

Aerosol and Air Quality  
Research

## Associations between Ozone and Emphysema: A Systematic Review and Meta-analysis

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### ABSTRACT

Air pollution is widely viewed as a serious threat to human health and a contributor to deaths. Air pollution appears to be linked to the progression of emphysema, according to epidemiological data. The objective of this study was to examine associations between air pollution and the progression of emphysema using a meta-analysis. A meta-analysis was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) protocol. A systematic literature search was conducted using the Cumulative Index to Nursing and Allied Health Literature (CINAHL), Medline, Embase, PubMed, and Web of Science bibliographic databases. A random-effects model for the meta-analysis was implemented to summarize effect estimates of sufficiently comparable outcomes and pollutants (e.g.: particulate matter, nitrogen oxides and ozone), and the results were visualized in forest plots. We observed that a 1-ppb rise in O<sub>3</sub> was associated with a 0.30 increase in the percent emphysema progression (95% CI: 0.02, 0.57,  $p < 0.05$ ). In contrast, no significant association was found between PM<sub>2.5</sub> or NO<sub>2</sub> exposure and the percent change in emphysema. Increasing O<sub>3</sub> concentrations may have an impact on and exacerbate human health conditions such as emphysema and respiratory diseases. Air quality and climate change should be concerns for future environmental policies and protection measures.

**Keywords:** Air pollution, COPD, Emphysema, Meta-analysis, Ozone

### 1 INTRODUCTION

For decades, outdoor air pollution has been the focus of concern around the world, due in part to the development of the global economy and urbanization. Air pollution has long been recognized as having serious effects on human health and being a contributing factor in deaths and illnesses (Burnett *et al.*, 2018; WHO, 2018). The major pollutants that have been linked to adverse health impacts are particulate matter (PM), which include PM of  $< 10 \mu\text{m}$  in aerodynamic diameter (PM<sub>10</sub>),  $< 2.5 \mu\text{m}$  (PM<sub>2.5</sub>), and  $< 0.1 \mu\text{m}$  (ultrafine particles; UFP) (WHO, 2013; Guarnieri and Balmes, 2014). According to studies conducted in Hong Kong, Taiwan, and China, for every 10- $\mu\text{g m}^{-3}$  increase in PM<sub>10</sub> levels, increases of the risk of heart disease (CVD) death by 0.36% and

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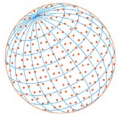
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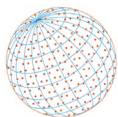
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of respiratory diseases death rates by 0.42% were detected, and for each  $10\text{-}\mu\text{g m}^{-3}$  rise in  $\text{PM}_{2.5}$  concentrations, mortality from cardiovascular diseases (CVDs) and respiratory illnesses respectively increased by 0.63% and 0.75% (Lu *et al.*, 2015). Mortality evaluation research of  $\text{PM}_{2.5}$  in a population of more than 40 million Europeans estimated that reducing  $\text{PM}_{2.5}$  concentrations to  $10\text{ }\mu\text{g m}^{-3}$  would reduce total deaths by 0.3% to 9.0% (Ballester *et al.*, 2008; Faustini *et al.*, 2014). Nitrogen dioxide ( $\text{NO}_2$ ) is a highly toxic gas that can be created both outdoors and indoors from various emissions sources (i.e., road traffic and cooking). Oxidation of nitrogen oxide (NO) by ozone ( $\text{O}_3$ ) is the principal source of  $\text{NO}_2$ . Tropospheric  $\text{O}_3$  is produced by a complex chain of events including sunlight (ultraviolet radiation),  $\text{NO}_2$ , and hydrocarbons. According to previous reports, each  $10\text{-}\mu\text{g m}^{-3}$  rise in  $\text{NO}_2$  and  $\text{O}_3$  results in excess relative risks of 1.2% and 2.0%, respectively (Fattore *et al.*, 2011; Khaniabadi *et al.*, 2017).

