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Air pollution and chronic obstructive pulmonary disease

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ABSTRACT

Limited data suggest that outdoor air pollution (such as ambient air pollution or traffic-related air pollution) and indoor air pollution (such as second-hand smoking and biomass fuel combustion exposure) are associated with the development of chronic obstructive pulmonary disease (COPD), but there is insufficient evidence to prove a causal relationship at this stage. It also appears that outdoor air pollution is a significant environmental trigger for acute exacerbation of COPD, leading to increasing symptoms, emergency department visits, hospital admissions and even mortality. Improving ambient air pollution and decreasing indoor biomass combustion exposure by improving home ventilation are effective measures that may substantially improve the health of the general public.

Key words: air pollution, chronic obstructive pulmonary disease, development, exacerbation.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is an important disease worldwide in both high-income and low-income countries.[1–3] By the year 2020, it has been estimated that COPD will rank fifth among the conditions with a high burden to society and third among the most important causes of death for both genders worldwide.[4] The economic burden of COPD on the society is enormous.[5] It is thus important to understand the environmental factors that are contributing to this great burden. Air pollution is closely related to both the development and exacerbation of COPD. In this review, we will discuss the impact of both outdoor and indoor air pollution on the development and exacerbation of symptoms of COPD.

AIR POLLUTION AND DEVELOPMENT OF COPD

Cigarette smoking is currently considered as the most important cause of COPD. However, cigarette smoking is not the sole cause for COPD. A recent study has shown that the population-attributable fraction for smoking as a cause of COPD ranged from 9.7% to 97.9%.[6] The majority of population-attributable fraction estimates are less than 80%. In a Swedish cohort study with a 7-year follow-up ($n = 963$)[7] involving subjects with objective lung function assessment for the diagnosis of COPD, a population-attributable fraction of 76.2% was found for smoking as a cause of COPD, whereas another cohort with 25-year follow-up in Denmark ($n = 8045$)[8] reported a population-attributable fraction of 74.6%. Like many other diseases, the development of COPD is multifactorial. Among the genetic factors, there is a strong evidence supporting α1-antitrypsin deficiency as a cause. Concerning the environmental factors, prolonged exposure to noxious particles and gases is related to the development of COPD.[9] A recent study has suggested that factors such as airway hyperresponsiveness, a family history of asthma and respiratory infections in childhood are important determinants of COPD.[10] Traffic and other outdoor pollution, second-hand smoke and biomass smoke exposure are associated with COPD. However, there are currently insufficient criteria for a causation relationship.[6]

Outdoor air pollution

Exposure to some degree of outdoor air pollution is unavoidable during the entire life span, as breathing

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is essential for survival. In urban areas, outdoor air pollution is a major public health problem largely due to emissions of air pollutants from both motor vehicles and industrial plants. The degree of exposure to outdoor air pollutants however is variable over time primarily due to changes in pollutant emissions and weather conditions.[6] There is evidence supporting that outdoor pollution and traffic-related air pollution have an adverse effect on lung development in children aged 10–18 years.[11,12] The effect of outdoor air pollution on the lung function of adults is less clear, and there appears to have a gender difference.[13] In a major community-based cohort study of the effects of traffic exposure and pulmonary function involving 15 792 middle-aged men and women in the USA, it was found that higher traffic density was significantly associated with lower forced expiratory volume in 1 s and forced vital capacity in women. Traffic density or distance to major roads did not appear to have any adverse effect on lung function in men. In addition, the forced expiratory volume in 1 s/forced vital capacity ratio was not significantly associated with traffic exposure in either men or women.[13] In adults, traffic-related air pollution was associated with the development of adult-onset asthma among never-smokers.[14] It remains unclear whether air pollution may lead to a decline in lung function and subsequent development of COPD.

