Impact of air quality guidelines on COPD sufferers

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Background: COPD is one of the leading causes of morbidity and mortality in both high- and low-income countries and a major public health burden worldwide. While cigarette smoking remains the main cause of COPD, outdoor and indoor air pollution are important risk factors to its etiology. Although studies over the last 30 years helped reduce the values, it is not very clear if the current air quality guidelines are adequately protective for COPD sufferers.

Objective: This systematic review was to summarize the up-to-date literature on the impact of air pollution on the COPD sufferers.

Methods: PubMed and Google Scholar were utilized to search for articles related to our study’s focus. Search terms included “COPD exacerbation”, “air pollution”, “air quality guidelines”, “air quality standards”, “COPD morbidity and mortality”, “chronic bronchitis”, and “air pollution control” separately and in combination. We focused on articles from 1990 to 2015. We also used articles prior to 1990 if they contained relevant information. We focused on articles written in English or with an English abstract. We also used the articles in the reference lists of the identified articles.

Results: Both short-term and long-term exposures to outdoor air pollution around the world are associated with the mortality and morbidity of COPD sufferers even at levels below the current air quality guidelines. Biomass cooking in low-income countries was clearly associated with COPD morbidity in adult nonsmoking females.

Conclusion: There is a need to continue to improve the air quality guidelines. A range of intervention measures could be selected at different levels based on countries’ socioeconomic conditions to reduce the air pollution exposure and COPD burden.

Keywords: air pollution, biomass, chronic bronchitis, COPD, intervention

Introduction

COPD is one of the leading causes of mortality and morbidity worldwide. While cigarette smoking is the primary cause and risk factor, many other risk factors contribute to the development or exacerbation of COPD. Outdoor air pollution has been recognized for its impact on human health for centuries, and in the past 50–60 years, particularly in the past 30 years, its adverse impact on COPD sufferers has been intensively studied worldwide. Indoor air pollution using biomass fuel in low-income countries has also been found to contribute to the COPD prevalence, particularly in nonsmoking females. However, over the years, efforts have been made to regulate air pollution levels in many countries around the world, which significantly reduced exposure levels compared to earlier times. It is not very clear how these air quality standards and guidelines, particularly the current ones, impacted the COPD sufferers. This review intends to evaluate the impact of air pollution on COPD sufferers in general and the current air quality standards or guidelines on the COPD sufferers.
specifically. Our objective was to conduct a comprehensive and systematic literature search and review and summarize up-to-date information to present an overall picture.

**Materials and methods**

This article reviewed the literature on the epidemiology of COPD, air pollution and its impact on COPD sufferers, and how air quality guidelines can improve the health of COPD patients.

PubMed and Google Scholar were the main databases utilized to search for articles related to our study’s focus. Search terms included “COPD exacerbation”, “air pollution”, “air quality guidelines”, “air quality standards”, “COPD morbidity and mortality”, “chronic bronchitis”, and “air pollution control” separately and in combination. We included articles from 1990 to 2015. We also used articles prior to 1990 if they provided historic background and were relevant in understanding air pollution and COPD epidemiologic studies. While articles written in English or with an English abstract were mostly considered, articles in other languages were occasionally used if relevant, and when online, an English translation was available.

We identified 972 articles from the main databases and 750 from other sources such as Scopus and Global Health (EBSCOHost) or from the reference lists of the searched articles. We removed some duplicates and came up with 1,120 articles. These articles were further screened for relevance. We then excluded 432 articles that were irrelevant. The final full text articles further assessed were 688. We then focused on studies that addressed outdoor air pollution related to COPD mortality, hospital admissions or emergency room visits, incidence, prevalence, respiratory symptoms and lung functions, exacerbation of COPD patients in both high- and low- to middle-income countries, and indoor biomass cooking and the risk of COPD prevalence in low-income countries. As a result, 324 articles were removed, leaving us with 364 articles. We further removed 257 articles based on the following reasons: 1) animal or human subject experimental studies; 2) studies on active and passive smoking; 3) occupational exposure to dust and fumes (although some were mentioned in the introduction); 4) studies on dust storms, haze, bushfires or wildfires, and volcanoes; 5) reviews, updates, reports, and meta-analysis studies; 6) studies where COPD cases were combined with asthma or other diseases such as interstitial disease as a single category; 7) studies with pollutants measured in exhaled air; 8) farm and agricultural area exposure studies; 9) studies with both mortality and hospital admission cases combined; 10) studies on mortality and morbidity of all diseases or cardiorespiratory diseases without a specific category for COPD; 11) irrelevant genetic studies; 12) indoor air pollution studies in high-income countries; and 13) negative studies where no relationships between air pollution and mortality and morbidity of COPD were found, although a few representative studies were discussed in the text. Articles in earlier studies and indoor air pollution studies often used chronic bronchitis, while later studies focused more on COPD with or without bronchitis. This final selection left us with eleven studies on COPD mortality in both high- and low- to middle-income countries (Table 1); 27 studies on COPD hospital admissions and emergency room visits in high-income countries (Table 2); 12 studies on COPD hospital admissions and emergency room visits in low- to middle-income countries (Table 3); 15 studies on respiratory symptoms, lung functions, and prevalence and incidence of COPD (Table 4); ten panel studies conducted with COPD patients to specifically evaluate their exacerbations (Table 5); 21 studies on indoor air pollution in low- to middle-income countries (Table 6); and eleven studies on intervention effectiveness (a total of 107 studies). Figure 1 shows a summary of the article screening and selection process. Additionally, other studies are cited in the text when necessary.

**Results**

**Introduction to the epidemiology of COPD**

**Definition of COPD**

In 1997, a Global Initiative for Chronic Obstructive Lung Disease (GOLD) was launched in collaboration with the US National Heart, Lung, and Blood Institute; National Institutes of Health; and the World Health Organization (WHO). GOLD works with health care professionals and public health officials around the world to raise awareness of COPD and develop and regularly update evidence-based strategy documents to guide COPD diagnosis, treatment, management, and prevention. In its most recent update document (2014), GOLD defines COPD as a preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with enhanced chronic inflammatory response in the airways and the lung to hazardous particles and gases. Exacerbations and comorbidities contribute to the severity in individual patients.

This definition is similar to that in the updated position paper by the American Thoracic Society and the European Respiratory Society. COPD is not a single disease, but several lung diseases combined. Emphysema and chronic
bronchitis are the most important conditions that compose COPD. They frequently coexist, but they are no longer used as separate disease categories and now are included within the COPD diagnosis. Although some patients with asthma also develop poorly reversible airflow limitations and are indistinguishable from patients with COPD, asthma is considered a separate entity not included in the diagnosis and treatment of COPD.

The significant airflow limitation in COPD patients is indicated by the value of forced expiratory volume in 1 second (FEV\textsubscript{1}) that does not return to normal and frequently worsens over time, but responds largely to bronchodilators. GOLD recommends that any patient with dyspnea, chronic cough or sputum production, and a history of exposure to risk factors such as tobacco smoke or occupational dusts or chemicals should be considered for a diagnosis of COPD, but spirometry is required to make the clinical diagnosis. The presence of a postbronchodilator ratio of FEV\textsubscript{1} and forced vital capacity (FVC) <0.7 is the confirmation of obstructive airflow limitation. GOLD also classifies the severity of airflow limitation in COPD into four categories in patients with FEV\textsubscript{1}/FVC <0.7: GOLD 1 (mild) – FEV\textsubscript{1} =80% predicted, GOLD 2 (moderate) – 50%≤ FEV\textsubscript{1} <80% predicted, GOLD 3 (severe) – 30%≤ FEV\textsubscript{1} <50% predicted, and GOLD 4 (very severe) – <30% predicted.

COPD prevalence and disparity

COPD remains a major public health problem worldwide, and is one of the leading causes of morbidity and mortality in both high- and low-income countries. Estimated prevalence rates varied a great deal among different regions and countries possibly due to different methods used in different studies. In the US, based on the National Health Interview Survey conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention and analysis conducted by the American Lung Association, 12.7 million US adults have been diagnosed with COPD. The actual number could be as high as 24 million if using the lung function test result, which indicates that there is an underdiagnosis. For chronic bronchitis, >10 million Americans reported a physician diagnosis in 2011. The total prevalence rate was 4.4%, whereas in 1999, the total number was 8.8 million although the prevalence was similar. For emphysema, 4.7 million Americans reported ever being diagnosed and the prevalence rate was 2.0% in 2011. This is a significant increase from 1999 where 2.8 million people were reported representing a prevalence rate of 1.4%.

The prevalence rate of COPD was strikingly variable among different races, sexes, and age groups. The rate for chronic bronchitis in 2011 (NCHS) was much higher in non-Hispanic whites (4.7%) and blacks (4.9%) than in Hispanics (2.9%) and other non-Hispanics (2.4%). The rate was twice as high in females (5.7%) as in males (3.0%). Prevalence rates were the highest among those 65 years or older (6.4%) and the lowest among those 18–44 years (2.9%) with 70% of cases occurring in those older than 45 years. For emphysema, the prevalence rate in 2011 followed a similar pattern among ethnic groups, which was the highest for non-Hispanic whites (2.4%) followed by blacks (1.8%), other non-Hispanics (1.3%), and Hispanics (0.7%). Females surpassed males in the prevalence rate (2.1% vs 1.9%), although historically, the rate was lower in females. Similarly, prevalence rates for emphysema were the highest among those 65 years or older (5.5%) and the lowest among those 18–44 years (0.3%) with the rate in between (2.7%) for the age group 45–64.

Geographically, COPD prevalence rates in the US also varied a deal among different states as surveyed by the Behavioral Risk Factor Surveillance System in 2011. Kentucky had the highest age-adjusted rate at 9.7%, followed by Alabama at 9.4%, while Minnesota (4.0%) and Washington (4.1%) had the lowest. This geographical difference in COPD prevalence by state parallels the difference in smoking rates where Kentucky was on the top (30.2%) and Washington (17.0%) and Minnesota (15.8%) were on the lowest end. COPD prevalence rate was also the highest for males in Kentucky (8.4%), while the lowest for males in Washington (3.3%) and Washington DC. Among females, Tennessee had the highest age-adjusted rate (11.5%) and Minnesota the lowest (4.3%). Rates tend to be higher in the Midwest and Southeast.

Worldwide, 65 million people have moderate-to-severe COPD, and the prevalence is also highly variable. Mannino and Buist summarized the rates from 12 sites in the Burden of Obstructive Lung Disease (BOLD) study and four sites in the Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) study and showed that in both males and females, the highest rate was in South Africa and the lowest in Mexico. The rate for the US was the fifth highest. In the BOLD study for females, the highest rate was in Cape Town, South Africa (16.7%) and the lowest in Guangzhou, People’s Republic of China (5.1%). For males, the highest rate again was in Cape Town, South Africa (22.2%) and lowest in Reykjavik, Iceland (8.5%). In the PLATINO study, crude rates of COPD ranged from 7.8% in Mexico City to 19.7% in Montevideo.
COPD Mortality and disparity

According to Antó et al,9 50% of patients are expected to live 10 years post-diagnosis with more than one-third of patients dying due to respiratory insufficiency. COPD is the third leading cause of death in the US after cancer and heart disease. Based on the data from NCHS, the total number of deaths has increased from 119,524 in 1999 to 133,965 in 2009. The number of deaths was consistently higher in females than in males from 2000 to 2009. Approximately 80% of COPD deaths are in non-Hispanic whites; Hispanics had the least number of deaths counting 3,724 in 2009. The overall age-adjusted death rate was 41.2/100,000 in 2009 with the rate the highest (46.0/100,000) for non-Hispanic whites than for other ethnic groups. Overall, non-Hispanic white males had the highest age-adjusted death rates (53/100,000), while other non-Hispanic females had the lowest age-adjusted death rates (11.0/100,000 population).3

WHO estimated that globally, more than 3 million people died of COPD in 2005, which corresponds to 5% of all deaths. It was known that almost 90% of COPD deaths occurred in low- and middle-income countries. In 2001, WHO estimated that COPD was the fifth leading cause of death in high-income countries and the sixth leading cause of death in low- and middle-income countries. In 2004, WHO updated their findings and concluded that COPD was the fourth leading cause of death for all ages, resulting in 3.0 million deaths worldwide.10 WHO also estimated that total deaths from COPD are projected to increase by >30% in the next 10 years and will become the third leading cause of death worldwide by 2030.4 In terms of disability-adjusted life years, COPD is currently seventh and is expected to rise to the fifth leading cause of burden of disease by 2030.10

Causes and risk factors

The primary cause of COPD is tobacco smoke, including secondhand smoke or environmental tobacco smoke.4 Most smokers develop some respiratory impairment due to COPD.11 WHO estimates that 73% of mortality is related to smoking in high-income countries and 40% to low-to-middle-income countries. In a population cohort study conducted in North Sweden,12,13 it was reported that 50% of smokers would develop COPD based on GOLD guidelines.11

Many other risk factors have been identified in past research9,14 that contributed to the development or exacerbation of COPD and have been well summarized in previous reviews.5,14,15 These include genetic and phenotypic traits, occupational exposures to dust and fumes, indoor and outdoor air pollutants, aging, infections, asthma, sex, and socioeconomic status. These risk factors can act singly or synergistically.