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory illness which manifests as air space dilatation and parenchymal destruction (GOLD, 2017). Tobacco smoking is one of the factors associated with COPD (CDC, 2012). Furthermore, a growing body of research has found that non-smokers can suffer from COPD as a result of exposure to indoor and outdoor air pollution (Salvi and Barnes, 2009). Epidemiological evidence has established strong links among various air pollutants and greater risks of respiratory diseases, particularly in people who have an underlying chronic lung disease such as COPD (Kim *et al.*, 2018). COPD prevalence is associated with greater amounts of  $\text{PM}_{2.5}$  (OR = 1.52) and  $\text{PM}_{10}$  (OR = 1.08) per  $5\text{ }\mu\text{g m}^{-3}$ , along with  $\text{NO}_2$  (OR = 1.12) per  $10\text{ }\mu\text{g m}^{-3}$  (Doiron *et al.*, 2019). Numerous studies reported links between air pollution and elevated chances of COPD and declines in lung function (Duan *et al.*, 2020; Elbarbary *et al.*, 2020). Hospitalizations and cardiovascular and respiratory mortality have all been linked to air pollution (Berend, 2016). Small airways also contribute as a major site of resistance in obstructive lung diseases (McDonough *et al.*, 2011; Hogg *et al.*, 2013). COPD is a chronic obstruction of airflow due to a combination of small airway illness (obstructive bronchiolitis) and parenchymal damage (emphysema) (Stewart and Criner, 2013). Although air pollution is recognized as a risk factor for COPD, the phenotypes of air pollution-associated COPD remain unclear.

Emphysema is a lung disease defined by the growth of persistent air gaps distal to the terminal bronchioles (Shah *et al.*, 2017). The disease process can cause hyperinflation, as implied by its Greek name, *emphusma*, which means inflation (Kemp *et al.*, 2009). The progression of emphysema is linked to a reduction in the lower respiratory tract neutrophil elastase inhibitory capacity that is induced by cigarette smoking (Ogushi *et al.*, 1991). However, lung function decline was shown to be associated with changes in air pollution in a study of 1391 non-smokers and 20-year estimated concentrations of sulfur dioxide ( $\text{SO}_2$ ),  $\text{O}_3$ , and indoor  $\text{PM}_{10}$  exposure (Abbey *et al.*, 1998). Decreased levels of ambient air pollutants per 1.0 ppb of  $\text{O}_3$ ,  $\text{SO}_2$ ,  $\text{NO}_2$ , and carbon monoxide (CO), and per  $1.0\text{ }\mu\text{g m}^{-3}$  of  $\text{PM}_{2.5}$  and  $\text{PM}_{10}$  were associated with lower emphysema death rates (Kravchenko *et al.*, 2014). Furthermore, among individuals who resided within 1 km of a cement factory, the level of air pollution exposure appeared to affect the prevalence of emphysema, with the OR of those who were more frequently exposed to air pollution being equal to that of smokers (Lee *et al.*, 2016). A recent cohort study from the Multi-Ethnic Study of Atherosclerosis (MESA) Air and Lung Study, which was performed in six large cities across the United States, concluded that long-term exposure to ambient air pollutants such as nitrogen oxides ( $\text{NO}_x$ ) and  $\text{O}_3$  was found to be substantially linked with progression in emphysema with a greater decrease in both forced expiratory volume in one second ( $\text{FEV}_1$ ) and forced vital capacity (FVC) as assessed by chest computed tomographic (CT) imaging and lung function (Wang *et al.*, 2019). A  $4.4\text{-}\mu\text{g m}^{-3}$  increase in  $\text{PM}_{10}$  exposure on a yearly basis was associated with a 0.13 liter decrease in the FVC (Kwon *et al.*, 2020). Prolonged  $\text{O}_3$  exposure to a 5-ppb increase was associated with an increase of 0.94 and 1.60 in the percentages of emphysema and air trapping, respectively (Paulin *et al.*, 2020). In a study of COPD patients, a unit increases in  $\text{PM}_{2.5}$  and  $\text{O}_3$  were both linked to the presence of emphysema in each lung lobe, particularly in the upper long lobes, which were associated with 2.772- and 3.052-fold increases (Tung *et al.*, 2021). The evidence for a causal relationship between air pollution and emphysema in humans remains sparse. A meta-analysis conducted by ESCAPE (European Study of Cohorts for Air Pollution Effects) found no consistent associations between current long-term average air pollution levels and symptoms of chronic bronchitis in adult European populations (Cai *et al.*, 2014). However, a few epidemiological evidence indicates an association between air pollution and the development of emphysema in COPD patients. Therefore, the