Few studies have reported the relationship between outdoor air pollutants and objectively defined COPD.[15–17] For example, in a consecutive cross sectional study conducted between 1985 and 1994, involving 4757 women living in the Rhine-Ruhr Basin of Germany, it was found that the prevalence of COPD (Global Initiative for Chronic Obstructive Lung Disease stages 1–4) was 4.5%, whereas COPD and pulmonary function were the strongest affected by particulates with an aerodynamic diameter <10 μm (PM10) and traffic-related exposure. A 7 $\mu g/m^3$ increase in 5-year means of PM10 (interquartile range) was associated with an odds ratio of 1.33 (95% confidence interval (CI): 1.03–1.72) for COPD. For women living less than 100 m from a busy road, COPD was 1.79 times more likely (95% CI: 1.06–3.02) than for those living farther away.[15] A subsequent follow-up study with lung function assessment in a subgroup of 402 women in 2008–2009 found a decrease in prevalence of COPD that was associated with improving air quality with decreasing PM10 level.[16] On the contrary, a study from Nottingham, UK involving a cohort of 2644 adults aged 18–70 years found no significant cross-sectional associations between living in close proximity to traffic or nitrogen dioxide (NO_2) level, and greater decline in forced expiratory volume in 1 s over time, and spirometry confirmed COPD.[17] Another study involving 57 053 participants in the Danish Diet, Cancer and Health cohort reported a positive association between subjects with the first admission for COPD in 1993–2006 and traffic-related air pollution exposure. COPD incidence was associated with the 35-year mean NO_2 level (hazard ratio 1.08, 95% CI: 1.02–1.14, per interquartile range of 5.8 mg/m^3).[18] Despite the fact that the authors have included a very long duration of air-pollutant concentration assessment, a 35-year accumulated exposure to traffic-related air pollution at home address, this study was limited by the lack of objective spirometric measurement for the diagnosis of COPD. Because there are few studies that have confirmed COPD by spirometry and the published data are conflicting, a causal relationship between outdoor air pollution and COPD cannot be drawn at this stage.

Previous studies have shown that air pollutants have harmful effects on the airway. Particulate pollutants, ozone (O_3) and NO_2 can all produce deleterious effects on the airway, such as increases in bronchial reactivity,[19] airway oxidative stress,[20] pulmonary and systemic inflammation,[21,22] amplification of viral infections,[23] and reduction in airway ciliary activity.[24] There is thus evidence of biological plausibility that air pollutants can cause damage in the lungs. Currently, there is insufficient evidence available to attribute outdoor air pollution as the causative factor for COPD due to the lack of long-term study with spirometric measurement. It would be ideal to follow up subjects from birth to over 60 years of age with serial assessment of their exposure to outdoor air pollutants in relation to their lung function. Analysis of the data from such studies would be expected to be very complex, as it would involve taking into account their indoor air-pollutant exposures, occupations and personal smoking history.

Indoor air pollution

Common indoor air pollutants consist of environmental tobacco smoke, particulate matter, NO_2, carbon monoxide (CO), volatile organic compounds and biological allergens. Environmental tobacco smoke and biomass exposure are the major indoor air pollutants that are related to the development of COPD. There is, however, insufficient evidence for drawing a causal relationship at present.[6]

Environmental tobacco smoke exposure has been recognized as a risk factor for lung cancer,[25] chronic respiratory symptoms[26] and low pulmonary function.[27] Some studies have suggested that second-hand smoking exposure is associated with development of COPD. For example, a cross-sectional study in China involving 15 379 never-smokers aged over 50 years (6497 with valid spirometry) has found an association between risk of COPD and self-reported exposure to passive smoking at home and work (adjusted odds ratio 1.48, 95% CI: 1.18–1.85 for high level exposure; equivalent to 40 h a week for more than 5 years).[28] Another cross-sectional study in the USA involving 2113 adults aged 55–75 years showed an association between second-hand smoking exposure and a self-reported physician diagnosis of chronic bronchitis, emphysema or COPD (odds ratio 1.36; 95% CI: 1.002–1.84).[29] The Adventist Health Study of Smog, which was a 15-year follow-up study in California, USA, has shown that self-reported environmental tobacco smoke exposure is a significant risk factor for spirometric defined airway obstruction in mul-

tiple logistic regression (relative risk 1.44, 95% CI: 1.02–2.01) in over 1300 subjects.[26] There is however not enough evidence to implicate second-hand smoking exposure as a cause of development of COPD on its own.

