The impact of acute air pollution fluctuations on bronchiectasis pulmonary exacerbation: a case-crossover analysis

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PG wrote the article and contributed to the design of the study. BC and TN contributed to the design of the study, performed the statistical analysis and reviewed the paper. TCF, SF, MRL, PB and ATH contributed to the design and review of the manuscript. KdH and JDC contributed to the design of the study, collected the data and wrote the article.

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Short sentence summary: Acute air pollution fluctuations are associated with increased exacerbation risk in patients with bronchiectasis.

Abstract:

In bronchiectasis, exacerbations are believed to be triggered by infectious agents, but often no pathogen can be identified. We hypothesized that acute air pollution exposure may be associated with bronchiectasis exacerbations.

We combined a case-crossover design with distributed lag models in an observational record linkage study. Patients were recruited from a specialist bronchiectasis clinic at Ninewells Hospital, Dundee, UK.

We recruited 432 patients with HRCT diagnosed and clinically confirmed bronchiectasis. After excluding days with missing air pollution data, the final model for PM_{10} was based on 6741 exacerbations from 430 patients and for NO_2 it included 6248 exacerbations from 426 patients. For each 10μg/m³ increase in PM_{10} and NO_2, the risk of having an exacerbation that same day increased significantly by 4.5% (95%CI:0.9-8.3) and 3.2% (95%CI:0.7-5.8) respectively. The overall increase in risk of exacerbation for a 10μg/m^3 increase in air pollutant concentration was 11.2% (95%CI:6.0-16.8) for PM_{10} and 4.7% (95%CI:0.1-9.5) for NO_2. Subanalysis showed significant higher relative risks during spring (PM_{10} 1.198, 95%CI 1.102-1.303;NO_2 1.146, 95%CI:1.035-1.268) and summer (PM_{10} 2.142, 95%CI:1.785-2.570;NO_2 1.352, 95%CI:1.140-1.602) when outdoor air pollution exposure would be expected to be highest.

In conclusion, acute air pollution fluctuations are associated with increased exacerbation risk in bronchiectasis.

Introduction

Exacerbations are key events in the natural history of bronchiectasis and are associated with an increased risk of mortality, hospital admissions, lung function decline and death. [1,2] The causes of bronchiectasis exacerbations are not known, although they are presumed to be primarily bacterial or viral and guidelines recommend that all exacerbations are treated with antibiotics.[3] Therapies aiming to reduce exacerbation frequency in bronchiectasis, however, have generally had modest effects and there is a high burden of exacerbation despite treatment. European registry data shows a median of two exacerbations per patient per year. [4] It is therefore important to gain further understanding of the causes of bronchiectasis exacerbations. Research shows that exposure to air pollution causes an inflammatory response. One study by McCreanor et al. showed that patients with asthma walking for two hours along a busy London street not only showed higher pollution exposure than their controls who walked through a nearby park, but they had decreased FEV_1 and FVC. These changes were accompanied by a significant increase in neutrophilic inflammation measured by sputum myeloperoxidase, also known to be a key mediator in bronchiectasis.[5,6]

Acute and chronic air pollution exposure have been linked with pulmonary exacerbations in patients suffering from cystic fibrosis. Acute fluctuations play a role in triggering pulmonary exacerbations in cystic fibrosis.[7,8] Furthermore, proximity to major roads predicts exacerbations and annual average exposure to air pollution is associated with an increased risk of a pulmonary exacerbation and a decline in lung function.[9,10]

For non-cystic fibrosis bronchiectasis (from now on referred to as bronchiectasis), data are scant. We recently showed that residential proximity to a major road and distance-weighted traffic density within 100 and 200 meters was associated with the risk of mortality.[11] To our knowledge, there are no data on the effect of acute air pollution on bronchiectasis pulmonary exacerbations.

This study aimed to determine the impact of acute air pollution fluctuations on the risk of pulmonary exacerbation in patients with bronchiectasis.

Materials and Methods

Patient population and patient data linkage

This manuscript describes a case-crossover observational record linkage study of patients with high resolution computed tomography (HRCT) diagnosed and clinically confirmed bronchiectasis attending a regional specialist clinic for bronchiectasis patients at Ninewells Hospital, Dundee, UK. The hospital is a national reference centre and therefore patients came from other cities around the country including Aberdeen, Dundee, Kirkcaldy, Perth, and Falkirk. The study was approved by the local research ethics committee (study number: 14/SS/1101) and all patients gave written informed consent to participate. Unique personal identifier codes were used to extract electronic medical records from an administrative database that covers more than 800,000 patients (approximately 16% of the Scottish population) from the date of first diagnosis of bronchiectasis (defined as the date of initial diagnostic HRCT scan). Linkage included data from January 1st 2000 to October 31st 2014 including all community drug prescriptions, hospital stays, diagnoses, interventions, laboratory tests (including sputum microbiology), radiology, and deaths. Patients were also included in the Tayside Respiratory Disease Information System (TARDIS) which provides annual data on spirometry, microbiology, respiratory symptoms and respiratory treatments and has been used for multiple previous record linkage studies.[12-14]

Exacerbation definition

During the study period there was no agreed definition of exacerbation of bronchiectasis, but most operational definitions previously required the acute prescription of antibiotics.[1] During the study period, exacerbations were identified as an acute prescription of antibiotics for episodes coded as exacerbation of bronchiectasis or lower respiratory tract infection at the time of clinical presentation. This method of identification of exacerbations was prospectively validated against exacerbations treated in a prospective cohort and was 100% sensitive and 87% specific (more details are provided in the online supplement). Severe exacerbations were defined as admissions to hospital for exacerbation of bronchiectasis. The first day of antibiotic prescription was considered to be the start date of the exacerbation.