objective of this study was to examine associations between air pollution and the progression of emphysema using a meta-analysis.

## 2 MATERIALS AND METHODS

### 2.1 Data Sources and Search Strategies

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria were followed in reporting this study (Moher *et al.*, 2009). This study's protocol was verified with PROSPERO (<http://www.crd.york.ac.uk/PROSPERO/>) with the number CRD42021290374. The PubMed, Embase, Medline, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Web of Science bibliographic databases were searched without restriction on publication year but restricted solely to English full-text items to find journal papers published that reported study results related to our study objective. Additional eligible studies were searched by manually screening relevant meta-analyses, reviews, and reference lists, including in Google Scholar. Terms related to the study were obtained using the PEOs tool for systematic review; Population ("general population," "patients"), Exposure ("air pollution," "ozone," "particulate matter," "nitrogen oxides"), Outcome ("pulmonary emphysema," "emphysema," and "lung emphysema"); Study design ("Human study," "cohort and cross-sectional study"). Endnote reference manager software, full version X9, was used to compile the results of the database searches.

### 2.2 Study Selection and Eligibility Criteria

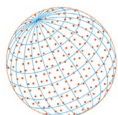
All eligible studies were collected as full texts after removing duplicates, and reference sections were searched for additional qualifying articles. This was checked by two investigators (A.M and V.L) through screening the titles and abstracts. Any inconsistencies discovered during the screening process were resolved through discussion. If a study met the following requirements, it was included in the current review: (1) a cohort and cross-sectional study assessing a prognosis developing emphysema as a result of an exposure; (2) a research article with a clear method and study design; and (3) an original article with primary sources and provided in full-text English. However, studies that were (1) clearly stated as animal studies, (2) population expose in occupational settings (3) preliminary study or without clear method and complete data including abstracts, conferences, book chapters, reviews, protocols, posters, or studies that did not investigate exposure increments for emphysema development were excluded.

### 2.3 Data Extraction and Quality Assessment

We extracted data from the primary articles of potential studies and approached the corresponding authors for any relevant data we discovered to be missing from the included articles. Reference information (authors and publication year), cohort details (cohort name, country, and study population), subject characteristics (mean age and sex), image analysis (chest CT), and details on air pollutants, such as PM<sub>2.5</sub> ( $\mu\text{g m}^{-3}$ ), PM<sub>10</sub> ( $\mu\text{g m}^{-3}$ ), NO<sub>x</sub> (ppb), NO<sub>2</sub> (ppb), and O<sub>3</sub> (ppb), were all collected. For each of the study units, such as effect estimation, the beta ( $\beta$ ) coefficient was used to determine the association between air pollution and emphysema progression. Since some of the effect estimates were provided in different units of an interquartile range (IQR) increase, we normalized those first to beta ( $\beta$ ) coefficients. Data from the articles were entered into an Excel (Microsoft, Redmond, WA, USA) document.