It has been suggested that susceptibility to COPD is, at least in part, genetically determined.16 While the best described genetic factor in COPD is alpha-1 antitrypsin deficiency (PiZZ genotype), present in 1%–3% of COPD patients,17 several genes have been studied for their associations with COPD.16,17 For example, five single nucleotide polymorphisms in ADAM33 gene were associated with COPD and lung function in long-term smokers.18 The MSR1-coding single nucleotide polymorphism P275A was associated with susceptibility to COPD in smokers and a lower percent predicted FEV1, FEV1/FVC, and percent predicted forced expiratory flow (25%–75%).19 Smokers who are carriers of the surfactant protein D AG and AA polymorphic genotypes may be at a higher risk of developing COPD.16 Retinoic acid receptor-related orphan receptor-α has been implicated in the development of COPD.20 The hedgehog-interacting protein gene and family with sequence similarity 13, member A (FAM13A1) gene, were suggested to be involved in COPD susceptibility in Chinese Han population.21,22

Occupational exposure may make a substantive contribution to the etiology of COPD, particularly, in nonsmokers, females, and young people.23 Exposed agents include cotton dust,24,25 grain dust,26 western red cedar dust,27,28 coal dust,29 cement dust,30 gases31 and metal fumes,32,33 or a mixture of them. Most studies reported relative risk (RR) or odds ratio (OR), and a few studies directly reported the percentage of attributable population risk (PAR%).34 For chronic bronchitis, reported PAR% varied from 11% to 26% with a median at 19%. For lung function impairment, the reported PAR% varied from 12% to 34% with a median at 19%. The reported PAR% also varied for different symptoms.34 Overall, the PAR% due to occupational exposure was estimated to be 15% in smokers and 20% in nonsmokers.11,23

It is suggested that up to 20% of cases of COPD worldwide can be attributed to indoor air pollution from exposure to smoke from cooking and heating with biomass fuels in poorly ventilated dwellings.11 Age contributing to the risk of COPD was due to the decline in lung function.5 Infection can predispose individuals for COPD development, and socioeconomic factors represent a combination of risk factors that contribute to the susceptibility for COPD, including poor nutrition and closer proximity to hazardous pollutants.5 This review focused on air pollution as an etiological factor or risk factor for the development and exacerbation of COPD; for other risk factors, the readers are directed to other review papers in this journal or other journals.
Review of the effects of air pollution on COPD sufferers

Outdoor air pollution and COPD mortality

Although outdoor air pollution can occur naturally (eg, volcanoes and forest fires), anthropogenic activities are the major cause of environmental air pollution.\textsuperscript{35} The concern of outdoor air pollution on human health has been recognized for centuries.\textsuperscript{36} The effects of outdoor air pollution have caused a spectrum of responses, such as irritation of the upper respiratory systems, increased prevalence of respiratory infections, and symptoms and clinical signs. Symptoms and signs of respiratory responses include coughing, phlegm production, chest tightness, wheezing, and chronically reduced pulmonary function in FVC and FEV\textsubscript{1}. These symptoms lead to increased incidences in exacerbation of cardiopulmonary diseases, asthma attacks, cancer, and mortality.\textsuperscript{3} While air pollution may affect all ages of the population, the elderly, particularly those with preexisting cardiopulmonary diseases such as COPD, are the most susceptible group.

Air pollution causing COPD-related mortality was well presented when air pollution catastrophes significantly increased death rates. For example, in the UK historically, the burning of coal in homes for domestic heat often created very high levels of air pollution and caused death rates to dramatically rise. One of the most well-known pollution events was the 1952 London Smog incident that resulted in 4,000 extra deaths, with 80%–90% of the deaths due to cardiorespiratory causes. The greatest relative increase was in deaths due to bronchitis, which rose ninefold.\textsuperscript{37,38} The pollutant involved in the London Smog incident was black smoke, defined as visual blackness of particles collected on a white filter expressed as equivalent mass concentration of standard coal smoke\textsuperscript{39} and sulfur dioxide (SO\textsubscript{2}). A later estimation indicated that 12,000 extra deaths occurred from December 1952 through February 1953 because of acute and persisting effects of the 1952 London Smog incident.\textsuperscript{40} A time series analysis conducted for the data from 1958 to 1972 indicated that particulates were strongly associated with mortality rates in London even at much lower levels, and the relation was likely causal.\textsuperscript{41} A more recent study on the health effects of an air pollution episode in London, December 1991, in which concentrations of nitrogen dioxide (NO\textsubscript{2}) rose to record levels with moderate increases in black smoke showed a 23% increase in COPD mortality.\textsuperscript{42}

Earlier, before the London Smog incident in 1930, the Meuse Valley, Belgium, experienced a period of intense fog in a heavy industrial area resulting in the death of 60 people.\textsuperscript{43} In October 1948, a lethal haze enveloped the town of Donora, PA, US. Over 5 days, approximately half of the town’s 14,000 residents experienced severe respiratory and cardiovascular problems. The death toll rose to ~40 people.\textsuperscript{44}

The 1952 London Smog and other air pollution events symbolized the beginning of the modern air pollution epidemiologic studies. They also prompted governments to pass legislation to reduce air pollution levels. As legislation over the years has led to a decrease in traditional air pollutants particulate matter (PM) and SO\textsubscript{2} from stationary sources, today’s major air pollutants come from motor vehicle traffic, and the main perpetrators include PM, ozone (O\textsubscript{3}), and NO\textsubscript{2}.\textsuperscript{37} A commentary and review by Dockery\textsuperscript{38} well described how studies on the health effects of particulate air pollution evolved and helped improve the air quality standards and regulations in the US. The year 1970 was a milestone year when Congress passed the Clean Air Act Amendments that required the Environmental Protection Agency (EPA) to set up the first National Ambient Air Quality Standards (NAAQS) that included six types of air pollutants: carbon monoxide (CO), lead, NO\textsubscript{2}, O\textsubscript{3}, PM, and SO\textsubscript{2}. NAAQS was promulgated in 1971. The particles used then were total suspended particles (TSP) with aerodynamic diameter between 20 µm and 50 µm, which was set up as maximum allowable ambient concentration.\textsuperscript{39} The Clean Air Act also encouraged scientists to identify pollutants that may reasonably be anticipated to endanger public health and welfare.\textsuperscript{39}

One of the earliest and largest air pollution studies in the US was the Harvard prospective cohort study of the respiratory health effects of respirable particles and SO\textsubscript{2} on a sample of adults and children in six US cities, that began in 1974. The particles measured in this study included two classes: fine particles (aerodynamic diameter <2.5 µm [PM\textsubscript{2.5}]) and inhalable particles (aerodynamic diameter <15 µm [PM\textsubscript{15}]) before 1984 and <10 µm [PM\textsubscript{10}] starting in 1984).\textsuperscript{45} Over the 16-year follow-up, the study found a positive association of air pollution with both mortalities from lung cancer and cardiopulmonary causes, after adjusting for smoking and other risk factors. The adjusted mortality rate ratio for the most polluted of the cities as compared with the least polluted was 1.26 (95% confidence interval [CI], 1.08–1.47) or 26% of excess mortality. Mortality was most strongly associated with air pollution with fine particulates, including sulfates.\textsuperscript{45} This study and others\textsuperscript{46–48} provided scientific evidence that supported the US EPA’s replacement of the TSP standard with a standard for PM\textsubscript{10} in 1987.\textsuperscript{49} In 1997, EPA further amended the particle standard and added PM\textsubscript{2.5} to recognize the potentially different health effects.\textsuperscript{49}
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<tr>
<th>Authors and year</th>
<th>City and country</th>
<th>Number and age of subjects</th>
<th>Study time period</th>
<th>Pollutants and concentrations</th>
<th>Lag days analyzed</th>
<th>Risk type and per unit increase</th>
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<tr>
<td>Schwartz and Dockery 1992</td>
<td>Philadelphia, USA</td>
<td>65 years, &gt;65 years</td>
<td>7 years (1973–1980)</td>
<td>24-hour mean: TSP (µg/m³) = 77 SO₂ (µg/m³) = 21</td>
<td>0–1 days</td>
<td>Percent increase in total, cardiorespiratory, and COPD mortalities per increase in TSP and SO₂ (100 µg/m³)</td>
<td>TSP: All causes = 7 (4–10) COPD = 9 (0–42) SO₂: All causes = 5 (3–7)</td>
</tr>
<tr>
<td>Xu et al 1994</td>
<td>Beijing, People’s Republic of China</td>
<td>1,419,123</td>
<td>1 year (1989)</td>
<td>Seasonal and annual means: TSP (µg/m³) = 375 SO₂ (µg/m³) = 102</td>
<td>None</td>
<td>Percent increase in total, cardiorespiratory, and COPD mortalities per doubling increase in natural log of concentration</td>
<td>TSP: All causes = 4 (2–11) Cardiorespiratory = 8 COPD = 38 SO₂: All causes = 11 (5–16) Cardiorespiratory = 19 COPD = 29</td>
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<tr>
<td>Rossi et al 1999</td>
<td>Milan, Italy</td>
<td>1.5 million</td>
<td>10 years (1980–1989)</td>
<td>24-hour mean: TSP (µg/m³) = 142 SO₂ (µg/m³) = 124 NO₂ (µg/m³) = 82</td>
<td>0–4 days</td>
<td>Percent increase in total and COPD mortalities per increase in 100 µg/m³ of pollutants</td>
<td>All causes: TSP = 3.3 (2.4–4.3) SO₂ = 2.8 (2.1–3.5) NO₂ = 7.6 (5.6–9.5) COPD: TSP Lag days 3–4 = 12 (6–17) TSP (&lt;200 µg/m³) = 18 (9–27)</td>
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<tr>
<td>Xu et al 2000</td>
<td>Shenyang, People’s Republic of China</td>
<td>&lt;65 years, 65–74 years, &gt;74 years</td>
<td>1 year (1992)</td>
<td>Overall mean: TSP (µg/m³) = 430 SO₂ (µg/m³) = 197</td>
<td>Current and proceeding 3 days</td>
<td>Percent increase in total, cardiorespiratory, and COPD mortalities per increase in TSP and SO₂ (100 µg/m³)</td>
<td>TSP: All causes = 1.7 COPD = 2.6 SO₂: All causes = 2.4 COPD = 7.4</td>
</tr>
<tr>
<td>Tellez-Rojo et al 2000</td>
<td>Mexico City, Mexico</td>
<td>≤65 years</td>
<td>1 year (1994)</td>
<td>24-hour mean: PM₁₀ (µg/m³) = 75 SO₂ (ppb) = 20 1-hour: NO₂ (ppb) = 38 1-hour maximum: O₃ (ppb) = 34</td>
<td>0–7 days Cumulative by 3 days, 5 days, and 7 days</td>
<td>Percent increase in COPD mortality per increase in PM₁₀ (10 µg/m³) and O₃ (40 ppb)</td>
<td>COPD outside medical unit: PM₁₀ = 4.1 (1.3–6.9), 3-day lag PM₁₀ = 6.1 (2.4–9.9), 5-day mean O₃ = 8.3 (1.0–16.1), 3-day lag</td>
</tr>
<tr>
<td>Wong et al 2002</td>
<td>Hong Kong, People’s Republic of China</td>
<td>All ages</td>
<td>3 years (1995–1998)</td>
<td>24-hour mean: PM₁₀ (µg/m³) = 52 SO₂ (µg/m³) = 17 NO₂ (µg/m³) = 56 O₃ (µg/m³) = 34</td>
<td>0–3 days</td>
<td>RR increase in total, respiratory and COPD mortalities per increase in all pollutants (10 µg/m³)</td>
<td>SO₂: Respiratory = 1.015 (1.001–1.029) COPD = 1.010 (0.990–1.029) O₃: Respiratory = 1.010 (1.004–1.016) COPD = 1.034 (1.017–1.052) NO₂: Respiratory = 1.013 (1.004–1.022) COPD = 1.023 (1.006–1.041) PM₁₀: Respiratory = 1.008 (1.001–1.014) COPD = 1.017 (1.002–1.033)</td>
</tr>
<tr>
<td>Kan et al 2003</td>
<td>Shanghai, People’s Republic of China</td>
<td>All ages</td>
<td>1.5 years (2000–2001)</td>
<td>24-hour mean: PM₁₀ (µg/m³) = 91 SO₂ (µg/m³) = 42 NO₂ (µg/m³) = 32</td>
<td>0–5 days</td>
<td>RR increase in COPD mortality per increase in all pollutants (10 µg/m³)</td>
<td>All ages: PM₁₀ = 1.005 (0.999–1.011) SO₂ = 1.035 (1.015–1.054) NO₂ = 1.032 (1.009–1.056) Age 65–75: PM₁₀ = 0.996 (0.986–1.007) SO₂ = 1.010 (0.977–1.043) NO₂ = 1.007 (0.967–1.047)</td>
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Air quality guidelines impact on COPD sufferers

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<tr>
<th>Study</th>
<th>Location</th>
<th>Population</th>
<th>Exposure Period</th>
<th>PM(_{2.5}) Concentration</th>
<th>Effect Size</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Zeka et al(^a)</td>
<td>20 US cities</td>
<td>All ages</td>
<td>12 years (1989–2000)</td>
<td>24-hour mean: PM(_{2.5}) = 29</td>
<td>N/A</td>
<td>Percent increase in COPD mortality per increase in PM(_{2.5}) (10 µg/m(^3))</td>
</tr>
<tr>
<td>Naess et al(^b)</td>
<td>Oslo, Norway</td>
<td>143,842</td>
<td>2007</td>
<td>6 years (1992–1998)</td>
<td>24-hour mean: PM(<em>{2.5}) = 19 PM(</em>{10}) = 15 NO(_2) = 39</td>
<td>N/A</td>
</tr>
<tr>
<td>Meng et al(^c)</td>
<td>Beijing, Shanghai, Guangzhou, People’s Republic of China</td>
<td>N/A</td>
<td>2013</td>
<td>1 year</td>
<td>0–1 day</td>
<td>Percent increase in COPD mortality per increase in 10 µg/m(^3) concentrations</td>
</tr>
<tr>
<td>Samoli et al(^d)</td>
<td>Ten European Mediterranean metropolitan areas</td>
<td>14 million</td>
<td>2014</td>
<td>10 years (2001–2010)</td>
<td>24-hour mean: PM(<em>{2.5}) = 20 PM(</em>{10}) = 12 PM(_{2.5-10}) = 33 NO(_2) = 49 O(_3) = 63</td>
<td>0–1 days 2–5 days 0–5 days</td>
</tr>
</tbody>
</table>

Notes: Most studies were time series studies to evaluate short-term exposure, in which variables of long-term trends, day of the week, temperature, humidity, dew point temperature, and influenza epidemic were controlled. Prospective cohort study to evaluate long-term exposure, in which Cox proportional hazard survival model was used and personal characteristics such as smoking, education, marital status, body mass index, occupational exposures, diet, and alcohol use were controlled. Percent increase = (RR – 1) × 100.

