Global associations between air pollutants and Chronic Obstructive Pulmonary Disease hospitalizations: a systematic review

Running head: Air pollution and COPD hospitalizations

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Abstract

Background: Exacerbations are key events in Chronic Obstructive Pulmonary Disease (COPD), affecting lung function decline and quality of life. The effect of exposure to different air pollutants on COPD exacerbations is not clear.

Objective: To carry out a systematic review examining associations between air pollutants and hospital admissions for COPD exacerbations.

Data sources: MEDLINE, EMBASE, BIOSIS & Science Citation Index, and the Air Pollution Epidemiology Database were searched from 1980 until September 2015.

Data extraction: Inclusion criteria focused on studies presenting solely a COPD outcome defined by hospital admissions, and a measure of gaseous air pollutants and particle fractions. The association between each pollutant with COPD admissions was investigated in meta-analyses using random-effects models. Analyses were stratified by geographical clusters to investigate the consistency of the evidence worldwide.

Synthesis: 46 studies were included and results for all the pollutants under investigation showed marginal positive associations; however the number of included studies was small with high heterogeneity between them and there was evidence of small-study bias. Geographical clustering of the effects of pollution on COPD hospital admissions was evident and reduced heterogeneity significantly.

Conclusions: The most consistent associations was between a 1mg/m^3 increase in carbon monoxide levels with COPD related admissions; Odds Ratio: 1.02 (95%CI: 1.01-1.03). The heterogeneity was moderate and there was a consistent positive association in both Europe and North America, although levels were clearly below WHO guideline values.

There is mixed evidence on the effects of environmental pollution on COPD exacerbations. Limitations of previous studies included the low spatio-temporal resolution of pollutants,

inadequate control for confounding factors, and the use of aggregated health data that ignore personal characteristics. The need for more targeted exposure estimates in a large number of geographical locations is evident.

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Introduction

Intense energy consumption together with industrial and transportation emissions, have led to population exposure to a diverse variety of unhealthy concentrations of air pollution, leading to increased morbidity and mortality primarily due to cardiovascular and respiratory causes (1).

Vulnerable groups include patients with chronic obstructive pulmonary disease (COPD), which is currently the fourth leading cause of death worldwide (2). Total deaths from COPD are predicted to increase by more than 30% in the next ten years and economic costs for the management of COPD are estimated at $36 billion annually in the United States (3). Although smoking is the most important cause of COPD, a substantial proportion of cases cannot be explained by this lifestyle factor alone (4).

Exacerbations of COPD are a common cause of adult emergency hospital admissions and are associated with increased mortality and decreased quality of life. Patients may experience at least one exacerbation per year, (5) and as the disease worsens, exacerbations become more frequent and severe (6). The effect of environmental exposure on COPD exacerbations is not clear. A number of variables may trigger COPD exacerbations (7), and understanding and addressing the effects of air quality may be key in managing COPD exacerbations. From a policy perspective, detecting air pollution-induced health effects early can lead to more effective control of exposures and more appropriate interventions.

The present review evaluates the strength and consistency of current literature documenting the effect of different air pollutants on hospital admissions for COPD exacerbations. Previous meta-analytic studies on the effects of air pollution on COPD-related hospital admissions and mortality have focused on the effects of particles (8–11) or the effects of gases such as ozone and nitrogen

dioxide (12,13). This review is unique in that it simultaneously assesses the effects of key atmospheric pollutants, including gases and particulate matter, on hospital admissions for patients with an established diagnosis of COPD from a large number of studies globally.

Methods

Objective

To assess the effects of air pollutants on COPD hospital admissions by reviewing the literature from time-series and case-crossover studies.

Search strategy

Two conceptual terms were developed for the search strategy: "*Environmental factors*" and "*health outcomes"* relating to COPD. Search terms were developed using combinations of controlled vocabulary and free-text terms. Only papers with title, keywords or abstracts including records from the search categories were included. Search terms from these categories were combined using the AND Boolean logic operator. "Environmental factors" refers to air pollution, including gases and particles suspected of affecting human health such as carbon monoxide (CO), nitrogen dioxide (NO_2), sulphur dioxide (SO_2), ozone (O_3), and particulates with a diameter of less than 10 and 2.5 micrometres in diameter (PM_{10} and $PM_{2.5}$ respectively). The primary "health outcome" of interest in this review is *COPD exacerbation* qualified by hospital admissions.