Exposure data

Daily PM_{10} (particulate matter with a diameter smaller than 10 μm) and NO_2 concentrations during the study period measured at the Aberdeen urban background site, which is part of the UK's Automatic Urban and Rural Network (AURN), were used for the analysis. Days with missing air pollution data were excluded. Because climate is a known confounder of the association between air pollution and respiratory diseases,[15] data on mean air temperature and relative humidity were obtained from the UK Meteorological Office. For temperature, we used data from the measuring stations Dyce, Mylnefield, Kinross, Dalwhinnie, and Tyndrum for the postcode areas Aberdeen, Dundee, Kirkcaldy, Perth, and Falkirk, respectively. As humidity data are not available for Mylnefield and Kinross, humidity recorded at the stations of Strathallan Airfield and Leuchars were used for the postcode areas Dundee and Kirkcaldy, respectively.

Statistical Analysis

The case-crossover design is widely used for analyzing short-term exposures with acute outcomes.[16] It is a variant of the matched case-control study, where each subject serves as its own control so that known and unknown time-invariant confounders are inherently adjusted for by study design.[17] This design samples only cases (exacerbations of bronchiectasis in this study) and compares each subject's exposure in a time period just before a case event (the hazard period) with that subject's exposure at other times (the control periods). Selection bias was avoided by applying a bidirectional time-stratified design.[18] Control days are taken from the same calendar month and year as the case day (*i.e.* day of the bronchiectasis exacerbation), both before and after the case, thus controlling for long-term trends and season by design. Cases and controls were additionally matched by day of the week to control for any weekly patterns in air pollution or bronchiectasis. In the main analysis recurrent event data were pooled, considering exacerbations as the unit of analysis rather than persons and assuming that within-subject correlation is completely accounted for by subject-specific variables (observed or unobserved).[19]

To investigate the association between bronchiectasis and air pollution exposure up to four days before the exacerbation, we combined the case-crossover design with distributed lag models, using separate models for PM_{10} and NO_2. A distributed lag (non-linear) model is defined through a “cross-basis” function, which allows the simultaneous estimation of a (non-linear) exposure-response association and non-linear effects across lags, the latter termed lag-response association. This study applies recent extensions of the distributed lag models methodology beyond aggregated time series data,[20] specifically implementing them in a conditional logistic regression model with individual-level exposure measures (at least for temperature). We assumed a linear association between

air pollution exposure and bronchiectasis and the lag structure was modelled with a natural cubic spline with three degrees of freedom (df). The knots in the lag space were set at equally spaced values in the log scale of lags to allow more flexible lag effects at shorter delays.[21]

We also included a cross-basis for mean temperature in the model to capture the (potentially delayed) effects of heat and cold on bronchiectasis exacerbations. The maximum lag was set to 25 days. We used a natural cubic spline with five df for the temperature–exacerbation function and a natural cubic spline with six df (with knots at equally spaced values in the log scale) for the lag structure. Spline knots for temperature were placed at equally spaced values of the actual temperature range to allow enough flexibility in the two ends of the temperature distribution.

In a secondary analysis we studied the effects stratified by *Pseudomonas aeruginosa* infection status (yes or no), by bronchiectasis severity index (≤4: mild; 5-8: moderate; ≥9: severe), and by deprivation index (divided into quintiles from the Scottish Index of Multiple Deprivation, a score from one to five where a lower index indicates higher deprivation) hospitalization (yes; no), chronic macrolide use at time of exacerbation (yes; no), and season (Mar-May: spring; Jun-Aug: summer; Sep-Nov: autumn, Dec-Feb; winter).[1,22,23] In sensitivity analyses we increased the maximum lag to six. We also used an unconstrained distributed lag model, that is, a model in which each lag is entered as a separate variable.[24] Because of the correlation between air pollution concentrations on days close together, the unconstrained distributed lag model will result in unstable estimates for the individual lags, but it is known as more flexible and less prone to bias for the estimate of the overall effect.[24] We also explored the potential confounding by temperature by excluding the temperature cross-basis from the model. We also explored potential confounding by humidity up to four days before the exacerbation (lag 0 to 4) by adding a cross-basis with a linear humidity-bronchiectasis function and a natural cubic spline with three df to model the lag structure. In a last sensitivity analysis, we used only one (the first) exacerbation per person, such that no assumption on the correlation among multiple events is needed.[25]

We calculated relative risks (RR) of bronchiectasis exacerbation for a 10 μg/m^3 increase in air pollutant concentrations. In our analysis, this acccords to almost one standard deviation (Table 2). Reported estimates, computed as the overall cumulative risk accounting for the 0–4 lag period, are presented as percent change in bronchiectasis with corresponding 95% confidence interval (CI). All analyses were performed with the statistical software R (R Foundation for Statistical Computing, Vienna, Austria) using the "dlnm" package.[20]

