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The Effects of Air Pollution and Temperature on COPD

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Abstract

Chronic Obstructive Pulmonary Disease (COPD) affects 12–16 million people in the United States and is the third-leading cause of death. In developed countries, smoking is the greatest risk factor for the development of COPD, but other exposures also contribute to the development and progression of the disease. Several studies suggest, though are not definitive, that outdoor air pollution exposure is linked to the prevalence and incidence of COPD. Among individuals with COPD, outdoor air pollutants are associated with loss of lung function and increased respiratory symptoms. In addition, outdoor air pollutants are also associated with COPD exacerbations and mortality. There is much less evidence for the impact of indoor air on COPD, especially in developed countries in residences without biomass exposure. The limited existing data suggests that indoor particulate matter and nitrogen dioxide concentrations are linked to increased respiratory symptoms among patients with COPD. In addition, with the projected increases in temperature and extreme weather events in the context of climate change there has been increased attention to the effects of heat exposure. Extremes of temperature—both heat and cold—have been associated with increased respiratory morbidity in COPD. Some studies also suggest that temperature may modify the effect of pollution exposure and though results are not conclusive, understanding factors that may modify susceptibility to air pollution in patients with COPD is of utmost importance.

Keywords

COPD; heat; nitrogen dioxide; ozone; particulate matter

Introduction

Chronic Obstructive Pulmonary Disease (COPD) affects 12–16 million people in the United States and is the third leading cause of death (1). The prevalence and mortality of COPD is

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expected to increase in the coming decades (2). COPD is characterized by symptoms of wheeze, shortness of breath and cough. In addition, intermittent exacerbations of disease often change the trajectory of disease course, leading to worse health related quality of life, hastened lung function decline, reduced functional capacity (3, 4) and increased risk of death (5–7). The World Health Organization (WHO) estimates that ambient air pollution is responsible for 3.7 million premature death worldwide in 2012 and 14% of these deaths were due to COPD or acute lower respiratory infections (8).

Integrated exposure-response modeling suggests that the population attributable mortality risk due to ambient air pollution for COPD varies and was estimated to range from < 1 to 21% depending on country (9). In particular, particulate matter (PM) which is a complex mixture of solid and liquid particles made up of a number of components [including acids, organic chemicals, metals and soil or dust particles]; nitrogen dioxide (NO_2), which is a gaseous product of high-temperature combustion [including emissions from automobiles, power plants and off-road equipment (10)]; and ozone (O_3) which is a strong oxidizing agent with a variety of effects including lung inflammation, alveolar epithelial damage and changes in chemical composition of lung lavage fluids (11) have been linked to COPD. In addition, there has been increased attention to the effects of heat exposure with the anticipated increases in temperature projected in the context of climate change (12–15). Extremes of temperature may affect COPD outcomes and may even modify the effects of pollutant exposure. Therefore, understanding the effects of air pollution and temperature on COPD is a crucial step to the development of preventative strategies and patient care.

Outdoor air pollution in COPD

Prevalence and incidence of COPD

Several longitudinal studies have shown that outdoor air pollution has long-term effects on lung function with higher pollution exposure leading to more rapid lung function decline in general population cohorts (16–18). This accelerated loss of lung function may contribute to the development of COPD and consistent with this literature, though studies are not definitive, results suggest that outdoor air pollution exposure is linked to COPD incidence and prevalence. For example, both PM and NO_2 have been linked to a varying degree with COPD incidence and prevalence. A recent meta-analysis showed that there was a trend towards increased prevalence of COPD, defined as chronic bronchitis or bronchitic symptoms, with higher PM exposure, but this association did not reach statistical significance (19). A study of 4,757 women investigated exposures to outdoor pollution over a 5-year look-back period and found that a 7 $\mu g/m^3$ increase in PM_{10} (PM with aerodynamic diameter less than 10 μm) and 16 $\mu g/m^3$ increase in NO_2 concentrations were associated with an increased prevalence of COPD [odds ratio (OR) of 1.33 (95% confidence interval (CI): 1.03–1.72) and 1.43 (95% CI: 1.23–1.66), respectively](20).