Searches were conducted through MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, BIOSIS & Science Citation Index from 1980 until September 2015 using PRISMA and MOOSE guidelines (14). We accessed the grey literature to address potential publication bias and searched additional sources including reports from the World Health

Organisation (WHO), the Committee on the Medical Effects of Air Pollution (COMEAP), and the Air Pollution Epidemiology Database (APED) from St George's University. The search strategy is included in the supplementary materials (SM).

Inclusion and exclusion criteria

Based on the above, inclusion and exclusion criteria (Table 1) were applied to titles, keywords and abstracts, before obtaining full reports on the studies that appeared to meet the criteria.

Classification and quality assurance

Two authors independently reviewed titles and abstracts for relevance and assessed whether they were related to the scope of this study. Relevant papers were included for full text review, and tested against the inclusion/exclusion criteria. The methodological quality of the studies was assessed based on population size, study duration and design, air pollutant exposure measurement, diagnosis of COPD, potential confounding factors, controls used, statistical methods, and length of follow up. A descriptive summary of the studies is included in Table 2 (SM).

Risk of bias assessment

A risk of bias assessment was devised based upon the Newcastle-Ottowa scale (15) and assessment domains included the representativeness of exposure, ascertainment of exposure, comparability i.e. controlling for confounders, and reporting of missing data (Figure 8).

Small study bias was assessed using the "trim and fill" method (16) (Figure 9 SM). The percentage of variation between studies due to heterogeneity was assessed with Galbraith (radial) plots (Figure 10 SM) and quantified with Cochran's Q measure in random effects models. The I^2

statistic was calculated as the weighted sum of squared differences between individual study effects and the pooled effect across studies as follows:

I^2 = 100% x (Q-degrees of freedom)/Q.

Data extraction and synthesis of evidence

Full text relevant studies were coded accordingly to address the topic focus of the review: study type (e.g. primary research, meta-analysis), focus of the study (e.g. health outcomes), country in which the research was conducted, duration of the study, and methodology employed (e.g. epidemiological study). Estimates of effects extracted from included studies were presented as odds ratios (OR), relative risks (RR) or percentage change (PC) in COPD hospital admissions. (See supplementary material for details).

Results

Methodological classification of studies

Among the 46 studies included in the meta-analysis, 15 were performed in North America and 19 in Europe. Eight studies were conducted in Asia, while limited information was available from South America and Australia. Therefore, three geographical clusters were defined based on available evidence from the literature.

Two methodological approaches were identified: time-series and case-crossover studies. The most common approach was ecological time-series investigations, where aggregated health outcomes of the total population were associated with daily variations in air pollutants after controlling for confounding factors, such as temperature or influenza epidemics. That approach has the potential for including a large number of days over several years for a large population

with advantages of improving the precision of estimate of effect of the exposure-response relationships. The vast majority of these studies analysed exposure-response relationships at single city level, with only six time-series multicity investigations (17–22).

Case-crossover studies measured COPD exacerbations in cohorts of COPD patients. Conceptually, case-crossover design is different from time-series as the unit of assessment is at the individual level, where each patient acts as their own control accounting for variation at the individual level. A total of 11 studies with a case-crossover design were included in the meta-analysis. The study population in those studies was relatively small compared with the time-series investigations, which would result in a smaller precision of the estimate. Only one case crossover study (23) was organised as a multicity study in 36 cities.

Air pollution exposure in all time-series and case-crossover studies used measurements from the nearest fixed air quality monitoring station. The number of fixed monitoring stations employed in each study was not always reported; but ranged from a single monitoring station up to 31 (24). The time-resolution of the measurements was most often 24-hour average values for meteorological parameters and particles, and 1-hour to 8-hour maximum levels for gaseous pollutants.

Meta-analysis of studies using single-pollutant models

Figures 2 to 7 show forest plots for the converted odds ratios of COPD hospital admissions for PM_{10}, $PM_{2.5}$, CO, SO_2, NO_2 and O_3 from single pollutant models.

