mean (SD), or n (%)**
Gender, male, n (%)	673	406 (60.3)
Age, in years	673	67.3 (10.1)
Education level ≤ 12 years, n (%)	671	166 (24.7)
BMI	673	27.3 (5.3)
Cigarette status, n (%)		
Never smokers	673	216 (32.1)
Former smokers	673	339 (50.4)
Current smokers	673	118 (17.5)
Smoking Pack-Year History (PYHx)	665	22.7 (24.8)
MRC ≥ 3, n (%)	639	53 (8.3)
CAT score	671	7.7 (6.6)
Asthma, n (%)	673	216 (32.1)
FEV_1, L	673	2.3 (0.8)
FEV_1/FVC, ratio	673	0.61 (0.8)
FEV_1, % predicted	673	82.4 (19.4)
GOLD Grade 1, n (%)	673	376 (55.9)
GOLD Grade 2–4, n (%)	673	297 (44.1)
Eos counts		
< 150 Eos count/microliter, n (%)	592	223 (37.7)
150 to < 300 Eos count/microliter, n (%)	592	218 (36.8)
≥ 300 Eos count/microliter, n (%)	592	151 (25.5)

(*Continued*)

Table 1 (Continued).

	All Participants (n=673)	
	N	**Mean (SD), or n (%)**
Eos percentage		
< 3%, n (%)	592	181 (30.6)
≥ 3%, n (%)	592	411 (69.4)

Abbreviations: SD, Standard deviation; BMI, body mass index; MRC, medical research council; CAT, COPD assessment test; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; GOLD, global initiative for chronic obstructive lung disease; Eos, eosinophil. Symbols: n, number; %, percent.

In the pre-pandemic period, the median follow-up duration was 77.3 months (IQR: 59.2–83.9). During this time, the symptom-based exacerbation rate was 0.41 events per person-year (95% CI: 0.37–0.45), and the event-based exacerbation rate was 0.22 events per person-year (95% CI: 0.19–0.25). In the COVID-19 pandemic period, the median follow-up duration was 33.8 months (IQR: 29.5–35.1). The symptom-based exacerbation rate decreased to 0.25 events per person-year (95% CI: 0.21–0.29), while the event-based exacerbation rate dropped to 0.15 events per person-year (95% CI: 0.12–0.18).

Air Pollutant Concentrations, Exacerbation Rates, and Air Pollutant-Exacerbation Associations

Median and IQR air pollutant concentrations, by both study city and study period, are shown in Table 2, and are presented by both season and study period in Figure 2. While seasonal variations were observed within both periods, compared with the pre-pandemic period the COVID-19 pandemic period was associated with lower NO_2 (−1.97 [−2.08, −1.86] ppb), $PM_{2.5}$ (−0.53 [−0.59, −0.47] μg/m^3), and O_x (−1.44 [−1.61, −1.27] ppb) concentrations. As previously reported,[6,7] O_3 concentrations were significantly higher during the COVID-19 pandemic period (0.36 [0.18, 0.55] ppb). Heterogeneity was observed across study sites.

Compared with the pre-pandemic period, significant reductions were observed in unadjusted symptom-based (RR: 0.58 [0.50, 0.68]) and event-based (0.66 [0.55, 0.80]) exacerbation rates, as well as in adjusted rates (Figure 3).

Regarding the association between each air pollutant and exacerbations across both periods, an IQR increment in NO_2 and in O_x were each associated with an increase in symptom-based and event-based exacerbation rates, while no associations were observed with each IQR increment in $PM_{2.5}$ or O_3 exposure (see Supplement Table S1). In adjusted

Table 2 Distribution of Median Air Pollutant Concentrations Stratified by the Two Periods and the Nine Study Centers

	Vancouver	Montreal	Toronto	Halifax	Calgary	Ottawa	Kingston	Quebec	Saskatoon
Pre-pandemic									
NO_2 median (IQR)	14.2 (5.2)	11.3 (3.9)	12.7 (4.4)	8.4 (1.8)	11.1 (10.0)	5.5 (4.6)	4.3 (2.6)	8.9 (3.8)	9.3 (5.7)
$PM_{2.5}$ median (IQR)	6.1 (1.7)	8.5 (2.2)	8.0 (1.5)	5.0 (1.0)	7.1 (1.3)	6.5 (1.9)	6.0 (0.8)	8.7 (2.5)	6.9 (3.1)
O_3 median (IQR)	12.5 (8.7)	22.3 (6.9)	25.9 (7.4)	21.1 (6.9)	21.1 (8.2)	25.3 (7.0)	30.8 (7.7)	23.8 (9.1)	23.5 (7.0)
O_x median (IQR)	28.9 (5.1)	32.9 (7.7)	38.5 (5.2)	31.3 (7.4)	35.3 (11.3)	32.5 (9.4)	35.0 (7.6)	32.8 (10.9)	33.8 (9.2)
COVID-19 pandemic									
NO_2 median (IQR)	12.5 (5.8)	8.1 (7.0)	11.2 (4.0)	4.4 (1.2)	15.1 (11.0)	5.2 (5.0)	4.0 (2.5)	5.1 (3.5)	5.8 (6.9)
$PM_{2.5}$ median (IQR)	5.1 (0.9)	6.7 (2.9)	7.5 (0.6)	5.4 (0.5)	6.8 (1.3)	6.1 (2.6)	5.7 (1.1)	8.5 (2.9)	7.8 (2.8)
O_3 median (IQR)	14.4 (7.0)	23.2 (8.2)	25.0 (6.9)	26.0 (8.7)	21.8 (9.9)	26.7 (8.9)	30.2 (9.5)	22.8 (7.4)	24.3 (5.1)
O_x median (IQR)	31.2 (6.1)	37.0 (7.6)	36.1 (6.8)	30.5 (9.1)	38.8 (5.3)	35.4 (10.1)	33.2 (7.6)	28.4 (6.2)	34.6 (6.5)

Abbreviations: NO_2, nitrogen dioxide (parts per billion); $PM_{2.5}$, fine particulate matter (micrograms per cubic meter); O_3, ozone (parts per billion); O_x, total oxidant (parts per billion); IQR, interquartile range.