Results

Patient population

Between January 6th 2000 and October 2nd 2014, 432 patients had a total of 7777 exacerbations. After excluding days with missing air pollution data, the final model for PM_{10} was based on 6741 exacerbations from 430 patients and the final model for NO_2 included 6248 exacerbations from 426 patients. The population was predominantly female (60.2%) with a median age of 68 years (IQR 59-74). *P. aeruginosa* chronic infection during the follow-up period was seen in 13.9% of the patient population. Bronchiectasis Severity Index had an equal distribution of mild, moderate and severe risk patients (mild 28.1%; moderate 39.5%; severe 32.3%) (table 1).

Ambient air pollution

Table 2 shows descriptive statistics for the overall daily number of exacerbations, mean temperature, and ambient air pollutants. Mean temperature ranged from -11.5 to 21.3°C, with an average of 8.1°C. Average (range) PM_{10} and NO_2 concentrations were 15.8 (1.0 to 82.6) μg/m^3 and 25.5 (1.7 to 85.7) μg/m^3

respectively. To highlight sufficient variation around a non-zero mean value as suggested in case-crossover studies,[26] Table 2 also presents the "relevant exposure term," which is the absolute difference between each pollutant's level on the case day and its average concentrations over the control days. The Spearman correlation coefficient between PM_{10} and NO_2 was 0.35. The correlation with mean temperature was 0.05 for PM_{10} and -0.30 for NO_2.

Effects of air pollution on exacerbation risk

The three-dimensional plots show the association between bronchiectasis and PM_{10} and NO_2 concentrations over the lag days (Figure 1). The effect of air pollution on bronchiectasis exacerbations was found to be acute, with highest RRs on the day of exposure (lag 0). Figure 2 presents the lag-specific RR for bronchiectasis associated with a 10 $\mu g/m^3$ increase in air pollutant concentrations. Significant RR were observed at lag 0 and 1 for PM_{10}, and at lag 0 for NO_2. The risk of having an exacerbation increased by 4.5% (95% CI 0.9 to 8.3) and by 3.2% (95% CI 0.7 to 5.8) for each 10 $\mu g/m^3$ increase in same-day (lag 0) PM_{10} and NO_2, respectively. Cumulative effects of air pollutant concentrations on bronchiectasis are presented in Table 3. The overall (lag 0-4) increase in the risk of an exacerbation for a 10 $\mu g/m^3$ increase in air pollutant concentration was 11.2% (95% CI 6.0 to 16.8) for PM_{10} and 4.7% (95% CI 0.1 to 9.5) for NO_2. Stratification according to *P. aeruginosa* chronic infection gave almost identical estimates in both groups, but confidence intervals for the infected group were wider. In chronic infected patients relative risks for bronchiectasis exacerbations associated with a 10 $\mu g/m^3$ increase in PM_{10} was 1.115 (95% CI: 0.989 – 1.257) and for NO_2 1.046 (95% CI: 0.937 – 1.169). In *P. aeruginosa* naïve patients relative risks for bronchiectasis exacerbations associated with a 10 $\mu g/m^3$ increase in PM_{10} was 1.114 (95% CI 1.056 – 1.175) and for NO_2 1.046 (95% CI 0.996 – 1.098) (Figure 3). Similarly, no difference was found between groups when stratifying according to Bronchiectasis Severity Index (BSI), Deprivation Index, hospitalization and chronic macrolide use at time of exacerbation (Figure 3). There was however a seasonal variation in the association between air pollution and bronchiectasis: higher relative risks were seen

during spring (PM_{10} 1.198, 95% CI 1.102 – 1.303; NO_2 1.146, 95% CI 1.035 – 1.268) and especially during summer (PM_{10} 2.142, 95% CI 1.785 – 2.570; NO_2 1.352, 95% CI 1.140 – 1.602) as compared to autumn (PM_{10} 0.922, 95% CI 0.828 – 1.027; NO_2 1.035, 95% CI 0.927 – 1.156) and winter (PM_{10} 0.984, 95% CI 0.891 – 1.086; NO_2 0.941, 95% CI 0.880 – 1.005)(Figure 3).

Increasing the maximum lag to 6 days, using an unconstrained lag structure, excluding the cross-basis for temperature and including a cross-basis for humidity produced similar results for PM_{10}, with cumulative lag 0-4 effects ranging from 10.0% (95% CI 5.1 to 15.1) to 11.8% (95% CI 6.5 to 17.4) (Table 4). Sensitivity analyses also showed robust results for NO_2, except for a decrease in cumulative estimates when increasing the maximum lag to 6 days (3.9%, 95 CI -0.5 to 8.5) and when adding the humidity cross-basis (3.6%, 95% CI -1.1 to 8.6). Same-day (lag 0) estimates from these models, however, remained significant (3.5% and 2.7% respectively). Limiting the analysis to the first exacerbation of each patient did not change the cumulative estimate for PM_{10} (11.1, 95% CI -9.2 to 36.0) but resulted in an increase in the estimate for NO_2 (9.0, 95% CI -7.3 to 28.1) and a considerable loss in precision for both air pollutants.