Effect of PM_{10}

The pooled estimates of a total of 31 studies included in the meta-analysis for PM_{10} showed a marginal effect of a 10 $\mu g/m^3$ increase of PM_{10} on COPD hospital admissions (Figure 2) with very high heterogeneity (I^2=79.4 %) between studies. Out of these, 23 were ecological time series, while the rest were organised as case-crossover investigations. While 28 estimated a positive association between COPD-related hospital admissions and PM_{10} exposure, only 15 found that the association was significant.

Most of the studies were conducted in Europe and North America, where a marginal effect was estimated (OR: 1.01, 95%CI: 1.00-1.01 for Europe and 1.00, 95% CI: 1.00–1.01 for America respectively), while a stronger effect was reported for studies conducted in Asia (OR: 1.02, 95%CI: 1.01-1.03). The stronger effect reported in Asian studies might be explained by the approximately three-fold higher mean pollution levels of 99.8 $\mu g/m^3$ ± 48.4 compared with 30.7 $\mu g/m^3$ ± 2.6 and 31.1 $\mu g/m^3$ ± 3.0 for North America and Europe respectively, which were lower than the annual mean WHO guideline values. The meta-regression model also indicates a non-linear relationship with stronger effects reported at higher ambient concentrations (Figure 11 SM). The heterogeneity among European studies (I^2= 1.93%) was significantly lower than in the other two subgroups. The “trim and fill” method identified evidence of small-study bias on the effect estimates of PM_{10}. Contrary to single-city studies, three multicity studies, one in Europe (25) and two in North America (20,21) did not find a significant association, while a case-crossover (23) and a time-series (22) study in ten US cities found a marginal association between PM_{10} and COPD hospital admissions.

There is insufficient evidence to assess the lagged effects of particle exposure on COPD morbidity, as most studies did not specify the temporal lags of the dependent variables in the

regression. A further limitation includes the low temporal resolution of collected PM_{10} data, which was in most studies the daily average.

Effect of $PM_{2.5}$

Due to the lack of available outdoor measurements for $PM_{2.5}$ or smaller particles, evidence available on their potential association with COPD morbidity is limited and the heterogeneity of the pooled meta-analysis was high (I^2 = 89.9 %). Out of the 12 studies included in the meta-analysis (Figure 3), ten studies found a positive association; however only four found that the association was significant. Studies that collected measurements for both $PM_{2·5}$ and PM_{10} fractions found similar associations between COPD hospital admissions and these fractions (21,22,26–31), but overall a stronger association was found with $PM_{2.5}$ (OR: 1.03, 95%CI: 1.01-1.05) compared with PM_{10}, which might be explained by the fact that smaller particles may penetrate deeper into the lungs.

Similarly with PM_{10}, the majority of studies were performed as time-series investigations, and most of the evidence comes from North America. When the effect estimates in the European and North American results were pooled, the heterogeneity was significantly reduced (I^2<50%). The effect of $PM_{2.5}$ was stronger in Asia (OR: 1.04, 95% CI: 1.00-1.08) but there was large heterogeneity. Highest concentration levels of $PM_{2.5}$ of 41.2 $\mu g/m^3$ ± 2.7, were reported in Asia (where the effect was stronger and significant), twice as high as in Europe (23.4 $\mu g/m^3$ ± 5.3) and four times higher than in North America (11.3 $\mu g/m^3$ ± 3.3), where the effects were lower and non-significant and levels were below annual mean WHO guideline values. The meta-regression model also pointed towards a non-linear relationship between COPD hospital admissions and ambient pollution levels, as there was a higher effect at higher concentrations (Figure 12 SM).

Although there appears to be a relationship between $PM_{2.5}$ and COPD hospital admissions, results should be interpreted with caution due to the limited number of included studies. The "trim and fill" method did not detect any small-city bias. Two studies were organised as multicity investigations, one in 202 US cities (18) and one in seven Canadian cities (21), and reported a non-significant association between $PM_{2.5}$ exposure and COPD exacerbations.

As in the case of PM_{10}, limited information exists on seasonal effects of fine particles on health outcomes with only one study in a tropical climate estimating larger effects in the cool season (32). Limited evidence is available on the lagged effects of $PM_{2.5}$ exposure on COPD morbidity and points towards a shorter temporal lag than PM_{10} of up to two days (30).