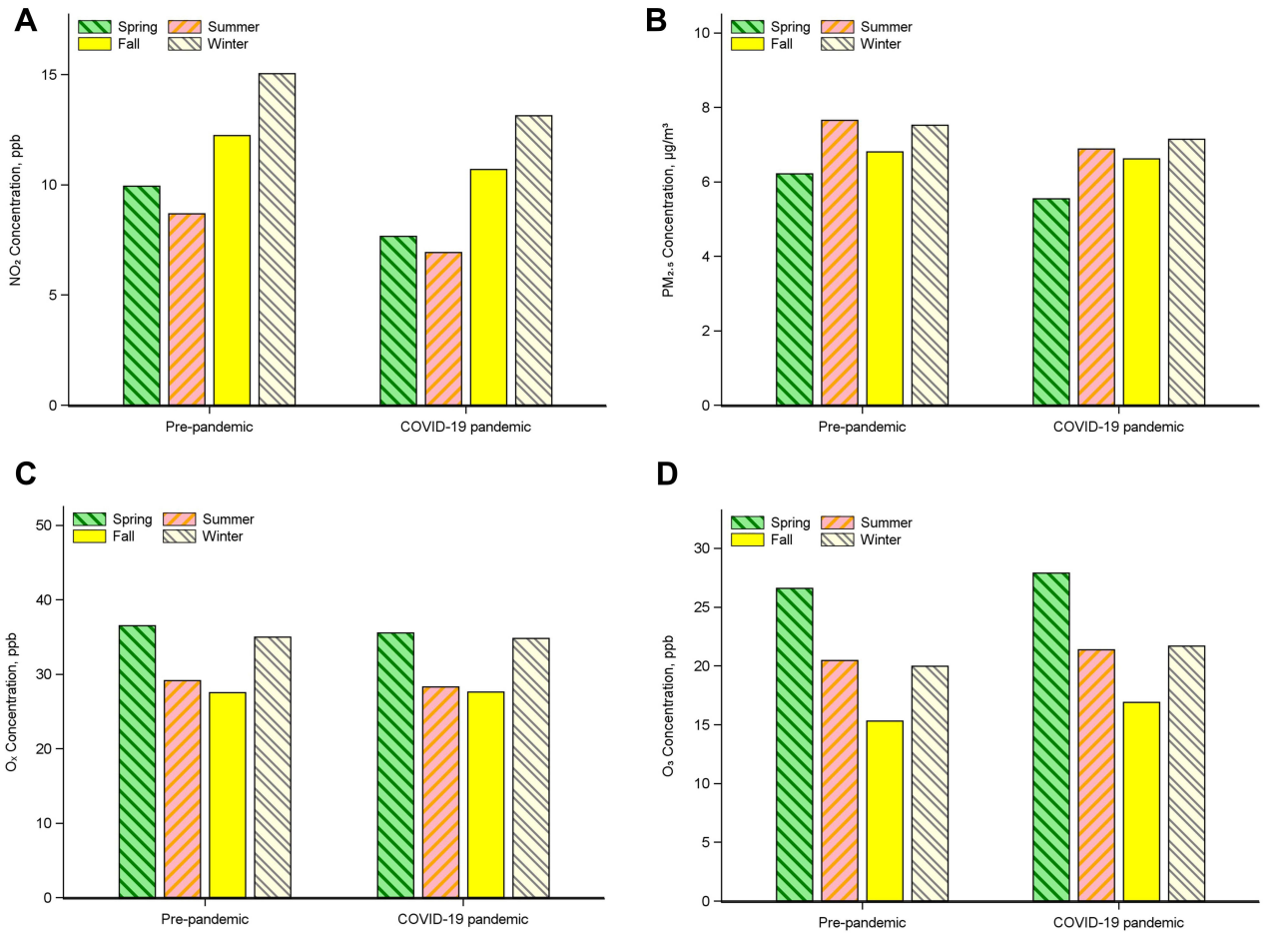

Figure 2 Air pollutant concentration in each study period for (**A**) nitrogen dioxide (NO_2), parts per billion (ppb); (**B**) fine particulate matter ($PM_{2.5}$), micrograms per cubic meter ($\mu g/m^3$); (**C**) total oxidant (O_x), parts per billion (ppb); and (**D**) ozone (O_3), parts per billion (ppb).

models, each IQR increment in O_x concentration alone was associated with an increase in symptom-based exacerbation rates, with no associations observed with the other air pollutants (Table 3).

In within-period analyses, during the pre-pandemic period unadjusted models demonstrated that each IQR increment in NO_2 and O_x were again associated with an increase in symptom-based exacerbations (1.30 [1.16, 1.45]; and 1.21 [1.08, 1.36], respectively), and event-based exacerbations for NO_2 alone (1.16 [1.02, 1.33]), with a trend for O_x that did not reach statistical significance (1.13 [0.96, 1.33], P=0.136). In adjusted models, no associations were observed, though a trend with each IQR increment for O_x alone with symptom-based exacerbations was observed (1.25 [0.99, 1.59], P=0.064). During the COVID-19 pandemic period, unadjusted models demonstrated that each IQR increment in NO_2 was associated with an increase in symptom-based exacerbations (1.24 [1.01, 1.54]), while in adjusted models, NO_2 was associated with a *decrease* in event-based exacerbations (0.69 [0.49, 0.97]). Each O_x increment was associated with an increase in both symptom-based (1.46 [1.13, 1.89]) and event-based (1.43 [1.00, 2.05]) exacerbations in unadjusted, but not adjusted, models.