It has been estimated that around 50% of the world's population (about 2.4 billion people) uses biomass fuel as the primary energy source for domestic cooking, heating and lighting.[30] Burning of biomass, which usually involves wood, crop residues, and animal dung for cooking and heating, emits a variety of toxins due to their low-combustion efficiency. In rural areas of the developing countries, biomass fuel burning is often carried out in indoor environment, with open fire using poorly functioning stoves with limited ventilation facilities. Concerning the harmful effects of biomass exposure, women are affected to a greater extent than men, as they spend more time cooking and staying indoor. It has been suggested that women with domestic exposure to biomass fuel combustion may develop COPD with clinical characteristics, impaired quality of life and increased mortality similar in extent to those of the tobacco smokers.[31] A recent meta-analysis has shown that solid biomass fuel exposure was associated with COPD in rural women (odds ratio 2.40, 95% CI: 1.47–3.93). In this study, women were at least 2.4 times more at risk of developing COPD when exposed to biomass fuel smoke compared with other fuels. In addition, women were 1.5 times more at risk of developing chronic bronchitis if they did not smoke and almost twice more at risk if they smoked.[32] In the meta-analysis, there were totally six studies[33–38] that involved the assessment of the relationship between COPD and biomass fuel exposure, but not all studies confirmed COPD with spirometry.

Inhalation of both second-hand smoke and biomass fuel smoke exposure are harmful to the body. Among the more than 7000 chemicals that have been identified in second-hand tobacco smoke, at least 250 are known to be harmful. Particulate matter concentrations in poorly ventilated kitchens burning biomass fuel can reach very high levels, with average) values in the range of milligrams per cubic metre and peak levels reaching 10–30 mg/m^3.[39] These levels greatly exceed most governmental standards for outdoor air. It appears that the airway damage resulting from biomass exposure is different from that of cigarette smoking, the known major risk factor for COPD. A study of women with COPD confirmed by autopsy lung pathology found that smokers with COPD had more emphysema and goblet cell metaplasia than women exposed to biomass smoke. On the other hand, women exposed to biomass smoke had more local scarring and pigment deposition in the lung parenchyma, and more fibrosis in the small airway wall.[40] The reason for this observation is not clear. Although there seems to be some linkage between biomass fuel exposure and COPD in women, there are currently not enough longitudinal studies with serial lung function assessment to establish a causative role of biomass fuel exposure for the development of COPD.

AIR POLLUTION AND ACUTE EXACERBATION OF COPD

Previous studies have demonstrated some associations between outdoor air pollution and increasing symptoms, acute exacerbations, hospital admissions and even mortality in patients with pre-existing COPD. Most of the studies have focused on hospital admissions for acute exacerbations.

Large-scale studies in the USA and Europe have observed a significant association between outdoor air pollution and COPD admissions. For example, in a study of hospital admissions related to heart and lung diseases in 10 cities in the USA with a combined population of 1 843 000 individuals older than 65 years, using a model that considered simultaneously the effects of PM10 up to lags of 5 days, it was observed that there was a 2.5% (95% CI: 1.8–3.3) increase in COPD admissions for a 10 ug/m^3 increase in PM10.[41] Another American study, based on the National Morbidity, Mortality and Air Pollution Study statistical model, found that 10 μg/m^3 increase in PM2.5 occurring at lag 0 and 1 day was associated with a risk of about 0.9% for COPD hospitalizations.[42] A major multicity ($n = 36$) study in the USA, with a study duration from 1986 to 1999, found that during the warm season, a 2-day cumulative effect of a 5-parts per billion (ppb) increase in O_3 was associated with 0.27% (95% CI: 0.08–0.47) increase in admissions for acute exacerbation of COPD (AECOPD). Similar effect was observed for another air-pollutant PM10 in which during the warm season, a 10 ug/m^3 increase in PM10 was associated with 1.47% (95% CI: 0.93–2.01) increase in AECOPD at lag 1 day.[43]