Effect of CO

Pooled results of 15 studies for CO (Figure 4) showed a small but significant effect of a 1 mg/m^3 increase in CO on COPD admissions (OR: 1.02, 95% CI: 1.01-1.03) with moderate heterogeneity (I^2 = 50.73%) between studies. We excluded one study in Asia from the pooled estimate (33) that increased the heterogeneity significantly (I^2=83.6%). The re-scaled ORs for this study were 1.67 (95% CI 1.37, 2.04) in the warm season and 2.70 (95% CI 2.04, 3.58) in the cool season. Apart from two European case-crossover studies (21,30) that found a strong positive association, all included studies were time-series investigations. There was some evidence of small-study bias in the trim and fill funnel plot, supported by the non-significant negative association estimated by the only multicity investigation from seven Canadian cities (21).

There is insufficient evidence on the association between COPD hospital admissions and CO exposure in geographical locations other than Europe (6 studies) and North America (7 studies). The heterogeneity between studies was significantly reduced in both these geographical

subgroups. Studies in Europe estimated overall stronger association of OR: 1.04 (95% CI: 1.02-1.06) (I^2 =47.3%) than in North America OR: 1.02 (1.01–1.03) (I^2=37.5%), possibly because CO concentrations in Europe were higher (2.1 mg/m^3 ± 0.7) compared with North America (1.5 mg/m^3 ± 0.2) and the meta-regression indicated that there is a non-linear association between effect and ambient concentrations (Figure 13 SM).

Most studies found significant associations with acute (25,34) or lagged effects of up to three days (21,30,31,35).

Effect of SO_2

The overall pooled estimate of SO_2 exposure indicated a borderline effect with COPD admissions with moderate heterogeneity between studies (I^2 = 50.8%). Out of the 23 studies included in the meta-analysis, 18 employed a time-series methodology. There was evidence of small-study bias (Figure 9).

Most of the studies were performed in Europe with small heterogeneity (I^2= 6.72%) between studies. The effects were clustered in geographical locations with a stronger positive effect estimate in Asia (OR: 1.03, 95% CI: 1.00-1.06) compared with the effects in North America, where studies failed to detect a significant association, and only a borderline effect in Europe. SO_2 levels in North America and Europe were similar with small SE (18.1 μg/m^3 ± 4.7 and 18.0 μg/m^3 ±3.2) while levels in Asia were higher with large SE (25.1 μg/m^3 ± 11.30). The meta-regression model approximated a linear relationship between effect size and pollution levels (Figure 14 SM).

Apart from the spatial variation of the effect of SO_2, a seasonal effect might also underpin the estimated association. Two studies in a tropical climate in Taiwan (33,36) found a significant association between SO_2 and COPD hospital admissions only in the cool season (Temp <25°C). A

possible explanation might be increased coal burning for heating during the cool season in developing countries where levels were higher. However seasonal differences were estimated in a five year European study (37) with a very small but insignificant association observed in winter but no relationship in the summer. Most studies estimated acute effects for SO_2 (21,34) or two-day lagged effects (21,30,38). Only one study (35) estimated longer lagged effects of up to 13 days.

Effect of NO_2

Results for NO_2 (Figure 6) showed an association (OR: 1.03, 95% CI: 1.02-1.05) between a 10μg/m^3 increase in NO_2 and COPD admissions with high heterogeneity (I^2=91.5%). We found evidence of small-study bias in single-city studies (Figure 9). A positive association was reported in 25 out of 27 studies, and a significant one in 11 studies. Only one multicity study in North America (21) and one in Europe (39) reported a negative non-significant effect.

The majority of evidence comes from Europe, where the heterogeneity between studies was moderate (I^2=55%). The estimated effects in Europe and North America were similar (OR: 1.01, 95% CI: 1.00-1.02), but lower than the effects in Asia, where the confidence intervals were wider (OR: 1.07, 95%CI: 1.01-1.13). Highest NO_2 levels were measured in Europe (57.9 μg/m^3 ± 8) and Asia (51.2 μg/m^3 ± 2.4) and lowest levels in North America (42.7 μg/m^3 ± 10.8), but in all geographical clusters were above mean annual WHO guideline values. A non-linear relationship between mean levels and effect estimates was estimated in the meta-regression with stronger effects at higher concentrations (Figure 15 SM).