A large longitudinal epidemiologic study investigated annual mean levels of NO_2 over 35 years and found an increased COPD incidence associated with cumulative exposure in over 57,000 subjects (21). However, in a recent large population-based cohort study of 812,063 patients in England without an initial COPD diagnosis who were followed from 2003 to 2007 for identification of first COPD diagnoses recorded either by a general practitioner or

on admission to hospital, found inconclusive evidence for associations between air pollution and COPD incidence (22). Similarly, a meta-analysis of five cohorts found that NO_2 and PM were not significantly associated with COPD incidence or prevalence. The only statistically significant associations were seen with traffic intensity in the nearest road and COPD incidence in never smokers and in females (23).

Mortality among individuals with COPD

Higher outdoor pollution levels have been related to increased mortality in general population studies, with greater effect sizes for respiratory deaths (24–27). Mortality studies of COPD populations are limited but have yielded similar results. In particular, several studies have suggested a link between outdoor particulate concentrations and increased mortality in patients with COPD. For example, there was a significant association between PM_{10} and mortality using Medicare data of subjects discharged with a COPD diagnosis between 1985 and 1999 (27). A case-crossover analysis in Barcelona, Spain found a strong association with respiratory death in COPD subjects with increases of black smoke particles (urban particle air pollution). Specifically, for an increase of 20 $\mu g/m^3$ in black smoke particles, there was an 11% increased odds of mortality for all causes (OR = 1.112, 95%CI: 1.017, 1.215) and the association was stronger for respiratory causes (OR = 1.182, 95%CI: 1.025, 1.365) (28).

Zhu et al. conducted a meta-analysis of PM_{10} and mortality in COPD patients and found an increased odds of COPD mortality with PM_{10} exposure with a 10 $\mu g/m^3$ increase in daily PM_{10} being associated with a 1.1% (95%CI 0.8–1.4) increase risk in COPD mortality (29). Although fewer studies have investigated the effect of other ambient pollutants on COPD mortality, those that do exist, suggest that other pollutants are also associated with COPD mortality. For example, several studies suggest that higher NO_2 concentrations are linked to higher COPD mortality (30, 31) and others have shown non-statistically significant associations between NO_2 concentrations and mortality (32, 33). Overall, results suggest that people with COPD are more susceptible to air pollution and at lower levels than the general population.

COPD exacerbations

Several studies link outdoor air pollution to increased risk of COPD exacerbations. The Air Pollution and Health, a European Approach (APHEA) project analyzed data from 6 European cities and found increased risk of COPD hospital admissions with several air pollutants, including NO_2, O_3, sulfur dioxide (SO_2) and black smoke (34). A study of PM_{10} and hospital admissions for COPD found a 2.5% increase in admissions for every 10 $\mu g/m^3$ increase in PM_{10} (35). In addition, a meta-analysis of 18 studies of PM_{10} and exacerbations found a 10 $\mu g/m^3$ increase in daily PM_{10} was associated with a 2.7% increase in COPD hospitalizations (29). The data linking air pollution with COPD exacerbations for O_3 is also convincing as higher O_3 concentrations have been shown to increase hospital and emergency department visits for lower respiratory disease, including COPD (36–38).

A recent meta-analysis of the association between short-term exposure to ambient O_3 and respiratory hospital admissions revealed a 1.9% increase in emergency hospitalizations for respiratory diseases per 10 ppb of 24-hour mean O_3 and a 5.06% increase in COPD-related emergency hospital admissions per 10 ppb of 24-hour mean O_3 (35). Two decades ago, 69.7 million people were estimated to have O_3 exposure levels above the National Ambient Air Quality Standards (11) and ambient O_3 levels are expected to continue to increase in the upcoming decades (39). Therefore understanding the contribution of O_3 and other outdoor pollutants to COPD morbidity should continue to be a high priority.