The Air Pollution on Health: a European Approach 2 Study was a large-scale study in Europe that assessed hospital admissions in eight European cities with a population of 38 million from the early to mid-1990s. A study by Anderson *et al*. as part of the Air Pollution on Health: a European Approach project assessed the data on admissions for COPD in six cities (Amsterdam, Barcelona, London, Milan, Paris and Rotterdam). In this study, the relative risk (95% CI) for a 50 μg/m3 increase in daily mean level of SO_2, black smoke, total suspended particulates, NO_2 and O_3 for AECOPD admissions were 1.02 (0.98–1.06), 1.04 (1.01–1.06), 1.02 (1.00–1.05), 1.02 (1.00–1.05) and 1.04 (1.02–1.07), respectively at lagged 1–3 days for all ages.[44] A study in Rome, Italy noted that CO and the photochemical pollutants of NO_2 and O_3 were determinants for acute respiratory conditions. It was noted that for all ages, the same day level of CO (at interquartile range of 1.5 mg/m3) was associated with 4.3% (95% CI: 1.6–7.1) increase in COPD admissions, and the effect of CO has been confirmed in multipollutant models.[45] A recent study from a rural county of England, where the pollutant concentration is lower than that in the urban area, found that increases in ambient CO, NO, NO_2 and NOx concentrations were associated with increases in hospital admissions for AECOPD, similar in extent to that in the urban areas.[46] Some studies have the limitation that the effect of air-pollutant asthma and COPD admissions were

grouped together instead of analysing separately, making it difficult to estimate the effect on COPD admissions.[47–50]

In Asia, the Health Effects Institute in the Public Health and Air Pollution in Asia program surveyed the available published literature on air pollution and published a web-based summary report in both 2004 and 2010.[51] The latest report in 2010 described the scope of the Asian literature on the health effects of outdoor air pollution, enumerating and classifying more than 400 studies. In addition, the report has included a systematic and quantitative assessment of 82 time-series studies of daily mortality and hospital admissions for cardiovascular and respiratory disease. It was observed that all-cause mortality was associated with increase in ambient PM10, total suspended particles and SO_2 levels. In addition, respiratory admissions were associated with NO_2 and SO_2 levels. However, COPD admissions or mortality were not separately addressed in this study. A single-city study in Hong Kong focused specifically on the effect of air pollutants on hospital admissions due to AECOPD from 2000 to 2004 and included 119 225 admissions for AECOPD. The study observed that the relative risk of hospital admissions for every 10 $\mu g/m^3$ increase in SO_2, NO_2, O_3, PM10 and PM2.5 were 1.007, 1.026, 1.034, 1.024 and 1.031, respectively, at a lag day ranging from lag 0 to cumulative lag 0–5.[52]

Few studies have been conducted on the association between air pollution and emergency department visits specific for COPD, with conflicting results. A study that assessed the association between daily emergency room admissions for COPD in Barcelona, Spain during 1985–1986 found that AECOPD emergency admissions increased by 0.02 and 0.01 for each μg of SO_2 and black smoke per cubic metre, respectively, and 0.11 for each milligram of CO per cubic metre, after adjusting for meteorological and temporal variables.[53] A time-series study from the city of São Paulo in Brazil with 1769 COPD patients found that PM10 and SO_2 readings showed both acute and lagged effects on COPD emergency department visits. interquartile range increases in their concentration (28.3 mg/m3 and 7.8 mg/m3, respectively) were associated with a cumulative 6-day increase of 19% and 16% in COPD admissions, respectively.[54] On the contrary, a time-series analysis conducted on nearly 400 000 emergency department visits to 14 hospitals in seven Canadian cities during the 1990s and early 2000s did not find a positive association of increasing level of pollutants and AECOPD emergency room attendance. An increase in each 18.4 ppb level of O_3 was associated with emergency room visits for asthma 3.2% (95% CI: 0.3–6.2%) but not COPD 3.7% (95% CI: –0.5–7.9%) with a lag of 2 days.[55]