### 2.4 Data Synthesis and Analyses

Review Manager software (RevMan vers. 5.4.1) was utilized for the meta-analysis. Since most of the included studies provided effect estimates as IQRs, we standardized effect estimates per a 1- $\mu\text{g m}^{-3}$  increase in each pollutant. Heterogeneity among studies was assessed using the I<sup>2</sup> value. Low, moderate, and high heterogeneity levels were respectively indicated by scores of 25%, 50%, and 75% (Higgins *et al.*, 2003). Low heterogeneity (I<sup>2</sup> of  $\leq 25\%$ ) implies a homogeneous data series and, in general, the analytical feasibility using a fixed-effect model. On the contrary, high heterogeneity (I<sup>2</sup> of  $\geq 75\%$ ) reflects significantly true variability of the data, justifying the need for a random-effects model (Haidich, 2010).



### 3 RESULTS AND DISCUSSION

In the beginning, 2970 publications were collected. After compiling search results and eliminating duplicates, 1937 studies remained for title/abstract screening. Additional Google Scholar searches were performed to identify potential published articles of gray source materials or the latest publications during the review process. However, no new research or reviews were discovered. The PRISMA flow diagrams showed the outcomes of the search strategy and screening process (Fig. 1). In total, 1930 studies were discarded because they did not fulfill the inclusion criteria. They were excluded for various reasons, including animal studies ( $n = 328$ ), conference abstracts ( $n = 43$ ), and review studies ( $n = 59$ ), as well as in a non-English language ( $n = 92$ ), unrelated topics ( $n = 1295$ ), and occupational exposure ( $n = 113$ ). Due to a limit of information on the link between air pollution and the development of emphysema, two additional studies were eliminated. Finally, five studies were eligible for inclusion in the final analysis for this study (Adar *et al.*, 2015; Wang *et al.*, 2019; Kwon *et al.*, 2020; Paulin *et al.*, 2020; Tung *et al.*, 2021). The five studies were conducted in three countries: The United States ( $n = 3$ ), South Korea ( $n = 1$ ), and Taiwan ( $n = 1$ ). The combined studies yielded a total of 23,120 persons whose average ages were 60–72 years. The sample sizes for these studies ranged 86–6860 persons. The evolution of emphysema was monitored using computed tomography (CT) and high-resolution (HR)-CT (Table 1).

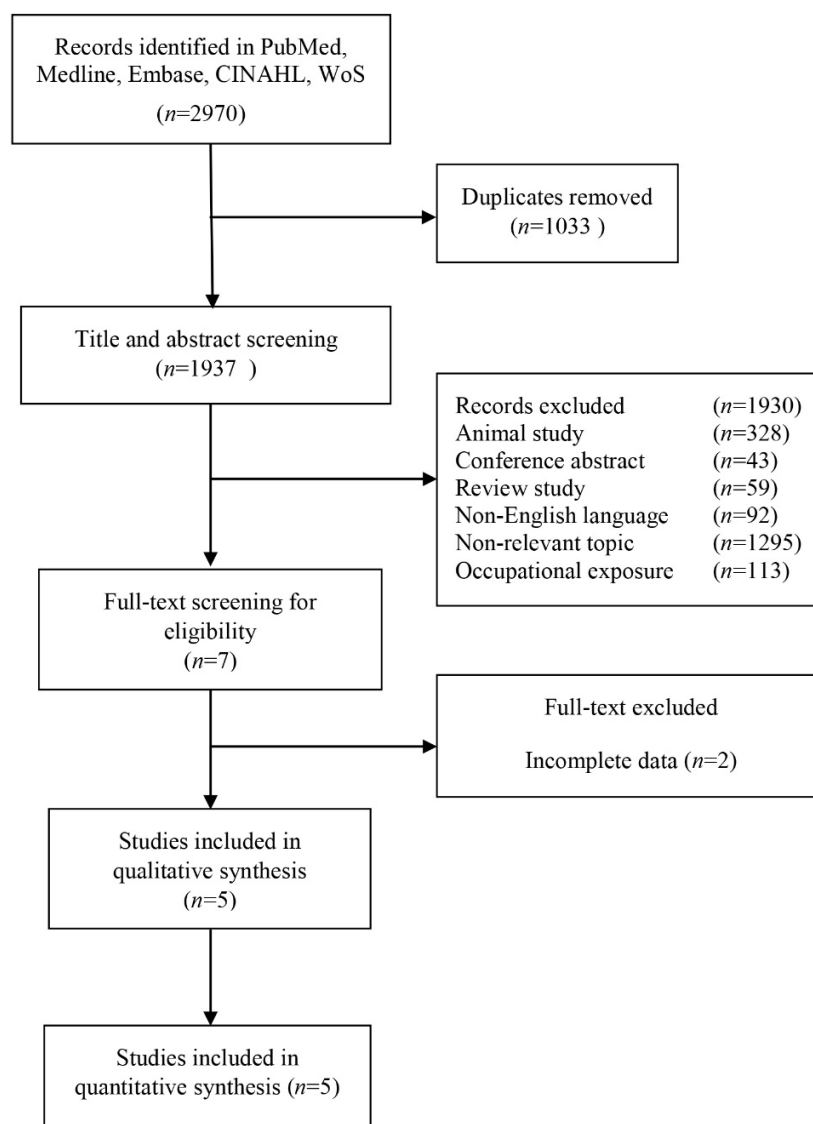
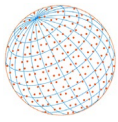