Each additional listed behavior (action taken) to reduce the risk of COVID-19 infection/transmission as captured in the COVID-19 Questionnaire data (n=413; see Supplement Figure S1) was associated with a reduction in event-based exacerbation rates (0.59 [0.43, 0.82]). Likewise, participants who reported <4 listed behaviors to reduce infection/transmission risk had a higher rate of symptom-based exacerbations (1.52 [1.02, 2.27]) compared with those who reported ≥4 behaviors. Regarding viral infectious symptoms, scoring>1 compared with scoring=1 (FLU-PRO

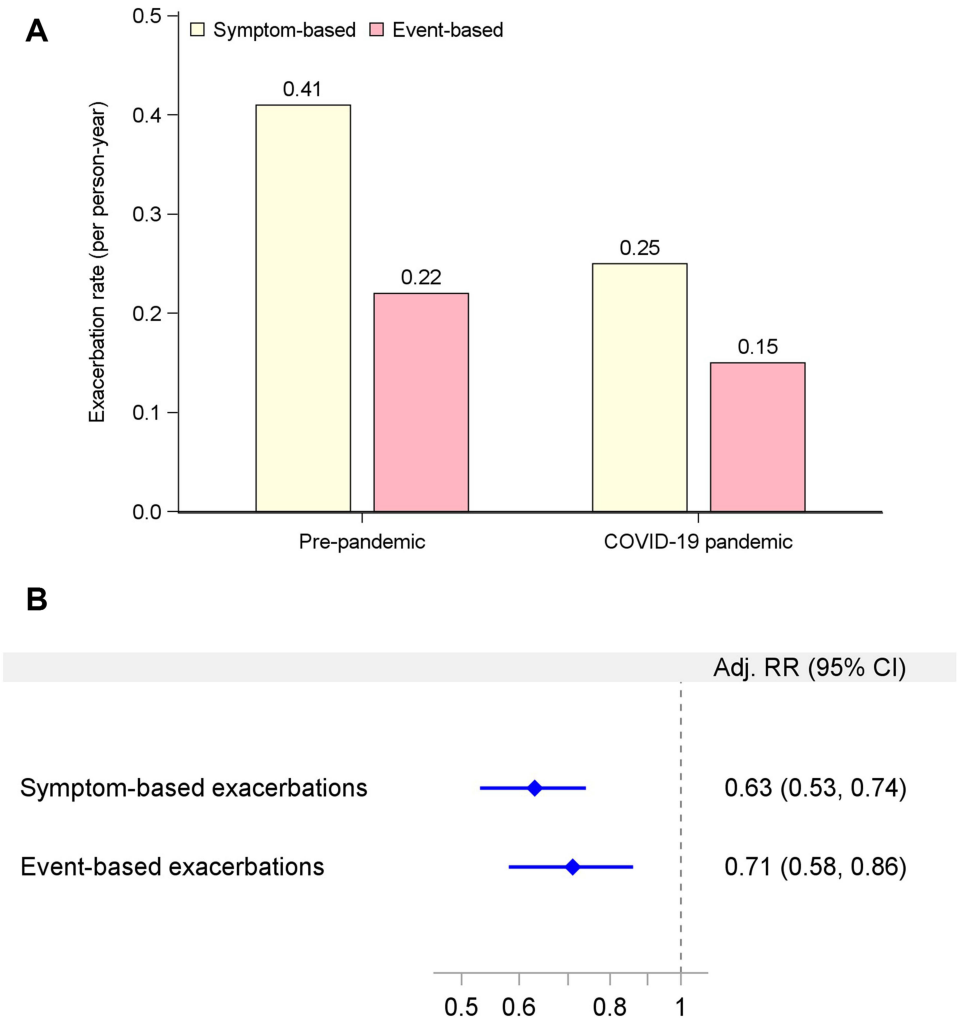

Figure 3 Comparison of symptom-based and event-based exacerbations between the two study periods, presented as rates in person-years (**A**) and as rate ratios (RR) and corresponding 95% confidence intervals (CI) estimated using Generalized Estimating Equation (GEE) models (**B**), adjusted (Adj) for baseline age, gender, season, and the spline terms for temperature and humidity. Symbols: %, percent.

questionnaire; see Supplement) was associated with an increased rate of symptom-based (2.96 [2.10, 4.18]) and event-based (2.72 [1.66, 4.46]) exacerbations. When both behaviors and viral infectious symptoms were inserted into each air pollutant-exacerbation adjusted model, the only association observed was a *decrease* in the rate of event-based exacerbations with each NO_2 increment (0.65 [0.46, 0.91]).

Table 3 Adjusted Associations Between Each Air Pollutant and Exacerbation Rates Across Both Study Periods

	Symptom-Based Exacerbations		**Event-Based Exacerbations**	
	Adj. RR (95% CI)	**P-Values**	**Adj. RR (95% CI)**	**P-Values**
NO_2, per IQR increase (ppb)	1.03 (0.88, 1.22)	0.681	0.91 (0.75, 1.10)	0.334
$PM_{2.5}$, per IQR increase (μg/m^3)	0.91 (0.81, 1.02)	0.100	0.96 (0.84, 1.11)	0.627
O_3, per IQR increase (ppb)	1.14 (0.96, 1.35)	0.149	1.05 (0.85, 1.30)	0.644
O_x, per IQR increase (ppb)	1.28 (1.04, 1.56)	0.019*	0.96 (0.74, 1.23)	0.726

Note: Adjusted for period, baseline age, gender, period, season, and spline terms for temperature and humidity.
Abbreviations: NO_2, nitrogen dioxide; $PM_{2.5}$, fine particulate matter; O_3, ozone; O_x, total oxidant; IQR, Adj, Adjusted; interquartile range; CI, confidence interval; RR, rate ratio; ppb, parts per billion; μg, microgram; m^3, meter cubed. Symbols: %, percent; *, P<0.05.