Discussion

This is to our knowledge the first report on the effect of acute air pollution fluctuations and its effect on exacerbations in a population suffering from bronchiectasis. This case-crossover analysis shows that the risk of having an exacerbation increased significantly on days with higher air pollution. For each 10 µg/m³ increase in PM_{10} and NO_2, the risk of having an exacerbation that same day increased significantly by 4.5 and 3.2% respectively. The overall increase in the risk of exacerbation for a 10 µg/m^3 increase in air pollutant concentration was much higher, reaching 11.2% for PM_{10} and 4.7% for NO_2.

The effects of air pollution fluctuations seem to be very acute and other researchers have found similar acute effects. Tramuto et al. investigated the effects of air pollution and emergency room visits for respiratory symptoms and found that PM_{10} and NO_2, amongst other pollutants, were positively associated in a similar acute fashion.[27] Further comparable acute effects of air pollution have been shown for other diseases as well. Nawrot et al. determined that air pollution is an important trigger for acute myocardial infarction.[16]

In our analysis, we could not show a predisposition towards the effects of air pollution fluctuations in any defined subgroup. Three subanalyses (*P. aeruginosa* chronic infection, deprivation index and bronchiectasis severity index) showed overlapping confidence intervals. These results seem to corroborate previous data from patients with in cystic fibrosis where *P. aeruginosa* status did not impact the effects of air pollution exposure.[7] Our data suggests that all subgroups of patients with bronchiectasis are potentially susceptible to the effects of acute air pollution.

Higher risks for bronchiectasis exacerbations associated with air pollution were, however, seen during spring and especially summer. We previously showed a similar stronger association between exacerbations and air pollution during the warmer months of the year in cystic fibrosis patients.[7] The reason remains unclear, but one interesting study showed that ambient pollution particles collected during spring and summer were more potent at inducing inflammatory cytokines in isolated macrophages of rats compared with samples collected during the winter months.[28] Moreover, Scotland has a relatively cold climate meaning patients spend more time indoors during the autumn and winter months and our results may indicate the effects are being driven by outdoor air pollution such as traffic pollution exposure during months that patients spend more time outdoors.[29] Finally, ambient temperature is associated with the prevalence of *P aeruginosa* and lower lung function in patients with cystic fibrosis.[30] We speculate that during the colder months exacerbations are

likely more viral in origin and less impacted by air pollution and that, during the warmer months, bacterial exacerbations are possibly worsened by air pollution or air pollution can have a direct effect on causing exacerbations because there are less viral infections during that period.

Our study has some limitations. One limitation is the lack of data on symptoms and days of symptoms before start of antibiotics as well as the definition we used for exacerbation. We deemed the need for antibiotic treatment essential, thereby following initial definitions used in large double-blind, placebo-controlled trials in bronchiectasis.[31,32] However, recently, an expert consensus definition was produced to assist further research. In this new definition the patient needs deteriorating symptoms and a decision to make a change in the patients' bronchiectasis treatment.[33] This suggests that non-antibiotic treatment started due to deteriorating symptoms might also fit the definition of a bronchiectasis exacerbation. This might have resulted in an underreporting of the number of exacerbations in our studied population.

Another limitation is the lack of $PM_{2.5}$ or black carbon data as these weren't available for the region in enough monitoring stations for that time period. PM_{10} consists of $PM_{2.5}$ and larger particles which are mainly of biological and crustal origin. These particles are capable of penetrating into the lower respiratory tract. Research has shown that the smaller $PM_{2.5}$ fraction is more potent to cause respiratory effects.[34] However, high correlations between PM_{10} and $PM_{2.5}$ in the region have been observed. For example, Auchencorth Moss pollution data between June 1st 2012 and December 31st 2015, show a PM_{10} and $PM_{2.5}$ correlation coefficient of 0.86. Moreover, we added NO_2 as black carbon is the particulate matter fraction that correlates best with NO_2.[35] NO_2 is mainly emitted by combustion processes (vehicle engines, heating, power generation) and is therefore a good proxy for the mixture of traffic related air pollution.
A third limitation is the use of outdoor measurements to reflect a patients personal exposure. It is possible that patients will spend more time indoor when media alert for high pollution concentrations. We do not believe this will have impacted our study in a significant way as media only alert peak pollution

concentrations and we studied continuous exposure effects. Research has also shown a good correlation between outdoor and indoor variation. Studies show a very good correlation among the day-to-day changes in measurement stations and personal exposure.[36,37] We also know from previous data that spatial variability in PM_{10} is less important than temporal variability, as the latter is largely caused by weather changes.[38] However, added personal exposure based on commute and travelling was not evaluated due to ethical and privacy reasons and could therefore influence the results.