Fig. 1. Flowchart of the assessment of potential studies.



**Table 1.** Summary of characteristics of studies included in the systematic review.

First author, year	Cohort	Study Population	Country	Sample size	Air pollutants	Biomarker analyses	$\beta$ (95%CI)	SE	Sex		Mean age (years)
									Male	Female	
Adar, 2015	Multi-Ethnic Study of Atherosclerosis (MESA)	General	USA	4813	PM <sub>2.5</sub>	CT	$\beta = 0.04 (-0.06, 0.14)$	0.0501	2262	2551	62
Kwon, 2021	COPD in Dusty Areas (CODA)	General	South Korea	504	NO <sub>2</sub>	CT	$\beta = 0.087 (-0.18, 0.357)$	0.1362	335	122	71.7
Paulin, 2020	SPIROMICS Air Pollution Study (SPIROMICS AIR)	General	USA	1874	O <sub>3</sub>	CT	$\beta = 0.188 (0.05, 0.326)$	0.0704	1013	861	64.5
Tung, 2021	COPD cohort	Patients	Taiwan	86	PM <sub>2.5</sub>	HR-CT	$\beta = 1.283 (0.769, 1.797)$	0.2622	79	7	70.4
					NO <sub>2</sub>		$\beta = 1.282 (0.461, 2.103)$	0.4189			
					O <sub>3</sub>		$\beta = 1.198 (0.662, 1.734)$	0.2735			
Wang, 2019	MESA	General	USA	6860	PM <sub>2.5</sub>	CT	$\beta = -0.02 (-0.075, 0.035)$	0.0281	3224	3636	62
					O <sub>3</sub>		$\beta = 0.06 (0.027, 0.093)$	0.0168			

CI, confidence interval; COPD, chronic obstructive pulmonary disease; CT, computed tomography; HR-CT, high-resolution computed tomography; SE, standard error.

Population exposed in occupational settings was excluded from this study because the effect may differ from that experienced by the general population due to the exclusivity and consistency of exposure resulting from the job type and working hours, which also makes it possible to summarize the possible causal relationship. Furthermore, animal studies that were considerably influenced by the same conditions were removed.