Little is known about air pollution and general practitioner consultations related to AECOPD. It was observed that an increase in air-pollutant levels was associated with increase in daily general practitioner consultations for asthma and other lower respiratory diseases. However, the effect of air pollutants on general practitioner consultations specific for AECOPD is unknown.[56] Recently, there are data on how pollutants are associated with AECOPD with increase in symptoms but without the need for medical attention. A panel study in London, UK involving 94 COPD patients (who were asked to complete diary cards recording their symptoms and lung function), with a median follow-up of 518 days, has found significant associations between respiratory symptoms, but not lung function, and raised levels of PM10, NO_2 and black smoke.[57]

There are studies showing that air pollution is associated with COPD mortality. An example is a study that assessed the effects of ambient particles on the mortality among persons ≥65 years from 29 European cities within the framework of the Air Pollution on Health: a European Approach 2 project. It was observed that a 10 $\mu g/m^3$ increase in PM10 and black smoke was associated with a daily number of deaths of 0.8% (95% CI: 0.7–0.9) and 0.6% (95% CI: 0.5–0.8%), respectively.[58] Among the ambient air pollutants, particulate matter pollution as opposed to gases such as PM10, NO_2 and O_3 appears to have the strongest association with increased mortality of COPD.[59]

It should be noted that the evidence of the effect of air pollutants on AECOPD is based mainly on association (like time-series studies) and the direct cause and effect relationship cannot be established. In fact, the causal interpretation of reported associations between daily air pollution and daily admissions requires consideration of residual confounding, correlation between pollutants, and effect modification.[60] In recent years, as the concentration of SO_2 has decreased strikingly, mainly due to cleaner fuels for motor vehicles. Attention on the health effect of air pollutants has now shifted to O_3, NO_2 and PM. Some examples of the effect of air pollution on COPD admissions in the US, Europe and Asia are presented in Table 1.

Pollutant exposure with resulting AECOPD is likely secondary to the harmful effects of pollutants on the respiratory epithelium. For example, studies in healthy human adults found that exposure to elevated concentrations of O_3 increased cellular and biochemical inflammatory changes in the lungs.[61] The gaseous pollutants of O_3 and NO_2, and the particulate pollutants like PM10 are highly reactive oxidants and can cause inflammation of the respiratory epithelium at high concentrations.[62–64] Oxidative stress-induced DNA damage also appears to be an important mechanism of action in urban particulate air pollution. Previous studies have noted that in both outdoor and indoor environment, guanine oxidation in DNA correlated with exposure to PM2.5 and ultrafine particles.[65] SO_2 is very soluble in the upper respiratory tract and thus may produce an immediate irritant effect on the respiratory mucosa that would account for the fact that no lag days were observed for SO_2.[52,66] There is also evidence that low levels of CO increase oxidative stress with competition for intracellular binding sites. This would increase the steady state levels of nitric oxide and allow generation of peroxynitrite by endothelium.[67] There is thus biological plausibility that exposure to increasing concentration of pollutants can lead to more inflammation in the airway of patients with pre-existing COPD. Although it seems very likely that AECOPD is related to increas-

Table 1 Some examples of the association between outdoor pollutants and acute exacerbation of chronic obstructive pulmonary disease admissions