Abbreviations: CI, confidence interval; TSP, total suspended particles with aerodynamic diameter ≤40 µm; SO\(_2\), sulfur dioxide; NO\(_x\), nitrogen dioxide; PM\(_{10}\), particulate matter with aerodynamic diameter ≤10 µm; O\(_3\), ozone; RR, relative risk; PM\(_{2.5-10}\), particulate matter with aerodynamic diameter 2.5 µm and 10 µm; N/A, not available.
Table 2: Outdoor air pollution and COPD-related hospital admissions or emergency room visits in high-income countries

<table>
<thead>
<tr>
<th>Authors and year</th>
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<th>Lag days analyzed</th>
<th>Risk type and per unit increase</th>
<th>Risk level (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunyer et al 1991</td>
<td>Barcelona, Spain</td>
<td>1.7 million &gt;14 years</td>
<td>1 year (1985–1986)</td>
<td>24-hour mean: BS (µg/m³)=72.9 SO₃ (µg/m³)=56.5 1-hour maximum: SO₃ (µg/m³)=141.9 CO (µg/m³)=5.4 O₃ (µg/m³)=63.3 NO₂ (µg/m³)=123.5</td>
<td>N/A</td>
<td>Percent increase in COPD per increase in BS and SO₃ (1 µg/m³) and CO (1 µg/m³)</td>
<td>SO₃ = 2</td>
</tr>
<tr>
<td>Sunyer et al 1993</td>
<td>Barcelona, Spain</td>
<td>1.7 million &gt;14 years</td>
<td>4 years (1985–1989)</td>
<td>24-hour mean: BS (µg/m³)=62 (winter) SO₃ (µg/m³)=49 (winter) 1-hour maximum: TSP (µg/m³)=76 SO₃ (µg/m³)=19 NO₂ (µg/m³)=39 O₃ (µg/m³)=22</td>
<td>0–2 days</td>
<td>Percent increase in COPD per increase in BS and SO₃ (25 µg/m³)</td>
<td>SO₃: Lag 0 = 1.31 (1.01–1.70)</td>
</tr>
<tr>
<td>Pönkä and Virtanen 1994</td>
<td>Helsinki, Finland</td>
<td>&lt;65 years 2 years (1987–1989)</td>
<td>24-hour mean: TSP (µg/m³)=76 SO₃ (µg/m³)=19 NO₂ (µg/m³)=39 O₃ (µg/m³)=22</td>
<td>0–7 days</td>
<td>RR increase in CB and emphysema admission per 2.7 fold increase in pollutants</td>
<td>SO₃: Lag 0 = 1.31 (1.05–1.70)</td>
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<tr>
<td>Schwartz et al 1994</td>
<td>Minneapolis, St Paul, USA</td>
<td>2.46 million ≥65 years</td>
<td>4 years (1986–1989)</td>
<td>24-hour mean: PM₁₀ (µg/m³)=36 O₃ (ppb)=26 1-hour maximum: O₃ (ppb)</td>
<td>0–1 day</td>
<td>RR increase in COPD per increase in PM₁₀ (100 µg/m³) and O₃ (50 ppb)</td>
<td>PM₁₀: 0–1-day weighted average: Above NAAQS = 1.57 (1.20–2.06)</td>
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<tr>
<td>Schwartz 1994</td>
<td>Detroit, USA</td>
<td>≥65 years 4 years (1986–1989)</td>
<td>24-hour mean: PM₁₀ (µg/m³)=48 O₃ (ppb)=21</td>
<td>N/A</td>
<td>RR increase in COPD per increase in PM₁₀ (10 µg/m³) and O₃ (5 ppb)</td>
<td>PM₁₀: 0-day lag = 1.22 (0.99–1.52)</td>
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<tr>
<td>Schwartz 1994</td>
<td>Birmingham, USA</td>
<td>≥65 years 4 years (1986–1989)</td>
<td>24-hour mean: PM₁₀ (µg/m³)=45 O₃ (ppb)=25 1-hour maximum: O₃ (ppb)</td>
<td>1–2 days</td>
<td>RR increase in COPD per increase in PM₁₀ (100 µg/m³) and O₃ (50 ppb)</td>
<td>PM₁₀: 1-day lag = 1.37 (1.12–1.68)</td>
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<tr>
<td>Burnett et al 1994</td>
<td>Ontario, Canada</td>
<td>All ages 6 years (1983–1988)</td>
<td>24-hour mean: SO₃ (µg/m³)=5.3 1-hour maximum: O₃ (ppb)=50</td>
<td>0–3 days</td>
<td>RR increase in COPD per unit increase and percent increase in COPD per increase in SO₃ (5.3 µg/m³) and O₃ (50 ppb)</td>
<td>RR (standard error) increase: SO₃: Lag 0 = 1.00216 (0.00061)</td>
<td></td>
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</tbody>
</table>

Note: RR stands for relative risk, SO₃, BS, CO, and NO₂ are pollutants, and PM₁₀ is a measure of particulate matter.
<table>
<thead>
<tr>
<th>Schuotens et al. 1996</th>
<th>Amsterdam, Rotterdam, the Netherlands</th>
<th>1.27 million</th>
<th>12 years (1977–1989)</th>
<th>24-hour mean: BS (µg/m³) = 18, SO₂ (µg/m³) = 34, NO₂ (µg/m³) = 52, CO (µg/m³) = 66, 1-hour maximum: O₃ (µg/m³) = 78, SO₂ (µg/m³) = 82, NO₂ (µg/m³) = 78, RR increase in COPD per 100 µg/m³ increase in pollutants</th>
<th>0–5 days</th>
<th>Rotterdam: Daily mean NO₂, Lag 2 = 1.051 (0.903–1.223), Daily mean NO₂, Lag 0–1 = 1.203 (1.011–1.430), 1-hour NO₂, Lag 2 = 1.166 (1.070–1.271), I-hour NO₂, Lag 0–1 = 1.196 (1.079–1.326)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson et al. 1997</td>
<td>Six European cities (Amsterdam, Barcelona, London, Milan, Paris, Rotterdam)</td>
<td>All ages</td>
<td>15 years (1977–1992)</td>
<td>24-hour mean: TSP (µg/m³) = 86, BS (µg/m³) = 22, SO₂ (µg/m³) = 33, NO₂ (µg/m³) = 53, 8-hour mean: O₃ (µg/m³) = 47, 1-hour maximum: SO₂ (µg/m³) = 60, NO₂ (µg/m³) = 82, O₃ (µg/m³) = 57, Best one day lag out of 3 days Cumulative (mean)</td>
<td>RR increase in COPD per increase in all pollutants (50 µg/m³)</td>
<td>TSP = 1.022 (0.998–1.047), BS = 1.035 (1.010–1.060), Lag 1, SO₂ = 1.038 (1.008–1.070), Lag 0–3, NO₂ = 1.021 (0.998–1.045), Lag 0–3, NO₂ 24 hour = 1.019 (1.002–1.047), Lag 1, NO₂ 24 hour = 1.026 (1.004–1.036), Lag 0–3, O₃ 8 hour = 1.043 (1.022–1.065), Lag 1, O₃ 8 hour = 1.056 (1.027–1.086), Lag 0–3, O₃ 1 hour = 1.029 (1.011–1.047), Lag 1, O₃ 1 hour = 1.024 (1.011–1.075), Lag 0–3</td>
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<tr>
<td>Morgan et al. 1998</td>
<td>Sidney, Australia</td>
<td>≥65 years</td>
<td>5 years (1990–1994)</td>
<td>24-hour mean: PM₁₀, bscat/10⁴ m³ = 0.32, NO₂ (ppb) = 15, 1-hour maximum: PM₁₀, bscat/10⁴ m³ = 0.76, NO₂ (ppb) = 29, O₃ (ppb) = 25, 0–2 days and cumulative Percent increase in COPD per 10th–90th percentile increase in all pollutants</td>
<td>0–day lag: PM₁₀, 24 hours = 2.41 (0.90–5.84), PM₁₀, max = 3.01 (–0.38–6.52), 1-day lag: NO₂, 24 hours = 4.30 (–0.75–9.61), NO₂, 1 hour = 6.60 (–0.17–9.61)</td>
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<tr>
<td>Chen et al. 2000</td>
<td>Reno-Sparks, NV, USA</td>
<td>≥65 years</td>
<td>4 years (1990–1994)</td>
<td>24-hour mean: PM₁₀ (µg/m³) = 37, RR increase in COPD per increase in PM₁₀ (26.6 µg/m³)</td>
<td>0 day</td>
<td>PM₁₀ = 1.049 (1.011–1.087), RR increase in COPD per increase in PM₁₀ (26.6 µg/m³), O₃ (25 ppb), and NO₂ (20 ppb)</td>
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<tr>
<td>Tobert et al. 2000</td>
<td>Atlanta, USA</td>
<td>N/A</td>
<td>5 years and 7 months (1993–1998)</td>
<td>24-hour mean: PM₁₀ (µg/m³) = 10, RR increase in COPD per increase in PM₁₀ (26.6 µg/m³)</td>
<td>0–2 days</td>
<td>PM₁₀ = 1.003</td>
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<tr>
<td>Fusco et al. 2001</td>
<td>Rome, Italy</td>
<td>3 million All ages</td>
<td>3 years (1995–1997)</td>
<td>24-hour mean: PM₁₀ (µg/m³) = 66, RR increase in total respiratory diseases including COPD per increase in PM₁₀ (23.0 µg/m³), SO₂ (6.9 µg/m³), NO₂ (22.3 µg/m³), CO (1.5 mg/m³), and O₃ (3.9 µg/m³)</td>
<td>0–4 days</td>
<td>0–day lag: Total respiratory diseases: NO₂ = 2.5 (0.9–4.2), CO = 2.8 (1.3–4.3), COPD: CO = 4.3 (1.6–7.1)</td>
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</table>
### Table 2 (Continued)

<table>
<thead>
<tr>
<th>Authors and year</th>
<th>City and country</th>
<th>Number and age of subjects</th>
<th>Study time period</th>
<th>Pollutants and concentrations</th>
<th>Lag days analyzed</th>
<th>Risk type and per unit increase</th>
<th>Risk level (95% CI)</th>
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<tbody>
<tr>
<td>Tenías et al²⁴</td>
<td>Valencia, Spain</td>
<td>0.75 million 1.289 COPD cases &gt;14 years</td>
<td>2 years (1994–1995)</td>
<td>24-hour mean: BS (µg/m³) =39 SO₂ (µg/m³) =27 NO₂ (µg/m³) =58 CO (ng/m³) =3 1-hour maximum: SO₂ (µg/m³) =56 NO₂ (µg/m³) =100 CO (mg/m³) =7 O₃ (µg/m³) =63</td>
<td>0–5 days</td>
<td>RR increase in COPD per increase in O₃ (10 µg/m³) and CO (1 mg/m³)</td>
<td>O₃ Lag 5 = 1.06 (1.02–1.101) CO Lag 1 = 1.039 (1.014–1.066)</td>
</tr>
<tr>
<td>Chen et al²⁵</td>
<td>Vancouver, Canada</td>
<td>2 million ≥65 years with acute COPD</td>
<td>3 years and 10 months (1995–1999)</td>
<td>24-hour mean: PM₁₀ (µg/m³) =13 PM₉₀ (µg/m³) =8 PMₑ₃₂,₅ (µg/m³) =6 COH (µg/m³) =0.3</td>
<td>1–7 days</td>
<td>RR increase in acute COPD per increase in 3-day average exposure of interquartile range</td>
<td>Single-pollutant model: PM₁₀ = 1.13 (1.05–1.21) PM₉₀ = 1.08 (1.02–1.15) PMₑ₃₂,₅ = 1.09 (1.03–1.16) COH = 1.05 (1.01–1.09)</td>
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<tr>
<td>Peel et al²⁶</td>
<td>Atlanta, USA</td>
<td>N/A</td>
<td>7 years and 8 months (1993–2000)</td>
<td>24-hour mean: PM₁₀ (µg/m³) =28 1-hour maximum: NO₂ (ppb) =46 CO (ppm) =2</td>
<td>0–2 days</td>
<td>RR increase in acute COPD per increase in PM₁₀ (10 µg/m³), NO₂ (20 ppb), and CO (1 ppm)</td>
<td>PM₁₀ = 1.018 (0.994–1.043) NO₂ = 1.035 (1.006–1.065) CO = 1.026 (1.004–1.048)</td>
</tr>
<tr>
<td>Yang et al²⁷</td>
<td>Vancouver, Canada</td>
<td>2 million ≥65 years with acute COPD</td>
<td>5 years (1994–1998)</td>
<td>24-hour mean: PM₁₀ (µg/m³) =14 SO₂ (ppb) =4 NO₂ (ppb) =17 CO (ppm) =0.7 O₃ (ppb) =14</td>
<td>0–6 days</td>
<td>RR increase in acute COPD per increase in PM₁₀ (8.3 µg/m³), SO₂ (2.8 ppb), NO₂ (5.5 ppb), CO (0.3 ppm), and O₃ (9.3 ppb)</td>
<td>Single-pollutant model for 7-day average exposure: PM₁₀ = 1.13 (1.05–1.21) NO₂ = 1.11 (1.04–1.20) CO = 1.08 (1.02–1.13)</td>
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<tr>
<td>Hinwood et al²⁸</td>
<td>Perth, Australia</td>
<td>1.2 million All ages</td>
<td>6 years (1992–1998)</td>
<td>24-hour mean: NO₂ (ppb) =10 PM₁₀ (ppb) =20 PM₉₀ (ppb) =9 Bsp (2.1/10³ m) =0.2 8-hour maximum: O₃ (ppb) =26 CO (ppm) =2 1-hour maximum: Bsp (2.1/10³ m) =0.2NO₂ (ppb) =25 O₃ (ppb) =32</td>
<td>0–3 days cumulative</td>
<td>OR for COPD hospitalizations per unit increase of Bsp</td>
<td>2-day lag = 1.30 (1.05–1.45)</td>
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<tr>
<td>Dominici et al²⁹</td>
<td>204 counties, USA</td>
<td>11.5 million &gt;65 years</td>
<td>3 years (1999–2002)</td>
<td>24-hour mean: PM₉₀ (µg/m³) =13</td>
<td>0–1 days</td>
<td>Percentage increase in daily admission rate of COPD per 10 µg/m³ increase in PM₉₀ concentration</td>
<td>Lag 0 = 1 (0.2–1.7) Lag 1 = 1 (0.2–1.7) Lag 2 = 0.2 (0.6–1.0) Total = 1.4 (0.1–2)</td>
</tr>
<tr>
<td>Medina-Ramón et al³⁰</td>
<td>36 cities, USA</td>
<td>≥35 years</td>
<td>13 years (1986–1999)</td>
<td>24-hour mean: PM₁₀ (µg/m³) =30 8-hour mean: O₃ (µg/m³) =37</td>
<td>0–1 days</td>
<td>Percent increase in COPD admission per increase in PM₁₀ (10 µg/m³) and O₃ (5 ppb)</td>
<td>PM₁₀ Lag 0 = 0.29 (0.01–0.58) PM₁₀ Lag 1 = 0.59 (0.30–0.88) O₃ Lag 0 = 0.32 (0.49 to –0.15) Lag 1 = 0.33 (0.19–0.47) Lag 0–2 = 0.04 (0.13–0.20)</td>
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<tr>
<td>Study</td>
<td>Location</td>
<td>Population</td>
<td>Exposure</td>
<td>Outcomes</td>
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<tr>
<td>Sauerzapf et al. 2009</td>
<td>Norfolk, UK</td>
<td>&gt; 18 years</td>
<td>13 months (2006–2007)</td>
<td>24-hour mean: CO (µg/m³) = 205 OR in COPD admission per increase in all pollutants (10 µg/m³)</td>
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<tr>
<td>Belleudi et al. 2010</td>
<td>Rome, Italy</td>
<td>2.7 million</td>
<td>4 years and 8 months (2001–2005)</td>
<td>24-hour mean: PM₁₀ (µg/m³) = 39 Percent increase in COPD admission per increase in PM₁₀ (14 µg/m³), PM₂₅ (10 µg/m³), and 9,392 particles/cm³</td>
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<tr>
<td>Cirera et al. 2012</td>
<td>Cartagena, Spain</td>
<td>185,799</td>
<td>4 years (1995–1998)</td>
<td>24-hour mean: TSP (µg/m³) = 52 Percent increase for COPD emergency room visits per increase in all pollutants (10 µg/m³)</td>
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<tr>
<td>Liu et al. 2012</td>
<td>New York State, USA</td>
<td>All ages</td>
<td>15 years (1993–2008)</td>
<td>Living close to fuel-fired power plant or hazardous waste site RR increase in exposure type</td>
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<tr>
<td>Faustini et al. 2013</td>
<td>Six Italian cities</td>
<td>38,577</td>
<td>5 years (2001–2005)</td>
<td>24-hour mean: PM₁₀ (µg/m³) = 35–54 Percent increase in COPD hospitalizations per 10 µg/m³ of pollutants</td>
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<tr>
<td>Kloog et al. 2014</td>
<td>Mid-Atlantic region, USA</td>
<td>58 million</td>
<td>6 years (2000–2006)</td>
<td>24-hour mean: PM₁₀ (µg/m³) = 46–66 Percent increase in COPD per increase in PM₁₀ (10 µg/m³)</td>
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<tr>
<td>Yorifuji et al. 2014</td>
<td>Okayama, Japan</td>
<td>6,925 residents</td>
<td>5 years (2006–2010)</td>
<td>1-hour mean: PM₁₀ (µg/m³) = 27 OR in COPD per interquartile range increase in pollutants</td>
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</table>