Ideally to capture spatial and temporal variations we would have used air pollution monitoring sites which were located near where the participants live, were located away from local sources (so-called background sites) and operated during the whole time period. During the time period concerned, the only site in Scotland fulfilling these requirements was an urban background site in Aberdeen. Therefore, all participants were assigned daily exposures from the same measurement site, giving us the temporal signal only. This could be a limitation, however, we don't believe that this influenced the results because evidence shows that temporal differences are much more determining than spatial differences in air pollution.[38]

The four major strengths of this analysis are the large number of patients, the large number of exacerbation events due to the long term follow-up, the case-crossover design and the use of distributed lag models. The case-crossover design is widely used for analyzing short-term pollution exposure with acute outcomes. A case-crossover analysis is a variant of the case-control in which each subject serves as her or his own control.[17] This reduces the influence of confounding covariates. The use of distributed lag models is an important strength as their bi-dimensional structure simultaneously describes the association along the space of the exposure and in the additional dimension of the lags. This enables the investigation of the temporal pattern of the association in one single model and provides an estimate of the "overall" effect of the exposure incorporating delayed effects."

In our analysis we've added deprivation index as a measure for socio-economic status as previous research in bronchiectasis has suggested that socio-economic status is linked with mortality and exacerbations.[39] We found no effect of acute air pollution fluctuations on bronchiectasis pulmonary exacerbations.To tackle the possible confounding of asthma or COPD, we used the case-crossover analysis as we don't expect that the chronic conditions of a person change within the month of exacerbation or any other factor that slowly changes over time. In bronchiectasis, asthma and COPD are important comorbid conditions. The existance of asthma in patients with bronchiectasis is associated with an independent increase in risk of bronchiectasis exacerbation and the relationship between asthma and pollution has been widely studied.[40,41] Similarly, bronchiectasis with associated COPD not only show increased mortality compared to bronchiectasis patients without COPD, but bronchiectasis patients with COPD also have higher rates of respiratory infections and hospitalization.[42,43] Additionally air pollution increases hospitalizations and mortality in COPD.[44]

This data adds to an increasing body of data that air pollution increases exacerbation risk in people with a respiratory illness. This presents a challenge for policymakers to address this growing problem. Pollution impacts the health of the whole population and certainly patients with a respiratory condition. Further action is needed as European data indicate that current exposure to particulate matter from anthropogenic sources leads to an average loss of 8.6 months of life expectancy in Europe.[45] Data also estimate that over three million life years were lost in the EU (25 countries) in 2000 through exposure to PM.[45] Estimates of loss in statistical life expectancy in the UK that can be attributed to anthropogenic $PM_{2.5}$ sources were 6.9 months in 2000 and 4.9 months in 2010. Experts estimate that the "no further climate measures" scenario for 2020 will still lead to a loss of life expectancy of 4.5 months in the UK. Previous data on chronic exposure combined with our findings on acute pollution fluctuations, suggest that caregivers should inform patients with bronchiectasis on the effects of air pollution on their disease. However, it remains to be established if certain interventions (such as mask protection during peak exposure) will impact disease morbidity. Our analysis might in part provide an answer to that questions. An intervention that would decrease PM_{10} by 10 $\mu g/m^3$ would

potentially lead to a reduction of 11.2% exacerbations. This means that during the study period of 5384 days, a reduction of PM_{10} by 10 µg/m³ will possibly prevent 871 exacerbations. This results in 59 exacerbations possibly prevented per year for a decrease of 10 µg/m³. For NO2, a decrease by 10 µg/m³ will likely prevent 25 exacerbations each year. Additionally, further research should also focus to unravel if certain patients have a particular sensitivity to air pollution. This could then lead to research testing interventions and patient education programs to improve their health status.

In conclusion, acute air pollution fluctuations are associated with increased exacerbation risk in patients with bronchiectasis. There was no difference in risk between patients stratified according to BSI, deprivation index or the presence of chronic *P. aeruginosa* infection, but there was a greater effect during the spring and especially during the summer months. Air pollution seems to be an important factor in bronchiectasis and patients should be aware of its effects.

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Table 1: Patient characteristics of the studied population.

Characteristic	Median (IQR) or number (%)
Total number of patients	430
Female sex	259 (60.2)
Age (years)	68 (59-74)
Number of exacerbations	7319
Average number of exacerbations per patient	13.5 (7-25) exacerbations/patient/over the study period 0.91 exacerbations/patient/year
FEV_1 % [a]	71 (50-90)
Deprivation index [b]	Index 1: 86 (20.5) Index 2: 70 (16.7) Index 3: 73 (17.4) Index 4: 115 (27.5) Index 5: 75 (17.9)
Bronchiectasis Severity Index	median 6 (IQR 4-10) Mild (≤4): 121 (28.1) Moderate (5-8): 170 (39.5) Severe (≥9): 139 (32.3)
Bacteria chronic infection status at enrolment	*Haemophilus influenza*: 136 (31.6) *Staphylococcus aureus*: 34 (7.9) *Moraxella catarrhalis*: 53 (12.3) *Enterobacteriaceae*: 59 (13.7) *Pseudomonas aeruginosa*: 60 (13.9)

[a] Forced Expiratory Volume in one second (N=429). [b] A lower index indicates higher deprivation (N=419). IQR = Interquartile Range.