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Table 4 Associations Between Individual-Level Factors and Exacerbation Rates

	Multivariable Analysis (Stepwise Approach)			
	Symptom-Based Exacerbations		Event-Based Exacerbations	
	Adj. RR (95% CI)	P-Values	Adj RR (95% CI)	P-Values
Gender, female vs male	1.23 (1.04, 1.45)	0.016*	1.41 (1.13, 1.76)	0.002*
Age, per 1-year increase	–	–	–	–
BMI, per 1-unit increase	–	–	–	–
Pack-years, per 1-unit increase	1.01 (1.00, 1.01)	<0.001*	1.01 (1.00, 1.01)	<0.001*
Biomass exposure	–	–	–	–
10 years				
Asthma, yes vs no	1.65 (1.34, 2.03)	<0.001*	1.54 (1.19, 2.00)	0.001*
Eos counts				
<300 Eos/microliter	–	–	–	–
≥300 Eos/microliter	–	–	–	–
Eos percentage				
<3%	–	–	REF	–
≥3%	–	–	1.42 (1.10, 1.84)	0.007*
FEV_1, % predicted, per 5% increase	0.95 (0.93, 0.97)	<0.001*	0.93 (0.89, 0.96)	<0.001*
NO_2, per IQR increase (ppb)	–	–	–	–
$PM_{2.5}$, per IQR increase (g/m^3)	–	–	–	–
O_3, per IQR increase (ppb)	–	–	–	–
O_x, per IQR increase (ppb)	1.31 (1.06, 1.61)	0.013*	–	–

Notes: Multivariable analysis with stepwise approach, adjusted for period, season, and spline terms for temperature and humidity.
Abbreviations: BMI, body mass index; Eos, eosinophil; FEV_1, forced expiratory volume in one second; NO_2, nitrogen dioxide; $PM_{2.5}$, fine particulate matter; O_3, ozone; O_x, total oxidant; IQR, interquartile range; Adj, Adjusted; CI, confidence interval; RR, rate ratio; ppb, parts per billion; µg, microgram; m^3, meter cubed. Symbols: %, percent; *, P<0.05.

Pollutant-Exacerbation Associations and Individual-Level Risk Factors

Female gender, co-morbid asthma, and Eos ≥3% were each associated with increased rates of both symptom-based and event-based exacerbations, respectively, in univariable analyses (see Supplement Table S1). Eos ≥300 was associated with event-based exacerbations alone. Cumulative cigarette smoking history (in pack-years) and FEV_1 (percent predicted) were also associated with both symptom-based and event-based exacerbations. Smoking history, FEV_1, female gender, co-morbid asthma, and Eos ≥3% were associated with an increase in both symptom-based and event-based exacerbations, while each IQR increment in O_x (and no other air pollutants) was associated with increased rates of symptom-based exacerbations, in stepwise adjusted multivariable analyses (Table 4).

In risk factor subgroup (effect modification) analyses, each IQR increment of O_x was associated with an increase in symptom-based exacerbation rates in females whereas in males, each IQR increment in $PM_{2.5}$ was associated with a *decrease* in symptom-based exacerbations (Figure 4). In the non-asthma subgroup, each IQR increment in $PM_{2.5}$ was associated with a *decrease* in symptom-based exacerbations (Figure 5). Finally, in the Eos <300 subgroup, each IQR increment in both NO_2, and O_x were associated with a *decrease* in event-based exacerbations, whereas in the Eos ≥300 subgroup, each O_x increment alone was associated with an increase in symptom-based exacerbations (Figure 6). Evidence of effect modification was observed for gender (both NO_2 and O_3 with event-based exacerbations) and for co-morbid asthma status ($PM_{2.5}$ with both symptom-based and event-based exacerbations).

Discussion

The present study investigated the associations between air pollutant concentrations and exacerbations of COPD in the global COVID-19 pandemic era, across which there was a substantial fluctuation in ambient air pollution, and additionally investigated relevant individual-level risk factors in these associations in a prospective cohort of participants with COPD. While a significant decrease in NO_2, $PM_{2.5}$, and O_x concentrations was observed during the COVID-19 pandemic period, O_3 concentration on average increased. We also observed a decrease in the rate of both symptom-based