**Notes:** The time-series studies evaluated short-term effects and mostly used Poisson regression with generalized additive models for data analysis and controlled for long-term trends, day of the week, temperature, humidity, dew point temperature, influenza epidemic, and other factors. Both single-pollutant and multiple-pollutant models and both crude and adjusted risks were used in most studies. Our report focused on single-pollutant models and crude risks or otherwise noted in the table. Percent increase = (RR − 1) × 100.

**Abbreviations:** CI, confidence interval; BS, black smoke; SO₂, sulfur dioxide; CO, carbon monoxide; O₃, ozone; NO₂, nitrogen dioxide; TSP, total suspended particles with aerodynamic diameter ≤ 40 µm; RR, relative risk; observed over expected; CB, chronic bronchitis; PM₁₀, particulate matter with aerodynamic diameter ≤ 10 µm; NAAQS, National Ambient Air Quality Standards; SO₂, sulfate; PM₂₅, particulate matter with aerodynamic diameter between 2.5 and 10 µm; PM₁₀, particulate matter with aerodynamic diameter 13 µm; PM₁₀, particulate matter with aerodynamic diameter ≤ 13 µm; PM₁₀, particulate matter with aerodynamic diameter ≤ 2.5 µm; PM₁₀, particulate matter with aerodynamic diameter between 10 and 2.5 µm; COH, coefficient of haze, a measurement of the amount of filterable particulate matter suspended in air; bscat/10⁵ m or Bsp, nephelometer particulate concentration scale with conversion; PM₁₀ (µg/m³) = 30 x bscat/10⁵ m; OR, odds ratio; NO, nitric oxide; NO₂, nitrogen oxides; PM₁₀, particulate matter concentration; PM₁₀, particulate matter with aerodynamic diameter ≤ 7 µm; N/A, not available.
Table 3 Outdoor air pollution and COPD-related hospitalizations or emergency room visits in low- to middle- income countries

<table>
<thead>
<tr>
<th>Authors and year</th>
<th>City/country</th>
<th>Number and age of subjects</th>
<th>Study period</th>
<th>Pollutants and concentration</th>
<th>Lag days analyzed</th>
<th>Risk type and per unit increase</th>
<th>Risk level (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Wong et al° 1999</td>
<td>Hong Kong, People’s Republic of China</td>
<td>N/A</td>
<td>2 years (1994–1995)</td>
<td>24-hour mean: PM\textsubscript{10} (µg/m\textsuperscript{3}) = 31, SO\textsubscript{2} (µg/m\textsuperscript{3}) = 12, NO\textsubscript{2} (µg/m\textsuperscript{3}) = 51; 8-hour mean: O\textsubscript{3} (µg/m\textsuperscript{3}) = 24</td>
<td>0–5 days</td>
<td>RR increase in COPD per 10 µg/m\textsuperscript{3} increase in pollutants</td>
<td>PM\textsubscript{10} (Lag 0–3) = 1.019 (1.011–1.027)</td>
</tr>
<tr>
<td>Burrillo et al° 2001</td>
<td>Valencia, Spain</td>
<td>207,602</td>
<td>2 years (1994–1995)</td>
<td>24-hour mean: PM\textsubscript{10} (µg/m\textsuperscript{3}) = 10, NO\textsubscript{2} (µg/m\textsuperscript{3}) = 1.023 (1.011–1.035)</td>
<td>0–5 days</td>
<td>RR increase in COPD emergency visits per 25 µg/m\textsuperscript{3} increase in O\textsubscript{3} and 3 mg/m\textsuperscript{3} increase in CO</td>
<td>O\textsubscript{3} = 1.142 (1.016–1.283) Lag 4</td>
</tr>
<tr>
<td>Pande et al° 2002</td>
<td>Delhi, India</td>
<td>All ages</td>
<td>2 years (1997–1998)</td>
<td>24-hour mean: TSP (µg/m\textsuperscript{3}) = 31, SO\textsubscript{2} (µg/m\textsuperscript{3}) = 12, NO\textsubscript{2} (µg/m\textsuperscript{3}) = 51, CO (µg/m\textsuperscript{3}) = 103</td>
<td>0–7 days</td>
<td>Percent increase in COPD emergency room visits based on upper permissible level of TSP and SO\textsubscript{2}</td>
<td>PM\textsubscript{10} = 1.049 (1.023–1.076)</td>
</tr>
<tr>
<td>Gouveia et al° 2006</td>
<td>São Paolo, Brazil</td>
<td>≥65 years</td>
<td>4 years (1996–2000)</td>
<td>24-hour mean: PM\textsubscript{10} (µg/m\textsuperscript{3}) = 54, NO\textsubscript{2} (µg/m\textsuperscript{3}) = 18, NO\textsubscript{2} (µg/m\textsuperscript{3}) = 103</td>
<td>0–2 days</td>
<td>RR increase in COPD per 10 µg/m\textsuperscript{3} increase in PM\textsubscript{10}, NO\textsubscript{2}, and O\textsubscript{3} or per 1 ppm increase in CO</td>
<td>PM\textsubscript{10} = 1.043 (1.028–1.058)</td>
</tr>
<tr>
<td>Yang et al° 2007</td>
<td>Taipei, Taiwan</td>
<td>All ages</td>
<td>8 years (1996–2003)</td>
<td>24-hour mean: PM\textsubscript{10} (µg/m\textsuperscript{3}) = 49, SO\textsubscript{2} (ppb) = 4, NO\textsubscript{2} (ppb) = 31, CO (ppm) = 1, O\textsubscript{3} (ppb) = 72</td>
<td>0–2 days</td>
<td>OR increase in COPD admission per increase in PM\textsubscript{10} 26.41 (µg/m\textsuperscript{3})</td>
<td>&gt;20°C: PM\textsubscript{10} = 1.133 (1.098–1.168)</td>
</tr>
<tr>
<td>Lee et al° 2007</td>
<td>Kaohsiung, Taiwan</td>
<td>1.46 million</td>
<td>All ages</td>
<td>8 years (1996–2003)</td>
<td>24-hour mean: PM\textsubscript{10} (µg/m\textsuperscript{3}) = 77, SO\textsubscript{2} (ppb) = 9, NO\textsubscript{2} (ppb) = 27, CO (ppm) = 0.8, O\textsubscript{3} (ppb) = 26</td>
<td>0–2 days</td>
<td>OR increase in COPD admission per interquartile increase in PM\textsubscript{10} 62.28 (µg/m\textsuperscript{3})</td>
</tr>
<tr>
<td>Ko et al. 2007</td>
<td>Hong Kong, People's Republic of China</td>
<td>&gt;65 years</td>
<td>6 years (2000–2005)</td>
<td>24-hour mean:</td>
<td>0–5 days</td>
<td>RR increase in COPD hospitalizations per 10 µg/m³ increase in all pollutants</td>
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<tr>
<td>PM₁₀ (µg/m³) = 50</td>
<td>Cumulative by 2 days, 3 days, and 6 days</td>
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<td>PM₂.₅ (µg/m³) = 36</td>
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<tr>
<td>SO₂ (µg/m³) = 15</td>
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<td>NO₂ (µg/m³) = 51</td>
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<td>8-hour mean:</td>
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<td>O₃ (µg/m³) = 31</td>
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<tr>
<td>Arbex et al. 2009</td>
<td>São Paulo, Brazil</td>
<td>48,109 patients &gt;40 years</td>
<td>3 years (2001–2003)</td>
<td>24-hour mean:</td>
<td>0–6 days</td>
<td>Percent increase in COPD emergency room visits per increase in PM₁₀ 28.3 µg/m³</td>
<td></td>
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<tr>
<td>PM₁₀ (µg/m³) = 49</td>
<td>Cumulative 2–7 days</td>
<td></td>
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<tr>
<td>SO₂ (µg/m³) = 14</td>
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<tr>
<td>NO₂ (µg/m³) = 120</td>
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<tr>
<td>O₃ (µg/m³) = 96</td>
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<tr>
<td>CO (ppm) = 3</td>
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<tr>
<td>Milutinović et al. 2009</td>
<td>Niš, Serbia</td>
<td>171,000 All ages</td>
<td>1 year (2002)</td>
<td>24-hour mean:</td>
<td>0–3 days</td>
<td>OR increase in COPD emergency room visits per 10 µg/m³ increase in BS and SO₂</td>
<td></td>
</tr>
<tr>
<td>BS (µg/m³) = 21</td>
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<tr>
<td>SO₂ (µg/m³) = 16</td>
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<tr>
<td>Qiu et al. 2013</td>
<td>Hong Kong, People's Republic of China</td>
<td>All ages (1998–2007)</td>
<td>10 years</td>
<td>24-hour mean:</td>
<td>0–3 days</td>
<td>Percent increase in excess RR of COPD admission per increase in pollutants, 10 µg/m³</td>
<td></td>
</tr>
<tr>
<td>PM₁₀ (µg/m³) = 53</td>
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<tr>
<td>NO₂ (µg/m³) = 58</td>
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<tr>
<td>O₃ (µg/m³) = 40</td>
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<td>SO₂ (µg/m³) = 20</td>
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<tr>
<td>Tsai et al. 2013</td>
<td>Taipei, Taiwan</td>
<td>2.64 million</td>
<td>5 years (2006–2010)</td>
<td>24-hour mean:</td>
<td>No lag days</td>
<td>OR increase in COPD per 17.46 µg/m³ increase in PM₂.₅</td>
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<tr>
<td>PM₁₀ (µg/m³) = 52</td>
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<tr>
<td>PM₂.₅ (µg/m³) = 30</td>
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<td>SO₂ (ppb) = 4</td>
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<td>NO₂ (ppb) = 25</td>
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<tr>
<td>CO (ppm) = 0.7</td>
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<tr>
<td>O₃ (ppb) = 25</td>
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<tr>
<td>Ghozikali et al. 2015</td>
<td>Tabriz, Iran</td>
<td>N/A</td>
<td>N/A</td>
<td>24-hour mean:</td>
<td>N/A</td>
<td>Attributable proportion (%) and RR increase in COPD per 10 µg/m³ increase in pollutants</td>
<td></td>
</tr>
<tr>
<td>SO₂ (µg/m³) = 19</td>
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<tr>
<td>NO₂ (µg/m³) = 34</td>
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<tr>
<td>1-hour maximum:</td>
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<tr>
<td>O₃ (µg/m³) = 63</td>
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</tbody>
</table>

**Abbreviations:** 95% CI, 95% confidence interval; PM₁₀, particulate matter with aerodynamic diameter ≤10 µm; SO₂, sulfur dioxide; NO₂, nitrogen dioxide; O₃, ozone; RR, relative risk; BS, black smoke; CO, carbon monoxide; TSP, total suspended particles; NOₓ, nitrogen oxides; OR, odds ratio; PM₂.₅, particulate matter with aerodynamic diameter ≤2.5 µm; N/A, not available.
### Table 4: Outdoor air pollution and respiratory symptoms, lung function, and COPD prevalence and incidence