Lung function and respiratory symptoms among individuals with COPD

Long-term exposure to outdoor air pollution has also been linked to lung function decline and short-term changes in outdoor air pollutant concentrations have been associated with acute changes in lung function and increased respiratory symptoms among individuals with established COPD. For example, a recent study has shown that $PM_{2.5}$ and O_3 exposures were associated with FEV_1 decline among 1,218 subjects with severe COPD enrolled in the National Emphysema Treatment Trial (NETT) followed for an average of 29.2 months (40). Similarly, among 401 individuals with COPD and α-1-antitrypsin deficiency, a 10 $\mu g/m^3$ increase in PM_{10} was associated with an additional 30 cc/year (95% CI: 2–60 cc/year) decline in FEV_1 (41).

There have also been several studies that have linked acute outdoor air pollution exposure to short term decrements in lung function and increased respiratory symptoms (42–45). For example, Peacock et al. recruited 94 COPD subjects who filled out daily symptom diaries. PM_{10} was significantly associated with dyspnea and symptomatic decreases in peak expiratory flow (PEF), defined as a fall in PEF for at least 2 days plus a reported increase in dyspnea. An interquartile range (IQR) increase in PM_{10} was linked to an approximately 13% increase in odds of symptomatic decreases in PEF and a similar increase in odds of dyspnea (46). In addition, in another study of 40 subjects with COPD, daily increases in PM_{10} concentrations were associated with night time chest symptoms and increases in NO_2 concentrations were associated with increased rescue medication use (43).

Several studies have sought to elucidate the pollutant-induced inflammatory response. These studies may shed light on the underlying pathway by which pollutant exposure is responsible for increased COPD morbidity. For example, PM, NO_2 and O_3 exposure have all been shown to trigger an inflammatory response, including in vitro and in vivo increases in IL-8 concentrations (47–49). IL-8 is a potent neutrophil chemoattractant (50), and neutrophil elastase is a powerful stimulant of mucin production (51). Increased systemic and sputum IL-8 concentrations have been associated with COPD exacerbations (52, 53). Air pollution exposure has also been linked to other markers of inflammation, which are related to outcomes in COPD. For example, Dadvand et al. found that increased exposure to ambient NO_2 resulted in an 8–12% increase in systemic levels of IL-8, as well as a 51% and 10% increase in C-reactive protein and fibrinogen, two other systemic COPD biomarkers (53). Similarly, air pollution exposure has been linked to increased markers of airway oxidative stress (54, 55). It is imperative that we continue to increase our understanding of the effects of air pollution on COPD morbidity.

Indoor air pollution and COPD

Although substantial evidence shows that outdoor air pollutants impact COPD development and morbidity, there is much less evidence for the impact of indoor air on COPD, especially in developed countries. Evidence from international studies in developing countries and several U.S. studies show that high concentrations of air pollution from indoor burning of biomass fuels cause and exacerbate existing COPD (56, 57). As a matter of fact, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) document identifies indoor air pollution resulting from burning wood and other biomass fuels, as a major risk factor for COPD (58).

However, exposures under these conditions are two to three orders of magnitude higher than in developed country households. Indoor air quality, even at low pollutant levels, may be important for individuals with COPD as they spend more time at home than their age-matched counterparts: approximately 82% of their time is spent indoors in their own home (59). Despite the likely importance of indoor air quality, studies focusing on indoor air quality in developed countries have been limited, but is the focus of this current review, given the recent literature reviews summarizing the effect of biomass exposure on COPD (60).

Indoor PM

There have been studies linking secondhand smoke (SHS) exposure to the development of COPD, and among those with COPD there is evidence suggesting the SHS exposure contributes to worse quality of life, dyspnea and heightened risk for COPD exacerbation (61–63); however, much less investigation exists exploring the role of other indoor pollutants to COPD morbidity. Osman et al. showed in a cross-sectional study that indoor $PM_{2.5}$ concentrations were associated with worse quality of life in COPD patients (64). The $PM_{2.5}$ concentrations were greater in homes of current smokers and the adverse effects of $PM_{2.5}$ on quality of life were also greater among current smokers, suggesting that the adverse effects of $PM_{2.5}$ in this population may have partly been due to active and secondhand cigarette smoke exposure. Results from Hansel et al. (65) showed that $PM_{2.5}$ concentrations measured in homes in the Baltimore area were independently associated with increased rescue medication use, risk of severe exacerbations and increased respiratory symptoms, including worse dyspnea, and increased risk of nocturnal symptoms and frequent wheeze among former smokers with moderate-to-severe COPD.