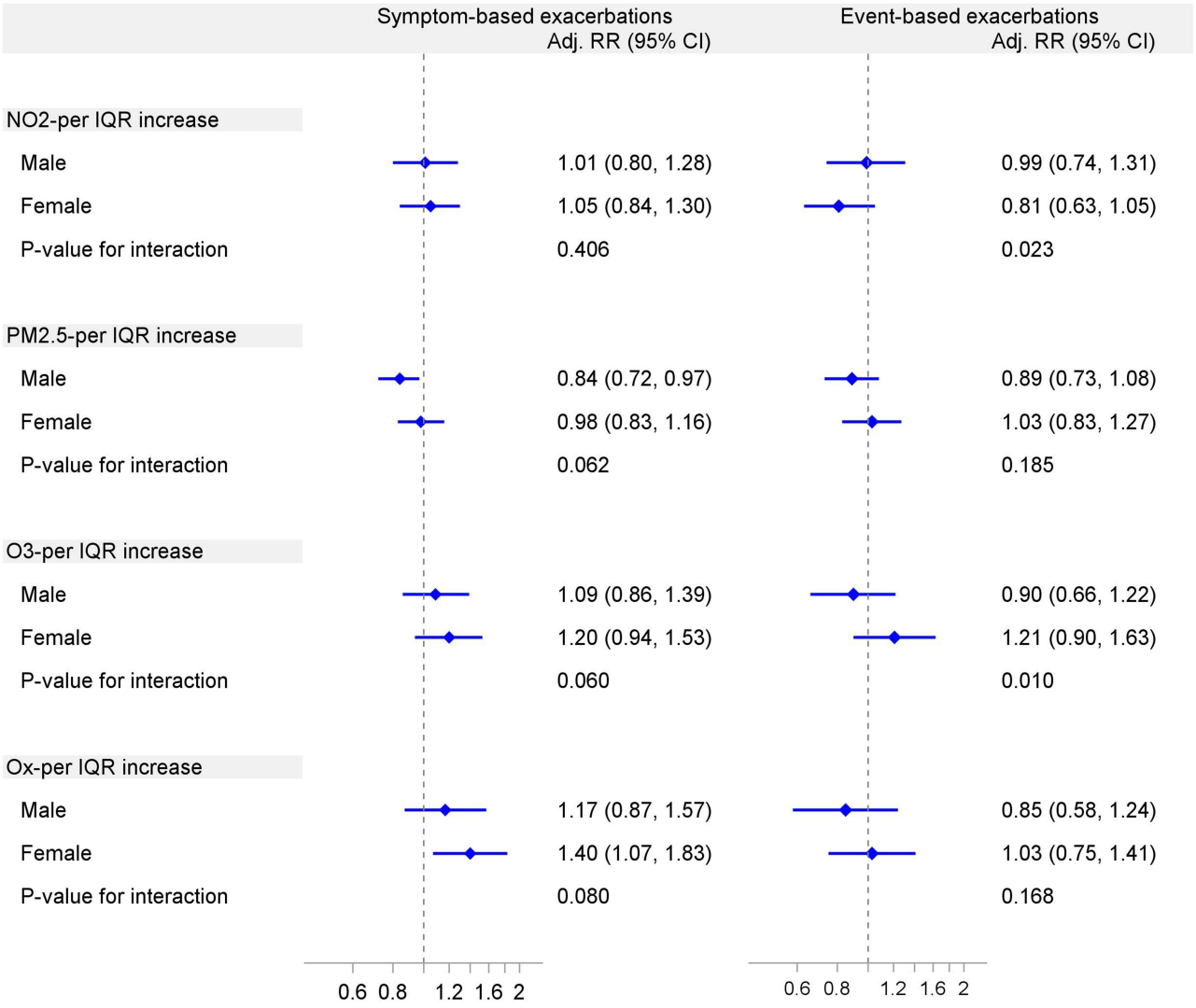

Figure 4 Forest plot of the association between air pollutant concentration and exacerbation rates stratified by gender across both pre-pandemic and COVID-19 pandemic periods. Rate ratios (RR) and 95% confidence intervals (CI) were estimated using Generalized Estimating Equation (GEE) models with a negative binomial distribution and exchangeable correlation, with time included as the offset term. Adjusted (Adj) for age, period, season, and spline terms for temperature and humidity. NO_2, nitrogen dioxide (parts per billion); $PM_{2.5}$, fine particulate matter (microgram per cubic meter); O_3, ozone (parts per billion); O_x, total oxidant (parts per billion); IQR, interquartile range. Symbols: %, percent.

and event-based exacerbations during the pandemic. The most consistent association across both periods, in both unadjusted and adjusted models, was observed between ambient O_x exposure and COPD exacerbations. NO_2 exposure was associated with both an increase, *decrease*, or no association with exacerbations across the different models, and likewise, some unexpected associations were observed with $PM_{2.5}$, such that $PM_{2.5}$ exposure in some models was associated with a *decrease* in exacerbations. When investigating behaviors and events during the COVID-19 pandemic period, interestingly, fewer self-reported health-protective behaviors were associated with an increase in exacerbations and higher self-reported symptoms of viral infection were associated with an increase in exacerbations. Including both of these variables into adjusted models led to a loss of the association between O_x and exacerbations that was observed consistently across the other models. Finally, beyond typical markers of disease severity including cumulative smoking history and lung function, female gender, co-morbid asthma, and high blood eosinophil count were each positively associated with exacerbations, and in stepwise multivariable modeling with air pollutants, these were relevant risk factors in the significant association between O_x concentration and exacerbations.