<table>
<thead>
<tr>
<th>Authors and year</th>
<th>City/country</th>
<th>Number and age of subjects</th>
<th>Study period</th>
<th>Pollutants and concentration</th>
<th>Risk type and per unit increase</th>
<th>Risk level (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsonou et al1992</td>
<td>Athens, Greece</td>
<td>110 COPD patients, 400 controls</td>
<td>4 months (1984)</td>
<td>Urban living</td>
<td>RR</td>
<td>2.0 (1.2–3.3)</td>
</tr>
<tr>
<td>Tashkin et al1994</td>
<td>Los Angeles, USA</td>
<td>621–763 nonsmokers, 317–479 former smokers, 472–691 continuing smokers, 25–29 years</td>
<td>3 years (1986–1989)</td>
<td>Very highly exposed (Glendora), Highly exposed (Long Beach), Moderately exposed (Lancaster)</td>
<td>OR in large reduction of lung function and actual reduction in FEV1 compared to Lancaster</td>
<td>OR: Glendora = 1.63 (1.63–2.11), Long Beach = 2.00 (1.53–2.61), FEV1 reduction in males: Long Beach = 23.6 mL/year, Glendora = 17.2 mL/year, FEV1 reduction in females: Long Beach = 9.6 mL/year, Glendora = 8.8 mL/year</td>
</tr>
<tr>
<td>Ackermann-Liebrich et al1997</td>
<td>Eight areas, Switzerland</td>
<td>9,651</td>
<td>1 year (1991)</td>
<td>Annual mean: PM10 (µg/m³) = 37, PM2.5 (µg/m³) = 21, NO2 (µg/m³) = 36, SO2 (µg/m³) = 12, O3 (µg/m³) = 43</td>
<td>Percent decrease in FVC per increase in pollutants, 10 µg/m³</td>
<td></td>
</tr>
<tr>
<td>Avino et al2004</td>
<td>Pietracupa, Rome, Italy</td>
<td>Sannino = 132,545, Rome = 2,643,581</td>
<td>1 month (2001)</td>
<td>24-hour mean: PM10 (µg/m³)</td>
<td>Prevalence of COPD admitted to hospitals</td>
<td>Pietracupa (low level) = 0.26, Rome (high level) = 0.62</td>
</tr>
<tr>
<td>Schikowski et al2005</td>
<td>Rhine-Ruhr basin, Germany</td>
<td>4,757 females, 54–55 years</td>
<td>9 years (1985–1994)</td>
<td>Annual mean: PM10 (µg/m³) = 44, NO2 (µg/m³) = 39</td>
<td>OR for COPD and percent decrease in FVC, FEV1 per increase in PM10 (7 µg/m³) and &lt;100 m to a major road</td>
<td>PM10: OR = 1.33 (1.03–1.72), FEV1 = 5.1 (2.5–7.7), FVC = 3.7 (1.8–5.5)</td>
</tr>
<tr>
<td>Sulyer et al2006</td>
<td>21 centers, ten European countries</td>
<td>3,232 males, 3,592 females</td>
<td>2 years (2000–2002)</td>
<td>City annual mean: PM10 (µg/m³) = 44, Sulfur (ng/m³) = 155–2015, Outdoor home: NO2 (µg/m³) = 6–71, Traffic volume</td>
<td>Prevalence (%) and OR in new onset of chronic phlegm (%)</td>
<td>Prevalence: Chronic phlegm = 6.9, New onset of chronic phlegm = 4.5, OR: Traffic intensity = 1.86 (1.24–2.77), Home outdoor NO2 = 2.71 (1.03–7.16)</td>
</tr>
<tr>
<td>Cesaroni et al2008</td>
<td>Rome, Italy</td>
<td>9,488</td>
<td>5 months (1994–1995)</td>
<td>Self-reported traffic, Home distance to major road, High traffic roads in 200 m, PM emission</td>
<td>OR in CB and emphysema</td>
<td>CB prevalence 4%</td>
</tr>
<tr>
<td>Lindgren et al2009</td>
<td>Scania, Sweden</td>
<td>9,319</td>
<td>1 year (2000)</td>
<td>Self-reported heavy traffic, Heavy road (cars/min), NO2 (µg/m³) = 7–22</td>
<td>OR for COPD prevalence</td>
<td>Self-reported heavy traffic: 1.36 (1.10–1.67), Heavy road: 6–10 cars/min = 1.57 (1.15–2.14), &gt;10 cars/min = 1.64 (1.11–2.41), NO2 (&gt;19 µg/m³) = 1.43 (1.04–1.95)</td>
</tr>
</tbody>
</table>
Benzayeb et al. 2010
Bordeaux, France
2,104
3 years
(1999–2001)
3-year mean: PM$_{10}$ ($\mu$g/m$^3$) =19–51
NO$_x$ ($\mu$g/m$^3$) =18–72
SO$_2$ ($\mu$g/m$^3$) =5–14
VOCs ($\mu$g/m$^3$) =0.01–116
Benzene ($\mu$g/m$^3$) =2–7
CO ($\mu$g/m$^3$) =350–1,337
Home distance to a major road
OR and percent increase in bronchitis symptoms per increase in PM$_{10}$ (10 $\mu$g/m$^3$) and SO$_2$ (1 $\mu$g/m$^3$)
% for cough =10
PM$_{10}$ OR for cough = 1.33 (1.00–1.77)
% for cough =23

Nuvolone et al. 2011
Pisa-Cascina, Italy
2,062
2 years
Distance to a major road
OR on wheeze, COPD diagnosis, and reduced FEV/$FVC$ for <100 m
COPD = 1.80 (1.03–3.08)
FEV/$FVC$ = 0.27 (1.13–2.27)
Males: Wheeze = 1.76 (1.08–2.87)
Females: Wheeze = 1.67 (0.98–2.84)
Dyspnea = 1.19 (1.03–1.38)
HR for NO$_2$: COPD = 1.08 (1.02–1.14)
COPD with diabetes = 1.29 (1.05–1.50)
COPD with asthma = 1.19 (1.03–1.38)
Home distance to a major road <100 m
OR in CB
Living close to a busy road >30 years
PM$_{10}$: OR for cough = 1.33 (1.00–1.77)
% for cough =10
PM$_{2.5}$ OR for cough = 1.55 (1.16–2.08)
% for cough =23

Andersen et al. 2011
Aarhus, Copenhagen, Denmark
52,799 people
50–64 years
35-year mean: NO$_x$ ($\mu$g/m$^3$) =18
NO$_2$ ($\mu$g/m$^3$) =32
HR per interquartile increase in pollutants, 5.8 $\mu$g/m$^3$
OR in CB
Home distance to a major road <100 m
PM$_{10}$ OR for cough = 1.33 (1.00–1.77)
% for cough =10
PM$_{2.5}$ OR for cough = 1.55 (1.16–2.08)
% for cough =23

Salamah et al. 2012
Beirut, Lebanon
New CB cases = 274
1 year and 2 months
Living close to a busy road
OR in CB
Home distance to a major road <100 m
PM$_{10}$ OR for cough = 1.33 (1.00–1.77)
% for cough =10
PM$_{2.5}$ OR for cough = 1.55 (1.16–2.08)
% for cough =23

Rice et al. 2015
Framingham, USA
6,339
16 years
(1995–2011)
Distance to a major road
Percent decrease in FEV$_1$ (% loss per increase in PM$_{2.5}$ (2 $\mu$g/m$^3$) and <100 m to a major road
PM$_{2.5}$ ($\mu$g/m$^3$) = 11
Loss due to PM$_{2.5}$ exposure:
FEV$_1$ =13.5 mL (0.3–26.6) per 2 $\mu$g/m$^3$
FEV$_1$ =1.17 (1.02–1.33)
PM$_{2.5}$ OR for cough = 1.33 (1.00–1.77)
% for cough =10
PM$_{2.5}$ OR for cough = 1.55 (1.16–2.08)
% for cough =23

To et al. 2015
Ontario, Canada
29,549
45–59 years
(1980–2013)
Long-term average:
PM$_{2.5}$ ($\mu$g/m$^3$) = 13
Increase in PR and IR of COPD per increase in PM$_{2.5}$ (10 $\mu$g/m$^3$)
IR = 1.17 (1.02–1.33)
PM$_{2.5}$ OR for cough = 1.33 (1.00–1.77)
% for cough =10
PM$_{2.5}$ OR for cough = 1.55 (1.16–2.08)
% for cough =23

Adamkiewicz et al. 2015
Warsaw and control areas, Poland
≥40 years
(2008–2012)
4 years
Period of residence close to road traffic stratified into 20 years, 30 years, and 40 years, PM$_{2.5}$ ($\mu$g/m$^3$)
RR of lung obstruction per increase in PM$_{10}$ (10 $\mu$g/m$^3$)
20 years = 1.27
30 years = 1.24
40 years = 1.19

Note: Percent increase = (OR – 1) × 100.
Abbreviations: CI, confidence interval; RR, relative risk; OR, odds ratio; FEV$_1$, forced expiratory volume in the first second; the maximal amount of air forcefully exhaled in 1 second; PM$_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5 µm; CB, chronic bronchitis; NO$_2$, nitrogen oxides; VOCs, volatile organic compounds; HR, hazard ratio; PR, prevalence rate ratio; IR, incidence rate ratio; PM$_{10}$, particulate matter with aerodynamic diameter ≤ 10 µm; NO$_x$, nitrogen dioxide; SO$_2$, sulfur dioxide; O$_3$, ozone; FVC, forced vital capacity, the amount of air a person can expire after a maximum inspiration; CO, carbon monoxide; PM$_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5 µm; CB, chronic bronchitis; NO$_2$, nitrogen oxides; VOCs, volatile organic compounds; HR, hazard ratio; PR, prevalence rate ratio; IR, incidence rate ratio; PM$_{10}$, particulate matter with aerodynamic diameter ≤ 10 µm.
<table>
<thead>
<tr>
<th>Authors and year</th>
<th>City/country</th>
<th>Number and age of COPD subjects</th>
<th>Study period</th>
<th>Pollutants and concentration</th>
<th>Lag days analyzed</th>
<th>Risk type and per unit increase</th>
<th>Risk level (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Lawther et al 1970</td>
<td>UK</td>
<td>334 patients with bronchitis, 27–78 years (1954–1959)</td>
<td>Four winters</td>
<td>24-hour mean: Smoke (µg/m³) =129–342, SO₂ (µg/m³) =264–296</td>
<td>0 day</td>
<td>Percent increase in worse symptoms over prior day using diary</td>
<td>Overall =28, Baseline =12.5, Peak exposure =37, Decline =7.5</td>
</tr>
<tr>
<td>Harré et al 1997</td>
<td>Christchurch, New Zealand</td>
<td>40 COPD patients, 55 years</td>
<td>3 months, Winter 1994</td>
<td>24-hour mean: PM₁₀ (µg/m³), NO₂ (µg/m³), SO₂ (µg/m³), CO (µg/m³), 8-hour mean: CO (µg/m³)</td>
<td>0–1 day</td>
<td>RR increase in symptoms and medication use per interquartile increase in PM₁₀ (35.04 µg/m³) and NO₂ (9.74 µg/m³)</td>
<td>PM₁₀ and night time chest symptoms =1.38 (1.07–1.78), NO₂: Inhaler use =1.42 (1.13–1.79), Nebulizer use (1-day lag) =2.81 (1.81–4.39)</td>
</tr>
<tr>
<td>Linn et al 1999</td>
<td>Los Angeles, USA</td>
<td>30 COPD patients, 16 males, 14 females, 56–83 years</td>
<td>4 days in fall and winter</td>
<td>24-hour mean and 1-hour maximum: PM₁₀ (µg/m³) =33</td>
<td>0–1 day</td>
<td>Blood pressure increase per unit increase in PM₁₀</td>
<td>Diastolic blood pressure =0.095 mmHg (Lag 0), Diastolic blood pressure =0.122 mmHg (Lag 1), Systolic blood pressure =0.172 mmHg (Lag 1)</td>
</tr>
<tr>
<td>Sunyer et al 2000</td>
<td>Barcelona, Spain</td>
<td>1,845 males, 460 females COPD patients, &gt;35 years (1990–1995)</td>
<td>5 years</td>
<td>24-hour mean: BS (µg/m³) =44</td>
<td>0–2 days</td>
<td>OR increase in mortality per interquartile increase in BS (20 µg/m³)</td>
<td>All causes =1.112 (1.017–1.215), Respiratory causes =1.182 (1.025–1.365), Cardiovascular causes =1.077 (0.917–1.264), All causes =1.11 (1.00–1.24)</td>
</tr>
<tr>
<td>Sunyer et al 2001</td>
<td>Barcelona, Spain</td>
<td>2,305 COPD patients, &gt;35 years (1990–1995)</td>
<td>5 years</td>
<td>24-hour mean: PM₁₀ (µg/m³)</td>
<td>Cumulative 2 days</td>
<td>OR increase in mortality per interquartile increase in PM₁₀ (27 µg/m³)</td>
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<tr>
<td>Desqueyroux et al 2002</td>
<td>Rhine-Ruhr basin in Germany</td>
<td>39 Parisian adults with severe COPD</td>
<td>14 months</td>
<td>Four air pollutants</td>
<td>0–3 days</td>
<td>OR in COPD exacerbation per increase of 10 µg/m³ for O₃</td>
<td>1.44 (1.14–1.82)</td>
</tr>
<tr>
<td>Silkoff et al 2005</td>
<td>Denver, USA</td>
<td>34 COPD patients, ≥40 years (1999–2001)</td>
<td>Two winters</td>
<td>24-hour mean: PM₁₀ (µg/m³) =25–30, PM₁₅ (µg/m³) =9–14, CO (ppm) =1, NO₂ (ppb) =16–29</td>
<td>0–2 days</td>
<td>Percent reduction in lung function and increase in rate ratios of symptom score per SD increase in pollutants</td>
<td>Second winter FEV₁ evening: CO Lag 2 =0.010 (−0.001 to −0.025), Second winter PEF morning: NO₂, Lag 0 =4.8 (−2.9 to 0.4), NO₂, Lag 1 =4.0 (−1.1 to 7), Second winter PEF evening: PM₁₀, Lag 2 =2.5 (−0.1 to 3.6), Second winter symptom evening: NO₂, Lag 0 =1.007 (1.001–1.013), FEV₁: Lag 0 =−8.9 (−0.4 to 0.4), Lag 1 =−45.2 (−102.6–121), PEF: Lag 0 =−1.8 (−106.6–6.9), Lag 1 =−48 (−146.6–4.9)</td>
</tr>
<tr>
<td>Trenga et al 2006</td>
<td>Seattle, USA</td>
<td>24 COPD, 65–89 years, 33 control, 56–88 years (1999–2002)</td>
<td>3 years</td>
<td>24-hour mean: PM₁₅ (µg/m³): Central =1, Outdoor =9, Personal =8</td>
<td>0–1 day</td>
<td>FEV₁ and PEF change per change in outdoor PM₁₅ (10 µg/m³)</td>
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</tr>
</tbody>
</table>
Lagorio et al. 2006
Central Rome
29 patients with COPD, asthma, and ischemic heart disease
50–80 years
2×1 months
24-hour mean:
P.M.0 (µg/m³) = 43
P.M.10–2.5 (µg/m³) = 16
P.M.2.5 (µg/m³) = 27
NO₂ (µg/m³) = 71
SO₂ (µg/m³) = 6
O₃ (µg/m³) = 43
CO (mg/m³) = 7.4
Zn (ng/m³) = 46
Fe (ng/m³) = 283
Percent change in increased COPD patients
Changes in FVC and FEV₁ per interquartile increase in pollutants
PM₁₀, NO₂, Zn, and Fe associated with reduced FEV₁ and/or FVC

Peacock et al. 2011
London, England
94 COPD patients
2 years and 1 month
24-hour mean:
P.M.0 (µg/m³) = 38
BS (µg/m³) = 10
SO₂ (ppb) = 8
8-hour mean: O₃ (ppb) = 16
1-hour maximum: NO₂ (ppb) = 51
Percent change in increased symptoms and reduced lung function per interquartile change in pollutants
Dyspnea and PM₁₀ = 13 (4–23)
Reduced lung function:
NO₂ = 6 (0–13)
PM₁₀ = 12 (2–25)
BS = 7 (1–13)

Note: Percent increase = (OR – 1) × 100
Abbreviations: CI, confidence interval; SO₂, sulfur dioxide; PM₁₀, particulate matter with aerodynamic diameter ≤ 10 µm; NO₂, nitrogen dioxide; CO, carbon monoxide; RR, relative risk; BS, black smoke; OR, odds ratio; PM₁₀, particulate matter with aerodynamic diameter = 2.5 µm; PM₁₀–2.5, particulate matter with aerodynamic diameter = 2.5–10 µm; PM₂.5–10, particulate matter with aerodynamic diameter = 2.5–10 µm and 2.5–10 µm; O₃, ozone; Zn, zinc; Fe, iron; FVC, forced vital capacity; the amount of air a person can expire after a maximum inspiration; SD, standard deviation.