A 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations was associated with 44% higher odds of having nocturnal symptoms and 38% higher odds of having a severe COPD exacerbation. These adverse health effects were seen even after adjusting for air and hair nicotine concentrations suggesting that PM has independent effects of respiratory health from SHS. In addition, the adverse health effects were seen even though average in-home PM levels were relatively low (mean indoor $PM_{2.5}$ concentrations ~ 12 $\mu g/m^3$).

Subsequent post-hoc analyses of this study, suggest that there may be subgroups of individuals with COPD that show increased susceptibility to pollutant exposure. For instance, those who also were atopic (66) or obese (67) were more likely to experience

increased respiratory symptoms upon exposure to higher PM levels. These findings of specific subgroups showing increased susceptibility to PM exposure is likely not unique to patients with COPD as obesity and other factors have been shown to modify the effect of pollutant exposure on health outcomes, in other chronic diseases, such as asthma (68).

Indoor PM has not been consistently linked to changes in lung function among individuals with established COPD (69, 70). A study including 35 subjects with COPD showed no association between indoor air quality and lung function (69) and another panel study including 17 subjects with COPD showed no consistent association between $PM_{2.5}$, $PM_{2.5–10}$ or its measured components with lung function over 12 days (70). Therefore, the adverse effects of indoor PM on respiratory symptoms and exacerbations in patients with COPD may be independent from changes in lung function or a result of changes in smaller caliber airways that is not adequately captured by the measurement of forced expiratory volume in one second (FEV_1). Alternatively, given the relatively small size of studies of indoor air pollution and COPD, they may not have been adequately powered to detect an association between pollutant exposure and lung function.

Indoor NO_2 and other pollutants

NO_2, a by-product of combustion with indoor sources including gas-burning appliances, is a common indoor pollutant and may lead to worse respiratory health through airway epithelial damage or reducing resistance to viral-induced exacerbations (71–73). A recent study suggests that NO_2 concentrations may be associated with increased risk of obstructive airway disease as assessed by spirometry, but not self-reported COPD diagnosis in elderly residents of nursing homes (74). Only few studies have investigated whether indoor NO_2 concentrations affect patients with COPD. Osman et al. found no association between indoor NO_2 concentrations and worse quality of life in subjects with COPD (64). Though Hansel et al. also did not show a significant association between NO_2 concentrations and quality of life, there was a link between indoor NO_2 concentrations in the main living area and increased dyspnea and higher rescue medication use. Furthermore, bedroom NO_2 concentrations were associated with higher risk of nocturnal symptoms and severe COPD exacerbations (65). Importantly, this adverse effect of NO_2 was independent of PM exposure.

Exposure to dust and endotoxin has been associated with decline in lung function, and risk of COPD in farming communities and occupational settings (75–78) but the role of in-home endotoxin levels in urban communities and patients with COPD is less clear. A recent study suggested that formaldehyde levels were associated with increased risk of reporting COPD in elderly nursing home residents (74), and few studies have suggested that exposure to aldehydes and volatile organic compounds (VOCs) may be linked to respiratory symptoms and lung function in the elderly (79); however, the role of aldehydes and VOCs in COPD, to our knowledge, has not been studied.

Temperature

There has been increased attention to the effects of heat exposure with the anticipated increases in temperature projected in the context of climate change (12–15). Studies of heat

exposure are often conducted in the context of heat waves, sustained periods of extreme heat that occur over consecutive days. Heat waves can have startling health consequences, as was seen during the summer of 2003 when over 70,000 deaths in Europe were attributable to extreme heat (80) and during the summer of 1995 when there were approximately 750 heat-related deaths in Chicago during only 5 days (81). Studies have consistently found that elderly individuals and those with underlying cardiac and respiratory diseases, including COPD, are at increased risk for adverse health effects of heat exposure (82–86). For example, a study across 12 U.S. cities estimated that the effect of hot temperatures during summertime can increase the risk of death attributable to COPD by as much as 25% (84).