Table 2: **Exposure and exacerbations summary statistics.**

Variable	Mean	SD	Min	Max
Daily number of exacerbations[a]	3.1	3.7	0.0	42.0
Exposure on case days				
Temperature (°C)[a]	8.1	5.1	-11.5	21.3
PM_{10} ($\mu g/m^3$)[a]	15.8	9.4	1.0	82.6
NO_2 ($\mu g/m^3$)[b]	25.5	13.6	1.7	85.7
Exposure difference between case days and average over control days[c]				
Temperature (°C)[a]	10.2	8.9	0.0	53.7
PM_{10} ($\mu g/m^3$)[a]	7.2	7.1	0.0	62.8
NO_2 ($\mu g/m^3$)[b]	2.3	1.8	0.0	13.6

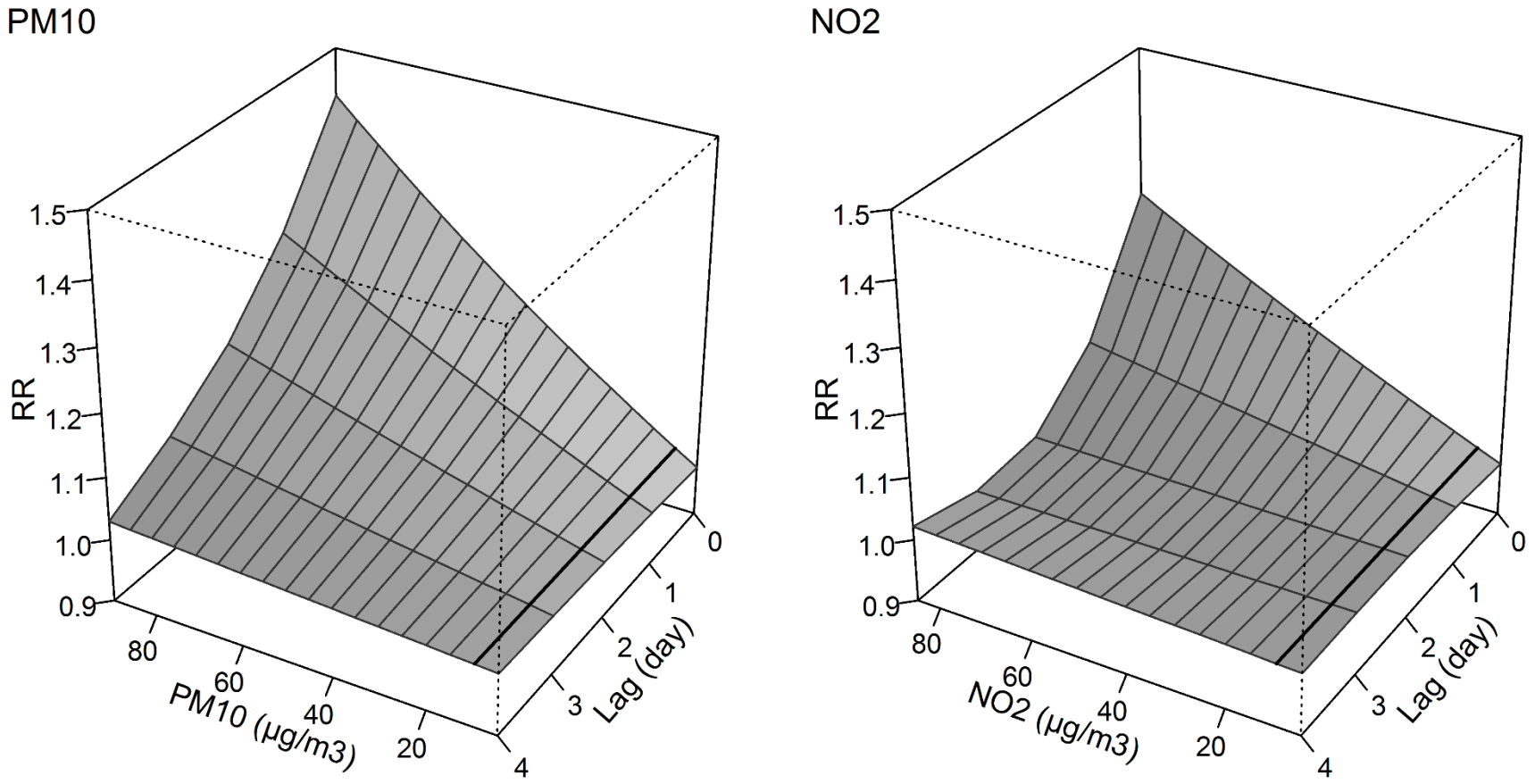
Summary statistics for daily bronchiectasis exacerbations, mean temperature and air pollution levels, and for the absolute differences between the daily levels of each variable (case days) and the average levels over the control days.

[a]Summary statistics for cases with PM_{10} data available (N exacerbations = 6741; Total number of patients = 430).

[b]Summary statistics for cases with NO_2 data available (N exacerbations = 6248; Total number of patients = 426).