This switch to a more health-related exposure metric has stimulated studies of the associations between ambient air pollution and COPD, asthma, and the effect size was often provided with higher units of exposure. The focus of these studies was on how PM₂.5 size evaluation evolved from TSP to PM₁₀ and then to PM₁₀. Earlier studies mostly focused on a single city, and many evaluated total mortality. The effect size was based on the world described earlier and the major finding of this study was that the effect size was based on the highest units of exposure for their independent effects or interaction with other pollutants. The main finding of this study was that the effect size was based on the highest units of exposure for their independent effects or interaction with other pollutants.
Table 6 Indoor air pollution and COPD incidence or prevalence in low-income countries

<table>
<thead>
<tr>
<th>Authors and year</th>
<th>Study design</th>
<th>City/country</th>
<th>Number and age of subjects</th>
<th>Study year</th>
<th>Exposure measured</th>
<th>Health outcome measured</th>
<th>Risk type</th>
<th>Risk level (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pandey et al.1984</td>
<td>Population based, cross-sectional Rural</td>
<td>Hill region, Nepal</td>
<td>1,375 rural residents</td>
<td>N/A</td>
<td>Time spent cooking</td>
<td>BMRC questionnaire</td>
<td>Prevalence for bronchitis</td>
<td>Non-smoking females: Crude prevalence: 12.57% Age-adjusted: 13.76% Prevalence increased with exposure time Overall prevalence =13% Mixed fuel =16.7% Biomass (chulla) =12.6% Kerosene stove =11.4% LPG =9.9% Bronchitis higher and lung function lower in chulla users Overall prevalence =12.7% CB OR =1.86 (1.16–2.99) 2/3 in case exposed 1/20 in control exposed</td>
</tr>
<tr>
<td>Behera and Jindal1991</td>
<td>Population based, cross-sectional Rural</td>
<td>Chandigarh, India</td>
<td>3,701 females</td>
<td>N/A</td>
<td>Exposure index (hours multiplied by years spent cooking)</td>
<td>BMRC questionnaire</td>
<td>Prevalence for respiratory symptoms</td>
<td>Prevalence and OR for chronic bronchitis Percentage of exposed Wood use =3.43 (1.69–7.05) Gasoline use =0.52 (0.28–0.95)</td>
</tr>
<tr>
<td>Menezes et al.1994</td>
<td>Population based, cross-sectional Urban</td>
<td>Pelotas, Brazil</td>
<td>1,053 people ≥40 years</td>
<td>N/A</td>
<td>Exposure scoring: No, moderate and high smoke</td>
<td>ATS-DLD-78 questionnaire</td>
<td>OR for chronic bronchitis OR for higher exposure =1.86 (1.16–2.99) 2/3 in case exposed 1/20 in control exposed</td>
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<tr>
<td>Dossing et al.1994</td>
<td>Case-control</td>
<td>Saudi Arabia</td>
<td>50 COPD cases 71 healthy controls Female</td>
<td>N/A</td>
<td>Exposed to indoor open fire of wood or biomass ≥20 years</td>
<td>Questionnaire</td>
<td>CB OR =3.9 (2.0–7.6) COPD + CB =9.7 (3.7–27) COPD =1.8 (0.7–4.7) Duration ≥200 hour-years: COPD + CB =75 (18–306) COPD =1.50 (5.6–40)</td>
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</tr>
<tr>
<td>Dennis et al.1996</td>
<td>Hospital-based, case-control</td>
<td>Bogota, Columbia</td>
<td>104 COPD cases 104 healthy controls Female ≥35 years</td>
<td>N/A</td>
<td>Exposed to indoor open fire ≥20 years</td>
<td>ATS questionnaire</td>
<td>OR for wood used for cooking Wood use =3.43 (1.69–7.05) Gasoline use =0.52 (0.28–0.95)</td>
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<tr>
<td>Pérez-Padilla et al.1996</td>
<td>Urban hospital-based, case-control</td>
<td>Mexico City, Mexico</td>
<td>126 cases (63 CB, 23 COPD, and 41 both) Four control groups (83 with TB, 100 with interstitial lung diseases, 97 with ear, nose, and throat ailments 95 healthy visitors Females ≥35 years</td>
<td>N/A</td>
<td>Exposed to wood smoke and duration (hour-years)</td>
<td>ATS questionnaire</td>
<td>OR for wood use for cooking CB =3.9 (2.0–7.6) COPD + CB =9.7 (3.7–27) COPD =1.8 (0.7–4.7) Duration ≥200 hour-years: COPD + CB =75 (18–306) COPD =1.50 (5.6–40)</td>
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<tr>
<td>Ellegård et al.1996</td>
<td>Population based, cross-sectional Suburban</td>
<td>Maputo, Mozambique</td>
<td>1,200 females ≥14 years</td>
<td>1992</td>
<td>Fuel use type Cumulative exposure PM&lt;sub&gt;10&lt;/sub&gt; (µg/m&lt;sup&gt;3&lt;/sup&gt;) Exposure time Peak expiratory flow (L/minute)</td>
<td>Zambia questionnaire</td>
<td>Frequency of symptoms</td>
<td>Wood use for fuel associated with more cough problems</td>
</tr>
<tr>
<td>Albalak et al.1999</td>
<td>Population based, cross-sectional Two highland villages (one indoor cooking and one outdoor cooking)</td>
<td>Aymara, Bolivia</td>
<td>241 villagers ≥20 years 102= indoor cooking 139= outdoor cooking</td>
<td>1995</td>
<td>Daily exposure index (PM&lt;sub&gt;10&lt;/sub&gt; µg/m&lt;sup&gt;3&lt;/sup&gt; multiplied by exposure time)</td>
<td>BMRC questionnaire</td>
<td>Prevalence and OR for CB</td>
<td>Prevalence for villages: Indoor cooking =22% Outdoor cooking =13% Unadjusted OR for outdoor cooking =0.5 (0.2–0.9) Adjusted OR for outdoor cooking =0.4 (0.2–0.8) OR for CB in &gt;40 age group =4.3 (2.0–9.3)</td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>Location</td>
<td>Sample Size</td>
<td>Methodology</td>
<td>Measures</td>
<td>Results</td>
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<tr>
<td>Golshan et al. 2002</td>
<td>Population based, cross-sectional</td>
<td>Isfahan, Iran</td>
<td>561 females 1 month–81 years</td>
<td>2000</td>
<td>TSP (ppb), PM$_{10}$ (ppb)</td>
<td>Questionnaire, Physical examination</td>
<td>OR for CB Using kerosene fuel = 1.27 (1.02–1.66) Using wood fuel = 2.91 (2.08–4.4)</td>
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<tr>
<td>Kiraz et al. 2003</td>
<td>Population based, cross-sectional</td>
<td>Kayseri, Turkey</td>
<td>242 rural 102 city Female ≥25 years</td>
<td>1999</td>
<td>Questionnaire for fuel type, years of use, and stove type</td>
<td>Physical examination</td>
<td>OR for CB and COPD Rural vs urban females: CB (%) = 20.7 vs 10.8 COPD (%) = 12.4 vs 3.9 OR for CB = 28.7 (8.7–95.9)</td>
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<tr>
<td>Ekici et al. 2005</td>
<td>Population based, cross-sectional</td>
<td>Kirikkale, Turkey</td>
<td>Rural biomass users = 397 Urban LPG control = 199 Female ≥40 years</td>
<td>2002</td>
<td>Exposure index (hours multiplied by years of biomass cooking): A ≤ 68.6 hour-year B = 68.8–152.4 hour-year C ≥ 152.4 hour-year</td>
<td>BMRC questionnaire, Physical examination, Lung function testing</td>
<td>OR for CB and COPD Prevalence: Biomass = 28.5% LPG = 13.6% Crude OR: Group A = 1.7 (1.0–3.1) Group B = 2.5 (1.4–4.4) Group C = 3.3 (1.9–5.7) Adjusted OR: Group A = 2.0 (0.9–4.5) Group B = 2.3 (1.1–4.5) Group C = 2.2 (1.1–4.4) Combined = 2.5 (1.5–4.0) Adjusted = 1.4 (1.2–1.7) AP = 23.1 (13.4–33.2)</td>
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<tr>
<td>Peabody et al. 2005</td>
<td>Population based, cross-sectional</td>
<td>Shanxi, Hubei, Zhejiang, People’s Republic of China</td>
<td>4,638 adults 2,285 children</td>
<td>N/A</td>
<td>Fuel type, Stove type, Duration in cooking CO in exhaled air</td>
<td>Adult and children questionnaires Heart rate, Respiratory rate, Blood pressure, Lung function testing (FVC)</td>
<td>Prevalence and OR for COPD COPD prevalence (%) = 3.8 Prevalence higher in coal users OR compared to coal: Wood = 0.48 (0.28–0.87) Crop = 0.57 (0.34–0.96) Clean fuel = 0.43 (0.05–0.36) OR for stove: Tradition vs improved = 1.87 (1.30–2.69)</td>
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<tr>
<td>Chapman et al. 2005</td>
<td>Retrospective cohort</td>
<td>Xuanwei, People’s Republic of China</td>
<td>20,453 people with traditional stoves 16,606 people changed to improved stoves</td>
<td>16 years (1976–1992)</td>
<td>Questionnaire for stove type and fuel type</td>
<td>Standard questionnaire Bronchitis, Emphysema, Death</td>
<td>RR for COPD in improved vs unvented stoves COPD prevalence (%): 7.3 COPD incidence (%) reduced: Males = 42 Females = 25 RR: Male = 0.58 (0.49–0.70) Females = 0.75 (0.62–0.92) ≥ 30 years of biomass exposure = 6.61 (2.17–20.18)</td>
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<tr>
<td>Sezer et al. 2006</td>
<td>Hospital-based case–control</td>
<td>Sivas, Turkey</td>
<td>74 cases with COPD 74 controls without COPD All housewives</td>
<td>1 year and 3 months (2001–2002)</td>
<td>Questionnaire for fuel type, years of use</td>
<td>COPD determined by hospital record OR for exposure</td>
<td>(Continued)</td>
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<tr>
<td>Authors and year</td>
<td>Study design</td>
<td>City/country</td>
<td>Number and age of subjects</td>
<td>Study year</td>
<td>Exposure measured</td>
<td>Health outcome measured</td>
<td>Risk type</td>
<td>Risk level (95% CI)</td>
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<tr>
<td>Akhtar et al\textsuperscript{157} 2007</td>
<td>Population-based, cross-sectional</td>
<td>Peshawar, Pakistan</td>
<td>Six villages: 1,426 females in three study villages, 1,131 females in three control villages</td>
<td>10 months (2003–2004)</td>
<td>Questionnaire for fuel type</td>
<td>ATS questionnaire</td>
<td>OR for CB</td>
<td>CB prevalence (%): Study village = 7.01, Control village = 2.92, Overall = 2.51 (1.65–3.83), Rice straws = 3.32 (1.11–9.88), Wood = 2.38 (2.12–3.01), Dung = 2.01 (1.72–2.42), Kai grass = 1.96 (1.75–2.45)</td>
</tr>
<tr>
<td>Liu et al\textsuperscript{158} 2007</td>
<td>Population-based, cross-sectional</td>
<td>Guangzhou, People’s Republic of China</td>
<td>Rural = 1,468 females, Urban = 1,818 females</td>
<td>7 months (2003–2004)</td>
<td>Geometric mean of biomass cooking in kitchen: PM\textsubscript{10} (mg/m\textsuperscript{3}) = 0.5, SO\textsubscript{2} (mg/m\textsuperscript{3}) = 0.25, NO\textsubscript{x} (mg/m\textsuperscript{3}) = 0.09, CO (mg/m\textsuperscript{3}) = 4.5</td>
<td>Standard questionnaire, Physical examination, Lung function testing</td>
<td>OR for COPD and respiratory symptoms</td>
<td>OR for COPD prevalence (%): Rural = 12, Urban = 7.4, OR for fuel type: Biomass = 1.72 (1.27–2.35), Coal = 1.55 (0.74–3.22) COPD prevalence (%) for nonsmoking females: Rural = 7.2, Urban = 2.5, OR for fuel type: Biomass = 3.11 (1.63–5.94), Coal = 2.77 (0.83–9.26) OR for SO\textsubscript{2} = 1.80 (1.04–3.11) COPD prevalence (%): Males = 12.4, Females = 5.1, Combined = 8.2, OR: Poor kitchen ventilation = 1.28 (1.14–1.43), Indoor biomass cooking and heating = 1.35 (1.20–1.52) CB prevalence (%): Biomass = 10.6, Nonbiomass = 2.8, CB OR = 3.75 (1.07–13.16), Lower lung function</td>
</tr>
<tr>
<td>Zhong et al\textsuperscript{159} 2007</td>
<td>Population-based, cross-sectional</td>
<td>Seven provinces/cities, People’s Republic of China</td>
<td>25,627 people (\geq) 40 years</td>
<td>0.5 years (2002–2003)</td>
<td>Indoor biomass cooking in kitchen: BOLD questionnaire, Kitchen ventilation, Lung function symptoms, Chest radiograph</td>
<td>Prevalence and OR for COPD and respiratory symptoms</td>
<td>Prevalence and OR for COPD and respiratory symptoms</td>
<td>Prevalence and OR for COPD and respiratory symptoms</td>
</tr>
<tr>
<td>Desalu et al\textsuperscript{160} 2010</td>
<td>Population-based, cross-sectional</td>
<td>Ekiti State, Nigeria</td>
<td>269 adult females</td>
<td>6 months (2009)</td>
<td>Biomass vs nonbiomass fuel use</td>
<td>ECRHS questionnaire</td>
<td>OR and prevalence for CB</td>
<td>CB prevalence (%)</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Population Type</td>
<td>Location</td>
<td>Sample Size</td>
<td>Fuel Type</td>
<td>Years of Cooking</td>
<td>Days Cooking</td>
<td>Test Methodology</td>
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<tr>
<td>Johnson et al (2011)</td>
<td>2011</td>
<td>Population-based, cross-sectional</td>
<td>Tamilnadu, India</td>
<td>900 females</td>
<td>Biomass: 30 years</td>
<td></td>
<td></td>
<td>Standard questionnaire</td>
</tr>
<tr>
<td>da Silva et al (2012)</td>
<td>2012</td>
<td>Population-based, cross-sectional</td>
<td>Joao Camara, Brazil</td>
<td>260 houses</td>
<td>Clean fuel: 2 years</td>
<td></td>
<td></td>
<td>ISAAC and BMRC questionnaires</td>
</tr>
<tr>
<td>Mahesh et al (2013)</td>
<td>2013</td>
<td>Population-based, cross-sectional</td>
<td>Mysore and Nanjangud, India</td>
<td>16 villages</td>
<td>Biomass: 30 years</td>
<td></td>
<td></td>
<td>BOLD questionnaire</td>
</tr>
</tbody>
</table>

**Notes:** Case–control and cross-sectional prevalence studies used chi-square test, Mantel–Haenszel method, and logistic regression or multivariate regression for data analysis on OR and trends, adjusting for variables such as age, sex, marital status, education, body mass index, alcohol use, active and passive smoking, occupational exposures, atopy and family history of COPD, place of birth, and residence and family income. Pollutant names are the same as in previous tables.