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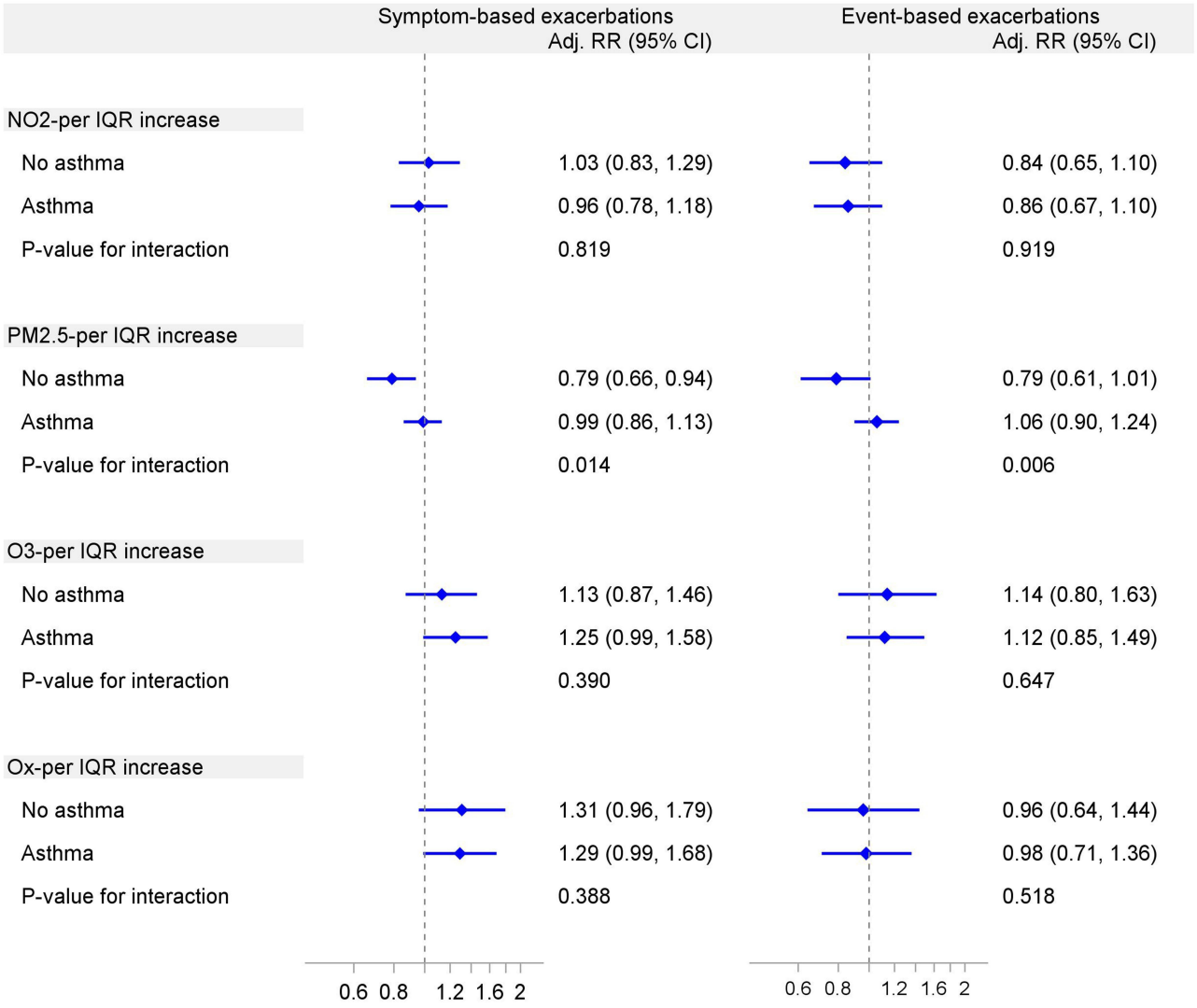

Figure 5 Forest plot of the association between air pollutant concentration and exacerbation rates stratified by asthma status across both pre-pandemic and COVID-19 pandemic periods. Rate ratios (RR) and 95% confidence intervals (CI) were estimated using Generalized Estimating Equation (GEE) models with a negative binomial distribution and exchangeable correlation, with time included as the offset term. Adjusted (Adj) for age, gender, period, season, and spline terms for temperature and humidity. NO_2, nitrogen dioxide (parts per billion); $PM_{2.5}$, fine particulate matter (microgram per cubic meter); O_3, ozone (parts per billion); O_x, total oxidant (parts per billion); IQR, interquartile range. Symbols: %, percent.

The significant reductions in NO_2, $PM_{2.5}$, and O_x concentrations, the increase in O_3 levels, and the reduction in both symptom-based and event-based exacerbation rates during the COVID-19 pandemic period are all consistent findings with the existing available literature. The same directionality of air pollutant fluctuations was reported during regional and pan-national lockdowns,[4,5] as were the observed reductions in COPD exacerbations, COPD-related hospitalizations,[4,9,26–29] and mortality.[30] $PM_{2.5}$ and NO_2 changes during lockdowns have been attributed to industrial and economic slowdowns and reduced human transportation and traffic;[6] meteorological factors were also considered to be, at least in part, contributory.[5] Another study during COVID-19 lockdowns in Europe demonstrated that, while O_x levels decreased slightly at "traffic" sites due to reduced primary NO_2 emissions, they remained nearly constant in "urban background" locations.[14]

The most consistent association observed in the present study was between ambient O_x exposure and symptom-based COPD exacerbations, while the associations between NO_2 and $PM_{2.5}$ exposure and exacerbations varied considerably. The strong association between O_x and symptom-based exacerbations, despite NO_2 and O_3 individually not being associated, may relate to their differing spatial distribution. NO_2 is typically higher in urban areas, while O_3 is higher