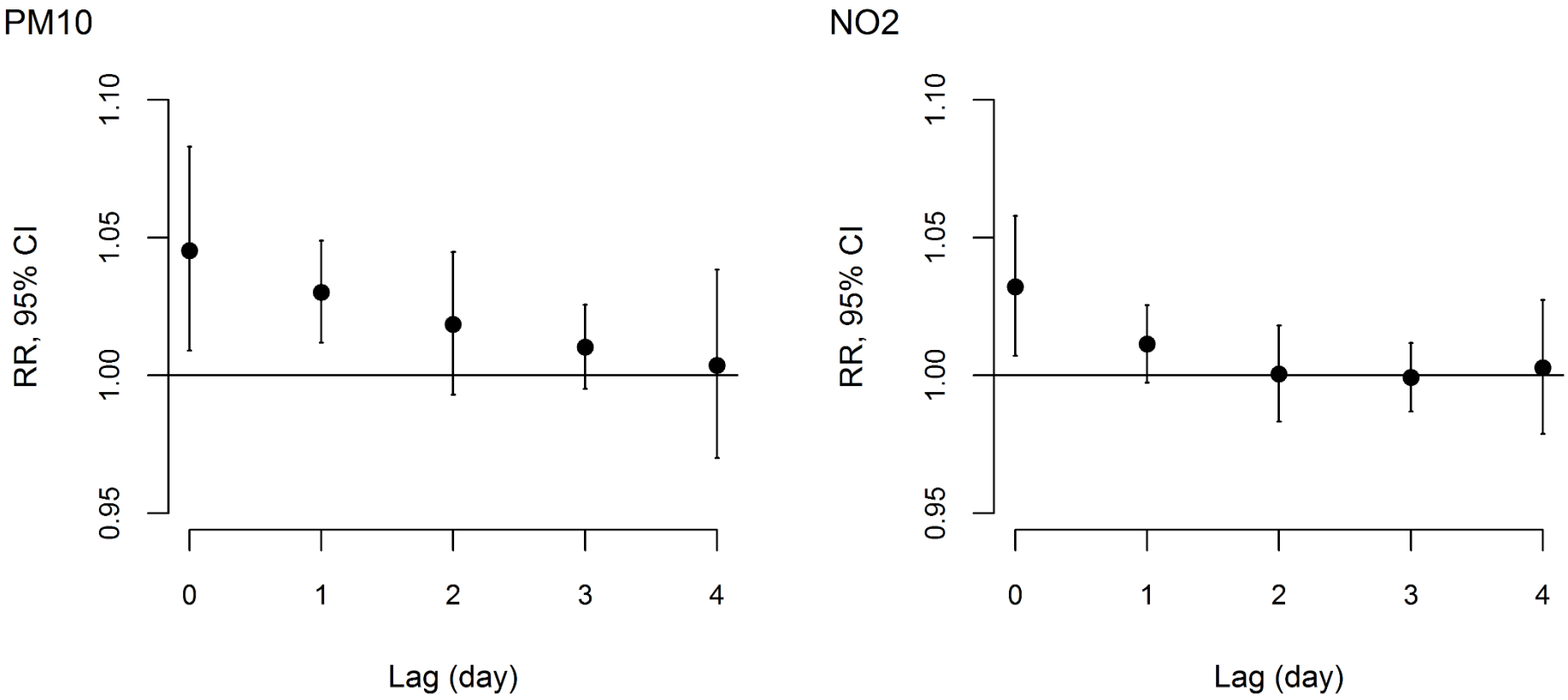
[c]The relevant exposure term in a case-crossover design (23). Min indicates minimum; Max, maximum.

Figure 1. Exposure-lag-response surfaces for the association between bronchiectasis exacerbations and exposure.



Exposure-lag-response surfaces for the association between bronchiectasis exacerbations and exposure to PM_{10} (left) and NO_2 (right). Relative risks (RR) are relative to the reference value of 10 µg/m^3 (bold line). Lag 0 is the day of exacerbation. Lag 1 is the day before the exacerbation. Lag 2, Lag 3 and Lag 4 are 2, 3 and 4 days before the exacerbation. RR = relative risk; PM_{10} = particulate matter with a diameter smaller than 10 µm.

Figure 2. Lag-specific relative risks for bronchiectasis exacerbations



Lag-specific relative risks (RR, with 95% confidence interval) for bronchiectasis exacerbations associated with a 10 μg/m^3 increase in PM_{10} (left) and NO_2 (right).

Table 3. Cumulative effects of PM_{10} and NO_2 on bronchiectasis exacerbations along the lag days.

Lay (day)	PM_{10}	NO_2
0	4.5 (0.9; 8.3)	3.2 (0.7; 5.8)
0-1	7.7 (3.7; 11.8)	4.4 (1.3; 7.5)
0-2	9.7 (5.4; 14.2)	4.5 (0.9; 8.1)
0-3	10.8 (6.1; 15.7)	4.4 (0.4; 8.5)
0-4	11.2 (6.0; 16.8)	4.7 (0.1; 9.5)