The findings on lagged effects of NO_2 exposure are inconsistent. Three studies found significant acute effects of same day NO_2 exposure with COPD exacerbations (25,40,41) or one to two day lagged effects (33,42). Longer three-day lag effects were reported in three large studies

(21,27,35), while four smaller studies reported longer lagged effects lasting of up to eight days (30,39,43,44).

Effect of O_3

In total, there were 23 studies investigating the effect of O_3 on COPD hospital admissions, nine were performed in North America, nine in Europe, three in Asia and one in Australia (Figure 7). As in the case of NO_2, the heterogeneity between studies was large (I^2 = 87.23%). Of the 22 studies, 18 reported a positive effect; however it was significant only in ten studies. Overall, the pooled estimates showed that there was a small positive effect of O_3 on COPD hospital admissions (OR: 1.02, 95% CI: 1.01–1.03). Mean levels of O_3 were similar in all geographical locations ranging from 43.9 μg/m^3 in Asia to 53.6 μg/m^3 in North-America and the meta-regression model estimated a linear relationship with the effects (Figure 16 SM).

The heterogeneity between studies in geographical subgroups remained high. The pooled models showed that the strongest effect (OR: 1.04, 95% CI: 1.03-1.05) was estimated for Asian countries, while the effects were marginally significant for North America (OR: 1.01, 95% CI: 1.00-1.02), and insignificant for Europe (OR: 1.01, 95% CI: 0.99-1.04). Contrary to the pooled models, the multicity studies found an insignificant effect in North America (21,23) and a significant positive effect in Europe (17). There was no evidence of small-study bias.

The effect of seasonality on the association between O_3 and COPD-related hospital admissions is unclear. One study in Canada (21) estimated that the effect was nearly twice as large during the warm season as over the whole year. Contrary, a study in a tropical climate (33) estimated that the effect was twice as large in the cool season.

Risk of bias assessment

The risk of bias (and the proportion of which had low, unclear or high risk) for the studies included in this review are shown in Figure 8. Detailed descriptions for each individual study are included in the supplementary materials.

Discussion

To our knowledge this is the first study to use meta-analytic techniques to pool the effect estimates of the associations between COPD admissions with gaseous pollutants (NO_2, O_3, CO and SO_2) and particulate matter simultaneously. The models showed suggestive evidence that all investigated pollutants may have a small but significant effect on COPD hospital admissions. These findings however, come from a relative small number of studies with high heterogeneity between them. Geographical clustering of the effects of pollution on COPD hospital admissions was evident and reduced heterogeneity significantly.

Particulate Matter

Previous systematic meta-analyses have focused on the association between COPD exacerbations (8,9) with exposure to particulate matter. Zhu and colleagues (11) estimated a 2.7% increase for COPD hospital admissions (95% CI: 1.9%-3.6%) for every 10 $\mu g/m^3$ increase in $PM_{10,}$ and reported large heterogeneity in effect estimates from I^2 = 83.9% (11) to 79.4% (9). We found a marginally significant effect estimate for PM_{10} (1·01, 95% CI: 1.0-1.02) similar to Song et al (9) but smaller than Zhu and colleagues (11). Song and colleagues (9) found that the strength of the association of COPD hospital admissions with PM_{10} varied among geographical locations with an effect of 1% in China and Europe but a larger effect of 2% in the United States. We estimated a similar effect of 1% in Europe with very little heterogeneity (I^2=1.93%); however a

smaller effect of 1% in North America, and a larger effect in Asia of 3% (95% CI: 2% to 5%). A possible explanation might be that unlike both previous meta-analyses (9,11), we did not include studies where asthma was not separated in the diagnosis. Moreover, we found evidence of a non-linear relationship where higher effects were reported at higher concentrations.