PM<sub>2.5</sub> results from the three studies were considered for quantitative synthesis. The overall effect of PM<sub>2.5</sub> concentrations was 0.21 (95% CI): -0.04, 0.46;  $p > 0.05$ ) (Fig. 2). In terms of NO<sub>2</sub> concentration, two studies were used for quantitative synthesis. The overall effect of NO<sub>2</sub> exposures was 1.12 (95% CI: -1.14, 3.38;  $p > 0.05$ ) (Fig. 3). A quantitative synthesis was also conducted using three studies that investigated the O<sub>3</sub> effect on emphysema. The overall effect of O<sub>3</sub> exposure estimates was 0.30 (95% CI: 0.02, 0.57;  $p < 0.05$ ) (Fig. 4). Results indicated that a 1-ppb rise in O<sub>3</sub> corresponded to a 0.30 percentage point increase in percent emphysema progression.

Our findings are consistent with the most recently published articles we investigated (Adar et al., 2015; Wang et al., 2019; Kwon et al., 2020; Paulin et al., 2020; Tung et al., 2021). We observed that effect estimates of neither PM<sub>2.5</sub> nor NO<sub>2</sub> showed an association with emphysema. However, in previous work, PM<sub>2.5</sub> exposure was associated with decreased lung function, emphysematous lesions, and increased inflammation (Zhao et al., 2019; Kim et al., 2021). Reduced NO<sub>2</sub> levels were also associated with a lower risk of death from emphysema (Kravchenko et al., 2014; Huangfu and Atkinson, 2020). Other studies, however, discovered no association between PM<sub>2.5</sub> and emphysema progression after 10 years of follow-up, and neither long-term NO<sub>2</sub> exposure nor emphysema phenotypes were shown to be associated (Wang et al., 2019; Kwon et al., 2020).

The amount of O<sub>3</sub> in the air has significant impacts on the development of respiratory illnesses (Amann, 2008). According to a study from Rome, Italy, a photochemical pollutant (O<sub>3</sub>) was a predictor of acute respiratory disorders (Fusco et al., 2001). In our study, exposure to O<sub>3</sub> was found to be significantly associated with emphysema progression in COPD patients. The association between yearly O<sub>3</sub> and respiratory deaths was 0.99 per 10 ppb (Huangfu and Atkinson, 2020). An increasing concentration of O<sub>3</sub> and a continuous change in temperature were also associated with acute exacerbation of COPD in older people (Lin et al., 2018). Therefore, exposure to O<sub>3</sub> is a risk factor for emphysema in COPD patients.

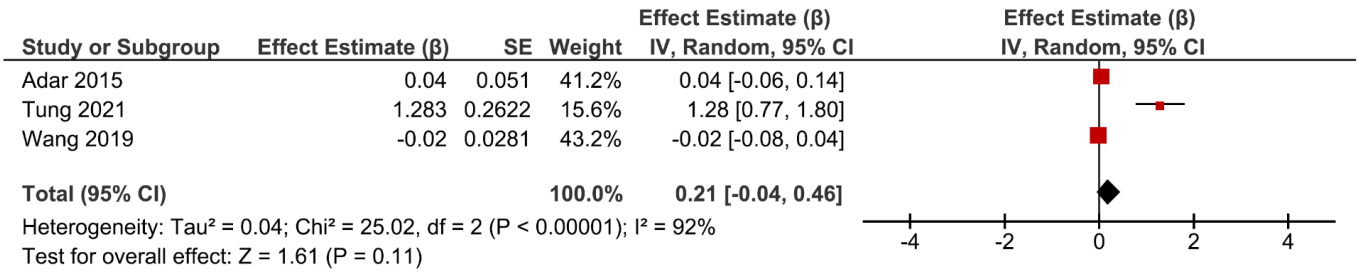
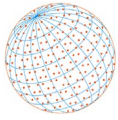


Fig. 2. Forest plot of associations between PM<sub>2.5</sub> concentrations and percent emphysema.