**Abbreviations:** CI, confidence interval; BMRC, British Medical Research Council; LPG, liquefied petroleum gas; ATS, American Thoracic Society; OR, odds ratio; CB, chronic bronchitis; PM\textsubscript{10}, particulate matter with aerodynamic diameter \#10 \(\mu\)m; TSP, total suspended particles; AP, attributable proportion = (OR – 1) \times \%OR, where \%OR is the prevalence of the exposure among the cases; CO, monoxide; FVC, forced vital capacity; the amount of air a person can expire after a maximum inspiration; RR, relative risk; SO\textsubscript{2}, sulfur dioxide; NO\textsubscript{2}, nitrogen dioxide; BOLD, Burden of Obstructive Lung Disease; ECRHS, European Community Respiratory Health Survey; PM\textsubscript{2.5}, particulate matter with aerodynamic diameter \#2.5 \(\mu\)m; ISAAC, International Study of Asthma and Allergies in Childhood; FEV\textsubscript{1}, forced expiratory volume in the first second; the maximal amount of air forcefully exhaled in 1 second; EL, exposure index or cumulative exposure = daily cooking hours multiplied by years of cooking; N/A, not available; TB, tuberculosis.
obstruction, and deranged gas exchange are also important contributors. Patients who die during air pollution episodes include not only those with a very short life expectancy (this mechanism has been called “harvesting”) but also patients and subjects with a much longer life expectancy.  

Outdoor air pollution and COPD morbidity

While mortality due to air pollution represents the extreme outcome for COPD sufferers, there is a continuum of health effects that also include the impact on the morbidity such as increased acute respiratory symptoms, reduced lung functions, exacerbation of COPD conditions that may be severe enough to require physician visits, use of ambulance, hospital respiratory admissions, and emergency room visits. COPD sufferers are particularly vulnerable to additional stress on the respiratory system caused by the toxic effects of inhaled pollutants. The London Smog incident of December 5–9, 1952, caused total hospital admissions to rise by 50% and respiratory admissions to rise by 160%. The later Smog event in 1991 caused a 43% increase in hospital admission. Similarly in the past 30 years, particularly since the early 1990s, many epidemiologic studies have been conducted around the world to evaluate short-term exposure to air pollution and the morbidity of respiratory diseases overall or COPD specifically. These studies that assessed the mortality often also evaluated the morbidity. Table 2 summarizes the 27 studies conducted in high-income countries that specifically evaluated the increased risk of hospital admission or emergency room visits due to COPD cause. Exposures assessed included both PM and gaseous pollutants, and the exposure unit used to assess the effect size of particles varied among studies and often was 50 µg/m³ and 100 µg/m³ or in the interquartile range (IQR) of the measured data in earlier studies. Recent studies tended to use 10 µg/m³. Figure 3A summarizes the effect sizes from different authors with different particle sizes and lag times per increase in 10 µg/m³. The percent increases ranged from 0.02 for PM$_{2.5}$ in Lag 5 in the study conducted by Belleudi et al in Rome, Italy, to 10.1 for PM$_{10}$ in Lag 0–7 in the study conducted by Sauerzapf et al in Norfork, UK. The average percent increase was 1.89. In 2006, a study in 204 counties in the US by Dominici et al found a total percent increase at 1.4 for PM$_{2.5}$. In the same year, another study by Medina-Ramón et al with 36 US cities identified percent increases at 0.29 (Lag 0) and 0.59 (Lag 1) for PM$_{10}$ based on per 10 µg/m³ increase in concentration. The most recent study by Kloog et al in the Mid-Atlantic region of the US identified a percent increase of 1.83 (Lag 1) for PM$_{2.5}$. The effect sizes

Figure 1 Article identification, screening, evaluation on eligibility and inclusion.
Air quality guidelines impact on COPD sufferers

The percent increases for gaseous pollutants were also variable among the studies. For SO$_2$, the percent change ranged from 2% in a study by Sunyer et al. in Barcelona, Spain, to as high as 39% in a study by Pönkä and Virtanen in Helsinki, Finland, although these studies were not directly comparable as they used different exposure units. For NO$_2$, recent comparable studies showed an increase in risk from 1.2% to 22%. For O$_3$, the percent change was 1.22 in Hong Kong, People’s Republic of China, to 26% in Kaohsiung, Taiwan, when the temperature was $<25^\circ$C. For CO, the percent change ranged from 4.9% in São Paulo, Brazil, to 39.8% in Kaohsiung, Taiwan, when the temperature was $<25^\circ$C.

Table 3 summarizes 12 studies conducted in the low- to middle-income countries. With different exposure units used, the percent increase for particles in these studies was from 0.74 in a study conducted by Qiu et al. in Hong Kong, People’s Republic of China, to 18.6% in a study conducted by Arbex et al. in São Paulo, Brazil. When the same exposure unit of 10 $\mu$g/m$^3$ was used, five studies showed a range of percent increase from 0.44 in Tabriz, Iran, to 4.3 in São Paolo, Brazil, with an average of 2.19 (Figure 3B). This is similar in magnitude to that in high-income countries. For SO$_2$, the reported percent increase with different exposure units ranged from 0.44 in Tabriz, Iran, to 19% in Kaohsiung, Taiwan, when the temperature was $<25^\circ$C. For NO$_2$, the lowest reported was 0.38 in Tabriz, Iran, and the highest was 97.5% in Kaohsiung, Taiwan. For O$_3$, the percent change ranged from 1.5% to 8.8% although again these numbers were not directly comparable because the exposure units used were different.

The above studies provided strong evidence that both particles and gaseous air pollutants can increase the hospital
admissions or visits to emergency departments due to COPD exacerbation in both high-income and low- to middle-income countries, although the effect size is variable among study locations and different pollutants. The effect size also seems to be higher in gaseous pollutants, particularly in low-income countries.

Outdoor air pollution on respiratory symptoms and lung function
Several studies have also been conducted to evaluate the prevalence and incidence of COPD or chronic bronchitis and/or respiratory symptoms and lung functions (FVC, FEV\textsubscript{1}, or both) due to short-term or long-term exposure to outdoor air pollution. Table 4 summarizes 15 of such studies\textsuperscript{109–123} Exposures often were measured qualitatively as how close the home was to a major road with high traffic, although air pollutants were also measured in some of the studies. The prevalence of COPD ranged from 0.26% in Pietracupa, Italy\textsuperscript{112} to 4.5% in Rhine-Ruhr basin, Germany\textsuperscript{113} and the prevalence of chronic bronchitis was 4\%\textsuperscript{115} Increased risks with different effect sizes were observed for symptoms such as cough and phlegm\textsuperscript{114,117,118} reduced lung functions\textsuperscript{110,112,113,118,121} and prevalence or incidence of COPD or chronic bronchitis\textsuperscript{113,116,118–120,122} in different populations and various regions of the world. The amount of decreased FEV\textsubscript{1} was reported to be from 2.1 mL/year per increase in PM\textsubscript{2.5} (2 µg/m\textsuperscript{3}) or 5.0 mL/year if living in <100 m distance to a major road in Framingham, US\textsuperscript{121} to 23.6 mL/year in males in a Los Angeles study\textsuperscript{110} These effect sizes delineated the risks of chronic exposure to outdoor air pollution in the general population.

Outdoor air pollution on COPD patients
Another type of time series study is the panel study with COPD patients to evaluate the daily variations of air pollution directly on their exacerbation (increased symptoms and reduced lung...
functions). However, relatively fewer of such studies have been conducted, and the results on the effects are inconsistent. Table 5 presents the details for ten panel studies. One of the earliest panel studies was conducted by Lawther et al. They used diary cards to assess the symptoms of bronchitis related to the change in air pollution levels in patients and found a 28% overall increase in worsened symptom rates. The panel studies in the past 25 years showed a variety of exacerbations on the COPD patients ranging from increased respiratory symptoms, blood pressure, and inhaler and nebulizer use, reduced lung function, and limits in physical activities to death, although the effect sizes were variable among different studies in different regions. Most of these studies used a small number of COPD patients. The largest study identified was conducted by Sunyer and Basagaña in Barcelona, Spain, with 2,305 COPD patients >35 years of age. An IQR increase of 27 µg/m³ in PM₁₀ resulted in an all-cause mortality increase of 11%.

The above review indicated that outdoor air pollution, especially particulate air pollution, has been consistently linked to various health effects on COPD sufferers ranging from increased respiratory symptoms, decreased pulmonary function, exacerbation leading to increased hospitalization admissions and emergency room visits, and mortality due to cardiopulmonary disease. These health effects are observed at levels common to many US cities, including levels below the maximum set by the US NAAQS at the time of the studies.

**Indoor air pollution and impact on COPD sufferers**

Human beings spend a large part of their time indoors such as in homes, workplaces, libraries, shopping malls, school classrooms, and daycare centers and inside vehicles. For example, Americans spend ~90% of their time indoors, where the concentrations of some pollutants are often two

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**Figure 3** Outdoor air pollution and COPD-related hospital admissions or emergency room visits: increased risk for COPD per increase in particle exposure (10 µg/m³).

**Note:** (A) High-income countries and (B) low- to middle-income countries.

**Abbreviations:** PM₁₀, particulate matter with aerodynamic diameter ≤10 µm; TSP, total suspended particles; PM₂.₅, particulate matter with aerodynamic diameter ≤2.5 µm; CI, confidence interval; BS, black smoke.
to five times higher than typical outdoor concentrations.\textsuperscript{135} According to WHO, almost three million people or 50% of the households worldwide use biomass as the main source of energy for cooking, heating, and other household needs, such as wood, crop residues, and animal dung in addition to coal. Biofuels have higher emission factors for PM and other pollutants, especially during incomplete combustion at lower temperatures.\textsuperscript{136} The burning of biofuels generates indoor airborne particles at levels much higher than those of cleaner fuels\textsuperscript{137} or outdoor levels,\textsuperscript{138} and well above levels in most polluted cities.\textsuperscript{139} Such particles also have small aerodynamic diameters (eg, ranging from 0.05 μm to 1 μm for wood smoke)\textsuperscript{140} and can penetrate deep into the alveolar region to induce adverse pulmonary effects.

Indoor air pollution studies dated back to as early as the 1960s when wood smoke exposure and chronic lung diseases were investigated in Papua and New Guinea.\textsuperscript{140–142} Since the early 1980s, there have been quite a few studies conducted to evaluate indoor exposure to biomass air pollution and the odds of increased chronic bronchitis or/and COPD, particularly in low-income countries where only lower grade energy resources are available and affordable. Table 6 summarizes 21 studies\textsuperscript{143–145,149–154,157–163} or case–control design,\textsuperscript{146–148,156} and only one study was identified as a (retrospective) cohort study;\textsuperscript{155} 2) used standard questionnaires such as questionnaires from American Thoracic Society and the British Medical Research Council with adaptations appropriate to local culture, along with or without the lung function testing to identify cases, but few studies used the GOLD standard for diagnosis; 3) assessed exposure using fuel type, stove type, poor ventilation, or time spent cooking and rarely measured actual exposure levels to particles and gases; and 4) measured the prevalence of chronic bronchitis and/or respiratory symptoms with COPD in most earlier studies or COPD only in recent studies, analyzed OR for indoor biofuel use, or conducted a crude dose–response relationship analysis using cooking time per year as a cumulative exposure measurement. Unit air concentration-based effect sizes were not available. However, a consistent relationship between indoor exposure to biomass cooking and excess risk was found from different countries. The prevalence (%) of chronic bronchitis in study villages with indoor biomass cooking varied from 1.79 in India\textsuperscript{163} to 28.5 in Turkey,\textsuperscript{153} which is overall higher than in high-income countries. The prevalence for urban control area homes, outdoor cooking practice, and cleaner fuels such as gas and electricity tended to be much lower. The prevalence of COPD varied from 2.4 in India\textsuperscript{161} to 12 in a rural community in Guangzhou, People’s Republic of China.\textsuperscript{158} The significantly increased OR for biomass cooking ranged from 1.86 (95% CI 1.16–2.99) in Brazil\textsuperscript{145} to 28.7 (95% CI 8.7–95.9) in Turkey\textsuperscript{152} for chronic bronchitis, 1.2 (95% CI 0.4–4.2) in India\textsuperscript{141} to 15.0 (95% CI 5.6–40.0) in Mexico\textsuperscript{148} for COPD, 9.7 (95% CI 3.7–27.0) overall to 75 (95% CI 18–306) when cooking was >200 hour-years in Mexico\textsuperscript{146} for chronic bronchitis and COPD combined, and 2.3 (95% CI 1.2–4.4) to 2.9 (95% CI 1.7–5.1) for various respiratory symptoms.\textsuperscript{161} It was reported that if cumulative exposure is >60 hour-years, the OR for chronic bronchitis is significantly increased.\textsuperscript{163} Reported attributable portion of risk was 23.1%.\textsuperscript{153} These results indicated that overall, evidence supporting an association between biomass smoke exposure and COPD in adult females in rural areas is fairly robust.\textsuperscript{164}

Impact of current air quality guidelines on COPD sufferers

Epidemiologic studies worldwide have provided strong evidence to link air pollution, especially particulate air pollution to the mortality, morbidity, and socioeconomic burden of cardiorespiratory disease in general and COPD in particular. This has prompted the legislation around the world to continuously modify the air quality standards or guidelines to reduce the disease burden over time such as in the US.\textsuperscript{49,165} WHO provides the basis for global standards in environmental quality and effective investments for public health.\textsuperscript{166} WHO published its air quality guidelines in 1987 and revised them in 1997. Based on the research developments thereafter, they updated the guidelines for PM, O\textsubscript{3}, NO\textsubscript{x}, and SO\textsubscript{2} in 2005.\textsuperscript{166} The values in the WHO guidelines are much lower than in the US NAAQS.\textsuperscript{167,168} We focused this part of the review on studies conducted in the last 10 years to specifically evaluate if the current air quality guidelines are protective of COPD sufferers.