In addition to impact of temperature on mortality, studies have demonstrated that heat exposure is associated with respiratory morbidity. A study in New York City found that the risk of COPD hospitalization increased by 7.6% for every 1°C increase above a threshold temperature of 29°C (87). Studies have used Medicare data to provide estimates of effect that are representative of a broader portion of the U.S. population (88, 89). In a study that included 12.5 million elderly individuals in 213 urban U.S. counties, there was a 4.7% increased risk of hospitalization for COPD for every 10 degree F increase in ambient temperature (88). Residents of more temperate climates are more likely to be adversely impacted by the effects of extreme heat exposure and access to air condition has been identified as a strong protective factor (81,84,90). The mechanisms by which heat exposure adversely impacts COPD are not entirely understood. In addition to thermoregulatory responses to heat exposure, there may be a direct effect of heat exposure on the respiratory system. Studies in asthma suggest that breathing hot humid air may result in bronchoconstriction that is mediated via cholinergic pathways (91).

The anticipated effects of climate change also include increases in temperature variability and in extreme cold weather conditions. Excessive cold temperatures have been linked to increases in mortality and morbidity among those with COPD. In a study of individuals over 65 years in Michigan, those with COPD had a 19% increased risk of dying on cold days (92). In a New Zealand study, the death rate was 18% higher in winter versus non-winter months and 31% of excess deaths were attributable to respiratory disease (93). Studies have also demonstrated an impact of cold temperatures on lung function and the risk of exacerbations among those with COPD. A large study in Taiwan using national health insurance registry data detected a 0.8% increase in COPD exacerbations for every 1°C decrease in mean daily temperature (94). In East London, cold temperatures were linked to decreases in lung function in a study of 76 participants with COPD. Investigators found that FEV_1 was 45cc less during the coldest versus warmest weeks during a 12-month period (95). In addition to bronchoconstriction and inflammation that may occur in the setting of cold exposure (96), recent evidence suggests a role for mucous hypersecretion as a potential mediator of the COPD response to cold temperature (97).

There is a potentially interactive effect of high temperatures and pollutant concentrations (98–100). Although there have been studies that have not detected evidence that increasing temperature modifies the effect of pollution exposure (101–103), several studies have detected interactive effects (104–108). Studies that have included respiratory specific outcomes have also had conflicting results. For example, studies in China and Europe

suggest an interactive effect of increases in temperature and pollution on the risk for cardiac death but not respiratory death (100, 109). A study in Brisbane, Australia did not suggest effect modification for respiratory emergency visits but demonstrated an interactive effect of increasing temperature and PM_{10} on respiratory hospitalizations (110). Further studies are needed to clarify these inconclusive findings.

Implications

A large body of literature suggests that outdoor air pollution is associated with increased respiratory symptoms as well as increased COPD exacerbations and mortality. Similarly, though studies are limited, indoor pollutant concentrations in high-income countries, despite relatively low overall pollutant burden, appear to be linked to worse respiratory morbidity in patients with COPD. This suggests that COPD patients are particularly susceptible to even low levels of exposure. In addition, extremes of temperature, including both extremes of hot and cold, have also been linked to excessive morbidity and mortality among individuals with COPD. Studies suggest that there may even be subgroups of patients with COPD that have increased susceptibility to exposure, but these susceptible subgroups need to be further elucidated. Clearly delineating the harmful impact of air quality and temperature on susceptible groups of individuals with COPD is critical to help guide both policy recommendations and individual clinical recommendations. Furthermore, defining the harmful impact of indoor air quality on COPD morbidity is of utmost importance as indoor air pollution is a highly modifiable exposure. Feasible interventions that improve in-home air quality (111–113) and optimize indoor temperature (114) may represent cost-effective and novel therapeutic arenas for a disease with limited treatment options.

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Abbreviations

CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
FEV_1	Forced expiratory volume in 1 second
NO_2	Nitrogen dioxide
O_3	Ozone
OR	Odds ratio
PM	Particulate matter
PM_{10}	Particulate matter < 10 μm diameter
$PM_{2.5}$	Particulate matter < 2.5 μm diameter
SO_2	Sulfur dioxide

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