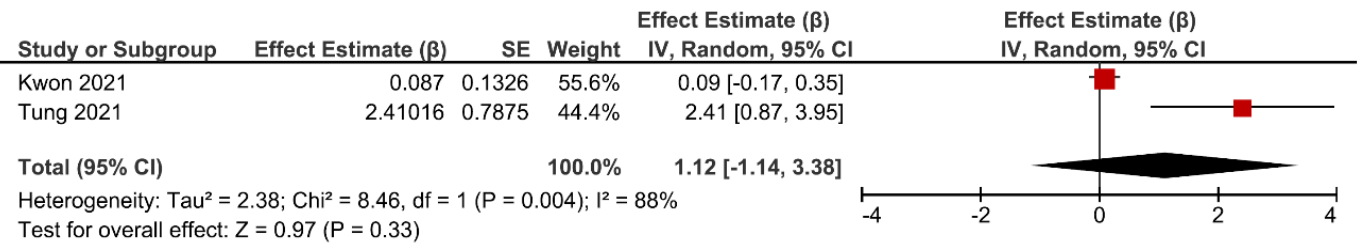


Fig. 3. Forest plot of associations between NO<sub>2</sub> concentration and percent emphysema.

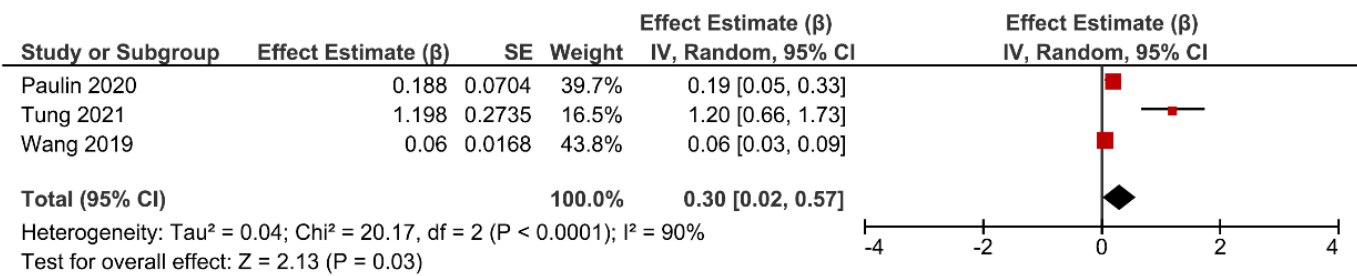
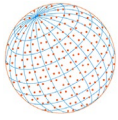


Fig. 4. Forest plot of associations between O<sub>3</sub> concentration and percent emphysema.

Our study had a substantial level of heterogeneity ( $I^2 \geq 75\%$ ) in all of the analyses of PM<sub>2.5</sub>, NO<sub>2</sub>, and O<sub>3</sub> concentrations. Since  $I^2$  is affected by the sample size of the included studies, a high  $I^2$  does not always imply that the study effects were dispersed over a wide range (Rücker *et al.*, 2008). A random effects model was additionally performed in the analysis. This model implies a true distribution of population associations, namely the significance of the relationship between pollutants and the development of emphysema in a study population that differs from other research populations. The variation in observed associations might be attributable to differences in study characteristics (e.g., different study countries and control for confounders). However, we were unable to perform any sub-group analyses to determine the source of heterogeneity because of the limited number of included studies, and the results are unlikely to change our overall estimates. As the occupational setting was not considered, it could also be a limitation in this study.

## 4 CONCLUSIONS

Significant relationships between O<sub>3</sub> and emphysema were reported in our systematic review and meta-analysis. Increasing ozone concentrations may have an impact on and exacerbate human health conditions such as emphysema and respiratory diseases. Air quality and climate change should be concerns for future environmental policies and protection measures.



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## ADDITIONAL INFORMATION AND DECLARATIONS

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### Conflict of Interest

The authors declare that they have no conflicts of interest.

### Authors' Contributions

All authors contributed substantially to the concept and design of the study, drafting of the article, and critically revising the manuscript for important intellectual content. All authors have read and approved the final version of the manuscript for publication.

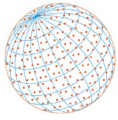
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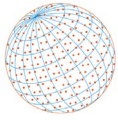
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