A prospective cohort study\textsuperscript{119} in Copenhagen, Denmark, with 57,053 participants assessed the effect of exposure to traffic air pollution (NO\textsubscript{x} and nitrogen oxides [NO\textsubscript{x}]) over 35 years on the incidence of COPD. The modeled 35-year mean of outdoor NO\textsubscript{x} level was 17.0 μg/m\textsuperscript{3} or 9 ppb for the total population and 18.1 μg/m\textsuperscript{3} or 9.6 ppb for COPD patients. These levels were well below the current NAAQS NO\textsubscript{x} standard of 53 ppb for annual mean. The study found that COPD incidence was associated with the 35-year mean NO\textsubscript{x} level (hazard ratio 1.08; 95% CI 1.02–1.14, per IQR
5.8 µg/m³ or 3.1 ppb), with stronger associations in subjects with diabetes (hazard ratio 1.29; 95% CI 1.05–1.50) and asthma (hazard ratio 1.19; 95% CI 1.03–1.38). Another cohort study followed up all residents in Oslo, Norway, aged 51–90 years from 1992 to 1998 to evaluate the mortality of COPD. The elevated risk was found at NO₂ levels >40 µg/m³ in the youngest age group and with a linear effect in the interval 20–60 µg/m³ for the oldest. The effects were particularly strong for COPD, which appeared to have linear effects. The levels (µg/m³) in this study were 39 for NO₂ (or 20.7 ppb) and 15 for PM₁₀, again well below the current NAAQS standard (24 hour mean =35 µg/m³ for PM₁₀). A recent mortality study enrolled 145,681 COPD patients aged 35 years or older from the residents of Rome with a comparison group of 1,710,557 subjects without COPD. The annual average daily concentrations were 36.4 µg/m³ for PM₂.₅ and 20.2 µg/m³ for PM₁₀, both below the limits recommended by European Union (EU) legislation (40 µg/m³ and 25 µg/m³, respectively). The annual average concentration of NO₂ (60 µg/m³) was higher than the EU limit (40 µg/m³), and the 8-hour running mean concentration of O₃ was <100 µg/m³. It was found that PM₁₀, PM₂.₅, and NO₂ (0- to 5 day lag) were associated with daily mortality with stronger effects in people with COPD. The mortality associated with PM₁₀ (per IQR 16 µg/m³) was five times more in COPD patients (3.5%, 95% CI −0.1%–7.2%) than in other subjects (0.7%, 95% CI −0.8%–2.2%). The effects on respiratory mortality among COPD subjects were particularly elevated for PM₂.₅ (IQR 11 µg/m³; 11.6%, 95% CI 2.0%–22.2%) and NO₂ (IQR 24 µg/m³; 19.6%, 95% CI 3.5%–38.2%). In Vancouver, Canada, a population-based study with 467,994 residents aged 45–85 years without COPD had a 5-year exposure period and a 4-year follow-up period. The 5-year average concentrations were 4.10 µg/m³ for PM₂.₅ and 32.2 µg/m³ (or 17 ppb) for NO₂. In unadjusted single-pollutant models, PM₂.₅, NO₂, and NO were associated with COPD hospitalization and mortality, although after adjustment for covariates, these air pollutants were not significantly associated with COPD hospitalization and mortality. As described earlier, Schikowski et al showed that chronic exposure to PM₁₀, NO₂, and living near a major road might increase the risk of developing COPD. The annual mean level was 39 µg/m³ (or 20.7 ppb) for NO₂ and 44 µg/m³ for PM₁₀ (Table 4). In a New Zealand study with COPD patients (Table 5), SO₂ and NO₂ and most PM₁₀ concentrations were well below their air quality guidelines, but increased risk of chest symptoms for PM₁₀ in the night time and increased use of an inhaler and nebulizer for NO₂ were observed.

Sulzbach commented that epidemiological studies have shown that sensitive populations are prone to exacerbated health effects even when the air quality measurements are within the EPA standards. Specifically, Sulzbach investigated Minnesota to determine the constituents of the air pollution and measure the level of air pollution in the Twin Cities. The result of the study showed that Minnesota was one of eleven states that met federal air quality health standards at the time. However, there were still a significant number of days when the air quality could trigger health problems in sensitive populations. Bell et al estimated a national average relative rate of mortality associated with short-term exposure to ambient O₃ for 95 large US urban communities from 1987 to 2000. They found that a 10 ppb increase in the previous week’s O₃ was associated with a 0.52% increase in daily mortality (95% posterior interval [PI], 0.27%–0.77%) and a 0.64% increase in cardiovascular and respiratory mortalities (95% PI, 0.31%–0.98%). They indicated that even though the US EPA’s 8-hour regulation was met every day in each community, there was still a 0.30% increase in mortality per 10 ppb increase in the average of the same and previous days’ O₃ levels (95% PI, 0.15%–0.45%). Therefore, they suggested that interventions to further reduce O₃ pollution levels should be implemented so as to benefit public health, even in regions that meet current regulatory standards and guidelines.

The WHO advised that due to the lack of thresholds of air pollutants at which adverse health effects occur, the guidelines proposed cannot fully protect human health. It should be noted that there were also some studies that do not support the associations between outdoor and indoor air pollution and the burden on COPD sufferers. For example, Schikowski et al used data from four cohort studies (10,242 subjects) participating in the European Study of Cohorts for Air Pollution Effects. The mean exposures varied from 9.5 µg/m³ to 17.8 µg/m³ for PM₁₀, 15.7 µg/m³ to 26.7 µg/m³ for PM₁₀ and 22.4 µg/m³ to 28.9 µg/m³ for NO₂ among the cohorts. No association was found between NO₂ and PM₁₀ and COPD in individual cohorts. The meta-analysis with all the cohorts only found a nonsignificant association between NO₂, NO₄, PM₁₀, and the traffic indicators and COPD, although a significant association was observed in females (1.57; 1.11–2.23 for prevalence and 1.79; 1.21–2.68 for incidence). Pujades-Rodriguez et al analyzed data from 2,644 adults aged 18–70 in Nottingham, UK, and found no significant cross-sectional associations between home proximity to the roadside or NO₂ levels and COPD or lung function measurements. Similarly, a prospective cohort study...
in Greece with 3,046 subjects found no association between air pollution and the development of COPD.\textsuperscript{176}

Although further research is needed to better assess the relationship, the majority of the literature has indicated that the impact on COPD suffers, including morbidity and mortality, due to air pollution is still detectable under the current air quality guidelines.

**Discussion**

Implications for future policy and decision-making

To reduce the impact of outdoor/indoor air pollution on COPD sufferers, a range of strategies and approaches need to be sought, which are summarized in the following categories based on this literature review.

**Amendment to further lower current standards and guidelines**

To evaluate whether improved air quality standards reduce the adverse health effects, the Harvard six cities study extended mortality follow-up for 8 years in a period of reduced air pollution concentrations.\textsuperscript{177} They focused on the PM\textsubscript{2.5} concentrations, which were measured between 1979 and 1988 and estimated for later years from publicly available data. It was found that an increase in overall mortality was associated with each 10 µg/m\textsuperscript{3} increase in PM\textsubscript{2.5}, modeled either as the overall mean (rate ratio 1.16; 95% CI 1.07–1.26) or as exposure in the year of death (rate ratio 1.14; 95% CI 1.06–1.22). Improved overall mortality was associated with a decreased mean PM\textsubscript{2.5} (10 µg/m\textsuperscript{3}) between periods (rate ratio 0.73; 95% CI 0.57–0.95).\textsuperscript{177} This suggests that the mortality effects of long-term air pollution may be at least partially reversible.\textsuperscript{69} Pope et al found that a decrease of 10 µg/m\textsuperscript{3} in the concentration of fine PM was associated with an estimated increase in mean (± standard error) life expectancy of 0.61±0.20 years (P=0.004). Reductions in air pollution accounted for as much as 15% of the overall increase in life expectancy in the study areas.\textsuperscript{178}

This indicates that it is beneficial to further tighten the current air quality guidelines around the world to reduce exposure levels and the effects on the general population and COPD sufferers.

**Interventions to reduce sources of outdoor air pollution**

The study conducted by Dockery et al\textsuperscript{179} in the Republic of Ireland well illustrated that reducing the air pollution from the source might be the most effective way to improve the air quality. In Ireland, domestic coal burning was a major source of repeated severe pollution episodes. The government introduced sequential bans in 1990, 1995, and 1998 on the marketing, sale, and distribution of coal in different cities. The authors compiled records of daily black smoke, total gaseous acidity (SO\textsubscript{x}), and counts of cause-specific deaths from 1981 to 2004 for several cities and counties. They also compiled daily counts of hospital admissions for cardiovascular, respiratory, and digestive diagnoses. They compared the results with counties not affected by the bans. The mean black smoke concentrations fell in all affected population centers post-ban compared with the preban period, with decreases ranging from 4 µg/m\textsuperscript{3} to 35 µg/m\textsuperscript{3} (corresponding to reductions of 45% to 70%, respectively). Respiratory mortality was reduced in association with the bans in 1990, 1995, and 1998 (17%, 9%, and 3%, respectively). A 4% decrease in hospital admissions for cardiovascular disease associated with the 1995 ban and a 3% decrease with the 1998 ban were found, and admissions for pneumonia, COPD, and asthma were reduced.\textsuperscript{179} Boogaard et al\textsuperscript{180} found that implementing local traffic policies including low emission zones directed at heavy duty vehicles (trucks) in five Dutch cities reduced all pollutant levels, especially PM\textsubscript{2.5} levels (20%–30%) and NO\textsubscript{x} and NO\textsubscript{y} levels (25%–41%) in various areas. A recent review indicated that overall air pollution interventions have succeeded at improving air quality and also have been associated with health benefits, mainly reduced cardiovascular and/or respiratory mortality and/or morbidity.\textsuperscript{181}

These studies suggest that exposure control at the source can more efficiently reduce the air pollution level and therefore the human exposure and adverse outcomes.

**Intervention to reduce indoor biomass air pollution in low-income countries**

Since most countries probably do not have indoor air pollution standards and indoor air environments are generally not regulated, other measures to reduce indoor exposures to air pollutants from biomass or other solid fuels need to be developed, which could include a range of methods targeting the emission source (improved cook stoves or cleaner fuels), the indoor environment (improved ventilation and better design to separate the sources from main activity rooms), and the residents’ behaviors (to avoid direct exposure to the sources and for females not to carry young children on their back during cooking as this is a tradition in some rural areas in low-income countries). A recent review focusing on the People’s Republic of China as a typical case by Zhang and Smith\textsuperscript{182} indicated that >180 million improved stoves...
with chimneys were introduced since the early 1980s. These stove programs have helped reduce the exposures. While randomized trials are difficult to do in the People’s Republic of China, natural experiments from Xuanwei County in Southwest People’s Republic of China indicated that installation of a chimney on the stove was associated with distinct reduction in the incidence of COPD.\(^\text{155}\) The RR comparing stove users with or without a chimney was 0.58 (95% CI 0.49–0.70, \(P<0.001\)) in males and 0.75 (95% CI 0.62–0.92, \(P=0.005\)) in females. A 9-year prospective cohort study was conducted among 996 participants aged 40 years or older from November 1, 2002, through November 30, 2011, in 12 villages in southern People’s Republic of China by Zhou et al.\(^\text{183}\) The intervention measures included improving kitchen ventilation (providing instruction or installing exhaust fans) and promoting the use of clean fuels (ie, biogas) instead of biomass for cooking (providing instruction and installing household biogas digesters). The study found that the combined intervention measures reduced the decline in FEV\(_1\), with a slowing rate of 16 mL/year (95% CI 9–23 mL/year). The longer the duration of the intervention measures used, the slower the decline of FEV\(_1\). The reduction in the overall risk of COPD was an OR of 0.28 (95% CI 0.11–0.73) for both intervention measures.

Intervention measures such as improved stoves, cleaner fuels, and other feasible and economical methods need to be tailored to the situation in each community based on affordability, effectiveness, and local culture so as to reduce the high exposure to biomass pollution and large COPD burden in nonsmoking females in low-income countries.

### Integrated intervention and management program for COPD sufferers

A total of 1,062 subjects with or without COPD in a study in Guangdong, People’s Republic of China, by Zhou et al.\(^\text{184}\) randomly evaluated the effectiveness of integrated interventions, which included systematic health education, intensive and individualized intervention, treatment, and rehabilitation. The annual rate of decline in FEV\(_1\) was significantly lower in the intervention community than in the control community, with an adjusted difference of 19 mL/year (95% CI 3–36) and 0.9% (0.1%–1.8%) of predicted values (all \(P<0.05\)), as well as a lower annual rate of decline in FEV\(_1\)/FVC ratio at 0.6% (0.1%–1.2%). Shofer et al.\(^\text{185}\) recommended that patients at increased risk for adverse effects of inhaled air pollutants, such as those who have been diagnosed with chronic lung disease and cardiovascular disease, including asthma, COPD, coronary artery disease, congestive heart failure, and peripheral vascular disease, should be educated regarding what symptoms may be related to poor air quality and how they can monitor the Air Quality Index to modify their activity to prevent symptoms and other adverse events. Heavy outdoor exertion should be avoided on days expected to have poor air quality or performed earlier in the day on days when outdoor activity cannot be avoided.

### Conclusion and future directions

While air quality standards and guidelines have reduced human exposure overall and exposure of COPD sufferers in particular to PM and gaseous air pollutants around the world, health effects measured as mortality and morbidity still occur with COPD patients in the form of exacerbation or lead to the increased incidence of COPD in the general population. Further improvement in current air quality guidelines seems necessary at the government level, but other policy and exposure control measures could be implemented locally or at the personal level. Continued epidemiologic research, particularly long-term prospective cohort studies involving multiple countries or cities to evaluate the effects of multiple pollutants and their interactions on the COPD burden, is needed in both high-income and low- to middle-income countries. Additionally, more intervention studies targeting reduced exposures and improved outcomes specifically for COPD sufferers are needed.

### Disclosure

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