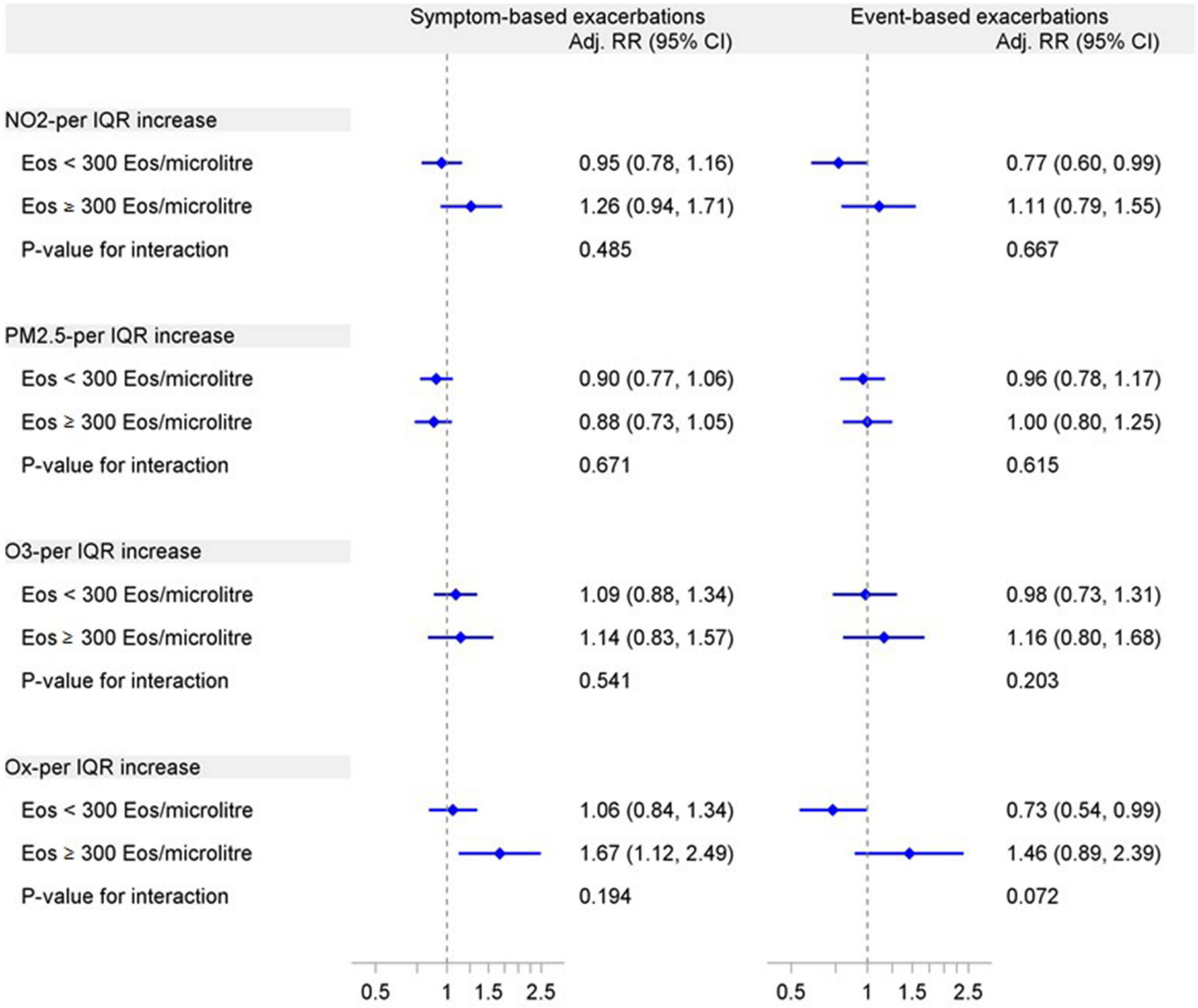

Figure 6 Forest plot of the association between air pollutant concentration and exacerbation rates stratified by blood eosinophil count across both pre-pandemic and COVID-19 pandemic periods. Rate ratios (RR) and 95% confidence intervals (CI) were estimated using Generalized Estimating Equation (GEE) models with a negative binomial distribution and exchangeable correlation, with time included as the offset term. Adjusted (Adj) for age, gender, period, season, and spline terms for temperature and humidity. NO_2, nitrogen dioxide (parts per billion); $PM_{2.5}$, fine particulate matter (microgram per cubic meter); O_3, ozone (parts per billion); O_x, total oxidant (parts per billion); IQR, interquartile range. Symbols: %, percent.

in rural areas, and O_x captures the overall oxidative potential across different geographic areas.[31] Recent studies suggest that gaseous and particulate pollutants contribute to exacerbations of COPD through different proposed mechanisms. While gaseous pollutants may trigger bronchoconstriction, particulate pollutants may promote airway inflammation and increased mucus production.[32–34] O_3 and NO_2 are gaseous pollutants with strong oxidative potential, with O_x representing the sum of their oxidative capacities.[35–37] One study in the UK investigated the impact of O_3, NO_2, and O_x on mortality and found that 24-hour mean concentrations of O_x were associated with greater increases in mortality compared to O_3 and NO_2 individually.[38] When analyzed together in two-pollutant modeling, the associations for O_3 and NO_2 were similar in magnitude to those for O_x.[38] The association between gaseous pollutants, in particular O_x, with respiratory exacerbations have been observed in Germany,[9] Greece,[18] and China.[35,39] Thus, considering the combined oxidative potential of gaseous pollutants, as encapsulated by O_x, this ambient air pollutant may be of particular value in future epidemiological studies in the investigation of the associations between air pollution exposure and exacerbations of COPD.

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Interesting additional findings in the present study were that adopting health protective behaviors and practices during the COVID-19 pandemic period was associated with a reduction in exacerbations, while experiencing viral infection symptoms was associated with an increase in exacerbations. In the subgroup with this data available, integrating both terms into the COVID-19 pandemic period adjusted models attenuated the observed association between O_x and exacerbations to the null. While this could be due to the reduced sample size (from 673 to 413, potentially leading to loss of associations), alternatively these findings may indicate that respiratory viral infection and health protective behaviors are associated with exacerbations and that exposure to O_x may be a potential modifier of these known associations. Previous studies demonstrated that COVID-19 pandemic-specific preventive interventions, such as lock-downs themselves but also behaviors such as hand hygiene, face coverings and physical distancing played a role in lowering the risk of infectious exacerbations.[15,26,40–42] These findings emphasize the impact of individual behaviors on exacerbation risk and indicate the need for tailored interventions to promote health-protective actions, especially during pandemic periods and/or periods of high respiratory viral infection. The consistency of the association between O_x in particular with symptom-based exacerbations across several different models (unadjusted and adjusted) and periods (pre-pandemic and COVID-19 pandemic), however, support this interesting relationship and its relevance beyond just viral transmission as contributory in the COPD patient population. A study from Germany supports this plausibility, wherein gaseous pollutants (NO_2) were found to have the highest risk ratios for hospital admissions of COPD and asthma, surpassing those of particulate matter pollutants, and moreover smoking and influenza infection were found to be minimally influential in those associations.[9] Finally, ambient air pollution and respiratory viruses may not actually be distinct and separate triggers per se but may instead interact in complex ways to precipitate exacerbations of COPD. In a notable study focused on a period preceding the COVID-19 pandemic era (1996–2015) in the East London Cohort, daily diary cards were used as a sensitive patient-reported outcome to identify exacerbations in order to examine the mechanistic relationship between air pollutant exposure, viruses, and exacerbations.[43] The authors of this study observed an association between elevated gaseous pollutants (oxides of nitrogen) and, specifically, viral-type exacerbations of COPD.[43]