Pollutants	Author/groups	Increase in concentration of pollutants	RR (%)	95% CI	Lag (days)	Remarks
NO_2	APHEA (Anderson *et al.*[44])	50 μg/m^3	1.02	1.00–1.05†	Lag 1–3	—
	HK (Ko *et al.*[52])	10 μg/m^3	1.03	1.02–1.03†	Lag 0–3	—
O_3	US multicity (Medina-Ramon *et al.*[43])	5 ppb	0.27	0.08–0.47†	Lag 0–1	Warm season only
	APHEA (Anderson *et al.*[44])	50 μg/m^3	1.04	1.02–1.07†	Lag 1–3	—
	HK (Ko *et al.*[52])	10 μg/m^3	1.04	1.03–1.04†	Lag 0–5	—
PM10	US multicity (Medina-Ramon *et al.*[43])	10 μg/m^3	1.47	0.93–2.01†	Lag 1	Warm season only
	US multicity (Zanobetti *et al.*[41])	10 μg/m^3	2.5	1.8–3.3†	Lag 0–5	—
	HK (Ko *et al.*[52])	10 μg/m^3	1.02	1.02–1.03†	Lag 0–5	—
PM2.5	NMMAPS (Dominici *et al.*[42])	10 μg/m^3	~0.9	~0.2–1.9‡	Lag 1	—
	HK (Ko *et al.*[52])	10 μg/m^3	1.03	1.03–1.04†	Lag 0–5	—
SO_2	APHEA (Anderson *et al.*[44])	50 μg/m^3	1.02	0.98–1.06†	Lag 1–3	—
	HK (Ko *et al.*[52])	10 μg/m^3	1.01	1.00–1.01†	Lag 0	—
TSP	APHEA (Anderson *et al.*[44])	50 μg/m^3	1.02	1.00–1.05†	Lag 1–3	—

†95% CI; ‡range.

APHEA2, The Air Pollution on Health: a European Approach 2; HK, Hong Kong; NMMAPS, National Morbidity, Mortality and Air Pollution Study; PM, particulate matter; ppb, parts per billion; RR, relative risk; TSP, total suspended particulates; —, not specified.

ing ambient air-pollutant levels based on the time-series studies, evidence for causal relation is lacking at this stage.

Indoor air pollution

There are limited data on the effect of indoor air pollution in aggravating the symptoms of subjects with pre-existing COPD when compared with the relationship of indoor air pollution and development of COPD. In a recent study of a cohort of 809 COPD patients in the USA, exposure to second-hand smoke was associated with poorer disease-specific health-related quality of life and less distance walked during the 6MWD. Furthermore, second-hand smoke exposure was related to increased risk of emergency department visits and a greater risk of hospital-based care for COPD.[68] There is no information on the effect of biomass exposure on the symptoms or exacerbations of subjects with pre-existing COPD.

INTERVENTIONS FOR IMPROVING AIR POLLUTION

There are data showing that improving air quality can lead to benefits on lung health. Interventions such as ban of coal sales in Dublin and restrictions on sulphur content of fuel in Hong Kong have been effective measures in improving air quality and reducing respiratory and cardiac deaths in the community, though COPD was not assessed separately from all other respiratory diseases.[69,70] Several studies in Xuanwei, China, where people live in homes with unvented coal stoves, have shown that improving the ventilation of the stoves can lead to health benefits.[71–73] The incidence of COPD has decreased markedly after installation of chimney on formerly unvented coal stoves.[71]

CONCLUSION

There are some data that outdoor air pollution (such as ambient air pollution or traffic-related air pollution) and indoor air pollution (such as second-hand smoking and biomass fuel combustion exposure) are associated with the development of COPD, but there is insufficient evidence to prove a causal relationship at this stage. It also appears that outdoor air pollutants are significant environmental triggers for AECOPD, from increasing symptoms to emergency department visits, hospital admissions and even mortality. Improving ambient air pollution and decreasing indoor biomass combustion exposure by improving home ventilation appear to be effective interventions that could substantially benefit the health of the general public. With the harmful effects of air pollution on health, public health measures are urgently needed globally to improve the air quality in order to reduce the morbidity and mortality of patients with this disabling disease.

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