Only one meta-analysis (45) estimated the association of COPD admissions (excluding asthma) with $PM_{2\cdot5}$ exposure and found a similar association 1.02 (95% CI: 1.01-3.71) to this study (OR: 1.03, 95% CI: 1.01-1.05). In line with the findings of Atkinson and colleagues (45), we found large heterogeneity between studies but no evidence of small-study bias in the effect estimates of $PM_{2.5}$ for COPD hospital admissions.

It is possible that the marginal effect of particulate matter estimated in this and previous meta-analytic studies might be influenced by small-study bias. Large multicity studies in North America and Europe (19–21) failed to detect a significant association between outdoor PM_{10} levels and COPD hospital admissions. Similarly, the two multicity studies in North America (18,21) did not find a significant association between $PM_{2\cdot5}$ exposure and COPD hospital admissions.

The effect of seasonal variation on the association between PM_{10} exposure and COPD exacerbations is not clear. One multicity study in Italy (19) reported that the association is 7.5 times stronger in the summer season. A study in Taiwan however (33), found a stronger effect in the cool season. A potential explanation for the observed differences might be related to behavioural patterns of the population regarding time spent outdoors, which may vary in different climates. Another possible explanation in the Asian study may be related to the extensive use of mechanical cooling and air filtration in the tropical climate during the warm season that may reduce exposure to PM. Similar results have been reported by Janssen et al (46) in the re-analysis

of the National Morbidity Mortality Air Pollution study (NMMAPS) in 14 US states, where the percentage of households with air handling units had a significant modification effect on COPD hospital admissions.

Gaseous pollutants

The systematic evaluation of the association between COPD exacerbations with gaseous pollutants indicates a potential link between CO and SO_2 levels with moderate heterogeneity and strong geographical clustering. Both pollutants appeared in most studies to have acute effects or short lagged effects of up to three and two days respectively on COPD admissions, and a stronger effect in the winter season. Marginally stronger effects of CO were estimated in Europe than North America. A potential explanation for the difference in effects estimated between Europe and North America may be related to different levels of ambient CO concentrations, or the methodological design of studies, such as the absence of multi-city investigations in Europe.

The effect estimates of SO_2 in each geographical subgroup indicated that the association was only significant in Asian countries with stronger effect in the winter season, marginally significant in Europe, and insignificant in North America where the majority evidence comes from, possibly because SO_2 remains a predominant pollutant in developing countries. The only two available multi-city studies on the effects of SO_2 found contradictive results; one study in Europe reporting a marginal positive association (17) and one study in North America (21) reported a negative non-significant association. A possible explanation is that the chronological difference between these two studies reflects differences in outdoor SO_2 concentrations.

The associations between NO_2 and O_3 exposure with COPD hospital admissions is less well understood, as the heterogeneity between studies in this review was large. Both pollutants showed

marginal associations in Europe and North America, and stronger effects in Asia. Only three studies in Asia found an association both with O_3 and NO_2 (29,33,40). Studies in Europe and North America found an association either with NO_2 (24,30,35,43) or O_3 alone (17,27,39,47,48).

Limitations

A number of limitations in the methodological design of the studies included in this review do not allow establishing a clear link between the effects of environmental pollution on COPD exacerbations. Using hospital admissions as an indication of exacerbation is a potential source of ecological fallacy, as it ignores individual-level characteristics and assesses health outcomes at group level. Relationships at individual level might not reflect group level relationships and vice versa. Health-care use in COPD can vary depending on access, and it was not always possible to separate emergency from scheduled admissions, adding further uncertainty to the estimation of exacerbations.

Although many studies employed both single-pollutant and multi-pollutant models, results were included only from single-pollutant models and the findings do not account for any covariance between air pollutants (such as NO_2 and O_3 or NO_2 and PM). Other unmeasured pollutants in the mixture might also be important in the observed health outcomes (such as ultrafine particles). The confounding effects of temperature and humidity add further challenges. Although we know that there are seasonal effects on COPD exacerbations in northern and southern regions (49), the relationships between temperature and humidity with COPD admissions is not clear.

The studies were grouped based in geographical location, which had the potential of reducing the heterogeneity of the subgroups, however the small sample size limited the interpretation of the results. We used random-effects models, which can account for the heterogeneity between studies better than fixed models. While this standardised method may reduce the small-study bias, it cannot differentiate multi-city from single-city studies if the standard error is similar. Moreover, while the RE pooled models assume a linear relationship between air pollutants and effect estimates, we found evidence of a non-linear relationship with higher effects reported at higher concentrations for all pollutants apart from O_3 an SO_2 that exhibited a linear relationship.