Female gender, comorbid self-reported physician-diagnosed asthma, and elevated blood eosinophils were each associated with increased exacerbation rates, and in stepwise multivariable modeling with air pollutants, these factors emerged as relevant in the significant association between O_x concentration and exacerbations. In females, each IQR increase in O_x alone was associated with higher rates of event-based exacerbations, while in males, each increase in $PM_{2.5}$ was associated with lower rates of symptom-based exacerbations. Evidence of effect modification based on gender for both NO_2 and O_3 and event-based exacerbations was also observed. Gender-specific disparities in the health impact of air pollution have been highlighted across several previous studies, including from our own group,[25] in other Canadian studies outside of the COPD patient population,[44] and in COPD populations outside of North America and Europe.[29] Asthma status also appears to be a relevant modifier in the association between O_x and exacerbations. Previous findings in patients with asthma and COPD identified various indoor and outdoor factors including air pollutants, allergens, and climate conditions, that can provoke respiratory symptoms and exacerbations.[45] Specifically, exposure to air pollutants such as particulate matter, O_3, NO_2, sulfur dioxide and carbon monoxide were associated with increased exacerbations and hospitalizations in these individuals. Studies show that O_3 exposure increases the odds of the development of COPD in individuals with asthma, indicating that O_3 may be an important risk factor in progression to irreversible airflow obstruction.[46] Finally, among participants in the present study with Eos $\geq$300, O_x was associated with increased symptom-based exacerbations. Reduced air pollution levels and fewer in-hospital admissions were observed in recent COVID-19 era research in patients with asthma and/or COPD during lockdown periods, and elevated blood eosinophils were observed in those patients with COPD who were ultimately admitted to hospital during those periods.[18] More recent work has found that the association between short-term air pollution and day-to-day lung function (FEV_1) in COPD may be influenced by blood eosinophil levels.[47] Our findings align with these emerging studies and further support the important role of eosinophilia in the COPD patient population and in particular, their mechanistic interaction with air pollution exposure in the occurrence of exacerbations.

This study has important and notable strengths. The inclusion of participants and prospectively collected data from a comprehensive multi-site and multi-regional national cohort, confirmation of disease status in each participant, the

inclusion of data both preceding and during the COVID-19 pandemic, the inclusion of clinically important acute respiratory events that did not necessitate hospital admission or ICD code reliance,[20,21,23,24] and the collection of self-reported potential confounding (behavioral and infectious status) variables are noteworthy strengths of the present study. There are also, however, important limitations that mandate consideration in the interpretation of these study findings. Firstly, the reliance on self-reported participant behaviors during the pandemic introduces the potential for recall bias, as individuals may not accurately remember or report their actions, particularly given this unprecedented period. Secondly, the study's focus on a specific geographic and temporal context may limit the generalizability of our findings to other settings and populations.[48] Thirdly, the consistent association between O_x and exacerbations were no longer observed following adjustment for COVID-19 pandemic period confounders, which may or may not have been limited by the smaller size of this subgroup as mentioned, and even by the reliability in estimating behavior or viral infection status during this unprecedented period. Fourthly, adjustments for multiple comparisons were not performed despite the large number of associations tested. Fifthly, the consistent associations between certain variables and exacerbations observed in our models may be attributed to unmeasured or unadjusted confounders, which is an important consideration and limitation in all observational studies. Lastly, air pollution exposure data from fixed-location monitoring stations was used rather than from satellite-based data due to the duration and frequency of sampling needed to conduct the present study.

Conclusion

In summary, the COVID-19 pandemic era was a monumental and unique period that has served to provide valuable lessons and information regarding the associations between ambient air pollution and exacerbations of COPD. Important findings include the reduction in some but not all air pollutants during the COVID-19 pandemic, largely consistent associations between O_x exposure and exacerbations of COPD, an influence of the effect of protective behaviors and self-reported viral infection on these associations, and the role of female gender, co-morbid asthma, and blood eosinophilia as individual-level risk factors on these associations. These findings emphasize the need for targeting more at-risk populations and for targeted interventions to reduce the impact of air pollution on exacerbations of COPD during crisis periods.

Abbreviations

CanCOLD, Canadian Cohort Obstructive Lung Disease; COPD, Chronic Obstructive Pulmonary Disease; COVID-19, Coronavirus Disease 2019; ECOPDs, Exacerbations of Chronic Obstructive Pulmonary Disease; FEV_1, Forced Expiratory Volume in 1 second; FVC, Forced Vital Capacity; FLU-PRO, Flu Patient Reported Outcome; GEE, Generalized Estimating Equations; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICD, International Classification of Diseases; IQR, Interquartile Range; NO_2, Nitrogen Dioxide; O_x, Total Oxidant ($NO_2 + O_3$); O_3, Ground-Level Ozone; $PM_{2.5}$, Fine Particulate Matter (particles smaller than 2.5 micrometers); RR, Rate Ratio; RRs, Rate Ratios; SAS, Statistical Analysis System; 95% CIs, 95% Confidence Intervals; Eos, Eosinophils.

Data Sharing Statement

Due to data privacy regulations, individual participant data collected during this study is not publicly accessible. However, access to anonymized data may be granted upon evaluation. Additional documents will also be available upon inquiry. All requests should be directed to the corresponding author (BAR).

Ethics Approval and Informed Consent

Written informed consent was obtained from all participants, and the study received institutional review board approval at each site (BMC09-025), coordinated through the McGill University Health Centre (MUHC) Research Ethics Board (REB).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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