A significant limitation of the studies included the low spatio-temporal resolution of air pollution measurements from fixed monitoring stations as a surrogate for personal exposure. However, in practise air quality is highly granular and people, particularly those with chronic respiratory diseases, may spend a large fraction of their time indoors, where they might be exposed to a mixture of emissions from indoor sources. Missing daily monitoring data add further uncertainty in the analysis of time-series studies with daily lags in the exposure variable. Rather than using fixed site monitors as a proxy for “true” exposures, the development of hybrid models that combine pollutant dispersion models with space-time-activity models may prove to be a more effective way of examining the effects of personal environmental exposure on health (50).

Conclusions

A key finding of this review is that the effects of separate pollutants on COPD admissions appears to vary across geographical regions. Effects were evident even at concentration below current guideline values indicating the need to lower thresholds to protect such vulnerable groups.

Competing Interests

JKQ reports grants from the Medical Research Council (MRC), GlaxoSmithKline (GSK), British Lung Foundation (BLF), Wellcome Trust, during the conduct of the study, and personal fees from AstraZeneca outside of the submitted work. LS reports grants from the Wellcome Trust, MRC, and National Institute for Health Research (NIHR) during the conduct of the study, and personal fees from GSK outside of the submitted work. All authors report no other conflicts of interest.

Author Contributions

EM and LC carried out the background research, literature search, screening of articles, data extraction, data interpretation, produced the figures and the first draft. MOK assisted with screening and data extraction. JKQ conceived the study, made critical revisions of the manuscript for intellectual content and supported completion of the first draft. BB provided oversight for the study, commented on subsequent drafts of the manuscript and approved the final version. RLJ and FJK commented on the first draft and gave advice on data interpretation and analysis. All other authors commented on subsequent drafts and approved the final version.

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Figures

Figure 1: Flow chart of the literature search and screening process.

Figure 2: Pollution levels and summary estimates (95% confidence intervals) for COPD related hospital admissions per 10 μg/m^3 increase in PM_{10}.

Figure 3: Pollution levels and summary estimates (95% confidence intervals) for COPD related hospital admissions per 10 μg/m^3 increase in $PM_{2.5}$.

Figure 4: Pollution levels and summary estimates (95% confidence intervals) for COPD related hospital admissions per 1 mg/m^3 increase in CO levels.

Figure 5: Pollution levels and summary estimates (95% confidence intervals) for COPD related hospital admissions per 10 μg/m^3 increase in SO_2 levels.

Figure 6: Pollution levels and summary estimates (95% confidence intervals) for COPD hospital related admissions per 10 μg/m^3 increase in NO_2 levels.

Figure 7: Pollution levels and summary estimates (95% confidence intervals) for COPD hospital related admissions per 10 μg/m^3 increase in O_3 levels.

Figure 8: Risk of bias assessment for studies included in the meta-analysis.

Table 1: Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
• Reports a specific outcome of COPD exacerbation defined by hospital or emergency department admissions. • Recorded by clinician or in hospital records using the codes for the International Classification of Diseases Ninth and Tenth Revisions (ICD-9 490-496 excluding 493 for asthma; and ICD-10 J44.1-J44.9). • Reports a measure of air quality, either from a fixed monitoring station, indoor environment or personal exposure (indoor to be analysed separately from outdoor). • Reports the findings of a primary research study or secondary analysis. • Published in English • Reported results from single-pollutant models.	• Studies of the same author that repeat results (the most recent were selected). • Studies that included asthma (ICD-9 493) were excluded because of clinical and pathological differences between COPD and asthma (19). • Incorrect outcome: Included other respiratory diseases combined with COPD in the statistical analysis. • Uncertain diagnosis of COPD. • Did not report or provide calculable Odds Ratio (OR), Relative Risk (RR), or Percentage Change (PC) and 95% Confidence Intervals (CIs). • Poor quality: lacked adjustment for potential confounders, missing data, inadequate statistical analysis.