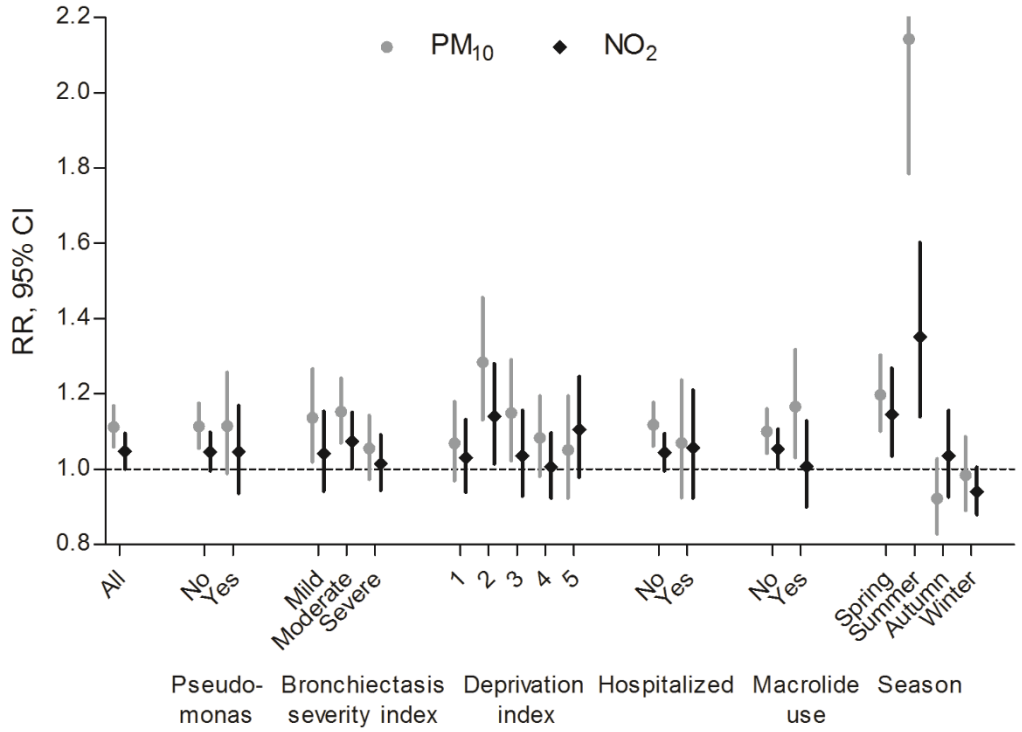
Estimates represent the percent change (95% confidence interval) in bronchiectasis exacerbations for a 10 μg/m^3 increase in air pollutant concentration.

Table 4 Sensitivity analysis estimates for the cumulative lag 0-4 effects of PM_{10} and NO_2 on bronchiectasis exacerbations.

Change in main model[b]	PM_{10}	NO_2
None	11.2 (6.0; 16.8)	4.7 (0.1; 9.5)
Maximum lag = 6 days	11.6 (6.5; 16.9)	3.9 (-0.5; 8.5)
Unconstrained lag model	11.8 (6.5; 17.4)	4.3 (-0.2; 9.1)
No temperature correction	10.0 (5.1; 15.1)	5.0 (0.7; 9.5)
Humidity correction	11.3 (5.8 ; 17.2)	3.6 (-1.1 : 8.6)
First event only	11.1 (-9.2; 36.0)	9.0 (-7.3; 28.1)

Estimates represent the percent change (95% confidence interval) in bronchiectasis exacerbations for a 10 $\mu g/m^3$ increase in air pollutant concentration. [b] In the main analysis recurrent event data were pooled, and the distributed lag model has a maximum lag of 4 days, 3 df for the lag-response function, and is adjusted for mean temperature (cross-basis function with a maximum lag of 25 days, 5 df for the temperature-response function, and 6 df for the lag-response function).

Figure 3: Association between bronchiectasis exacerbations and PM_{10} and NO_2 air pollution, overall and by subpopulation



Cumulative relative risks (RR, with 95% confidence interval) for bronchiectasis exacerbations associated with a 10 µg/m^3 increase in PM_{10} (grey circles) and NO_2 (black diamonds) stratified according to *Pseudomonas aeruginosa* culture positivity, bronchiectasis severity index, deprivation index, hospitalization, chronic macrolide use at time of exacerbation, and season.

Method used to identify exacerbations of bronchiectasis

We used a modification of methods previously used in UK medical records to identify exacerbations of COPD and applied this to the identification of bronchiectasis exacerbations. [1-3]

Guidelines for the management of bronchiectasis exacerbations locally recommended amoxicillin 500mg to 1g three times daily or doxycycline 100mg twice daily for acute exacerbation treatment during the study period. Additional options were clarithromycin 500mg twice daily, co-amoxiclav 625mg three times daily and ciprofloxacin 500mg twice daily only in patients with *P. aeruginosa*.

In the absence of a diagnostic code indicating a bronchiectasis exacerbation (or primary respiratory diagnostic code - see below -) exacerbations were identified by the acute prescription of one of the above recommended antibiotics. “Non-respiratory antibiotics” could be associated with bronchiectasis if a sputum sample was sent for culture concurrently or if the prescription was appropriate to the available microbiology data from a sputum culture within 12 months e.g co-trimoxazole with recent isolation of *Stenotrophomonas maltophilia* within 12 months. The assignment of exacerbation status is shown below (figure E1). The investigators that coded events as exacerbation or not were blinded to the air pollution data when determining whether events were included in the analysis or not. The analysis excluded chronic macrolide use, inhaled antibiotic use and drugs prescribed for *P. aeruginosa* eradication protocols.

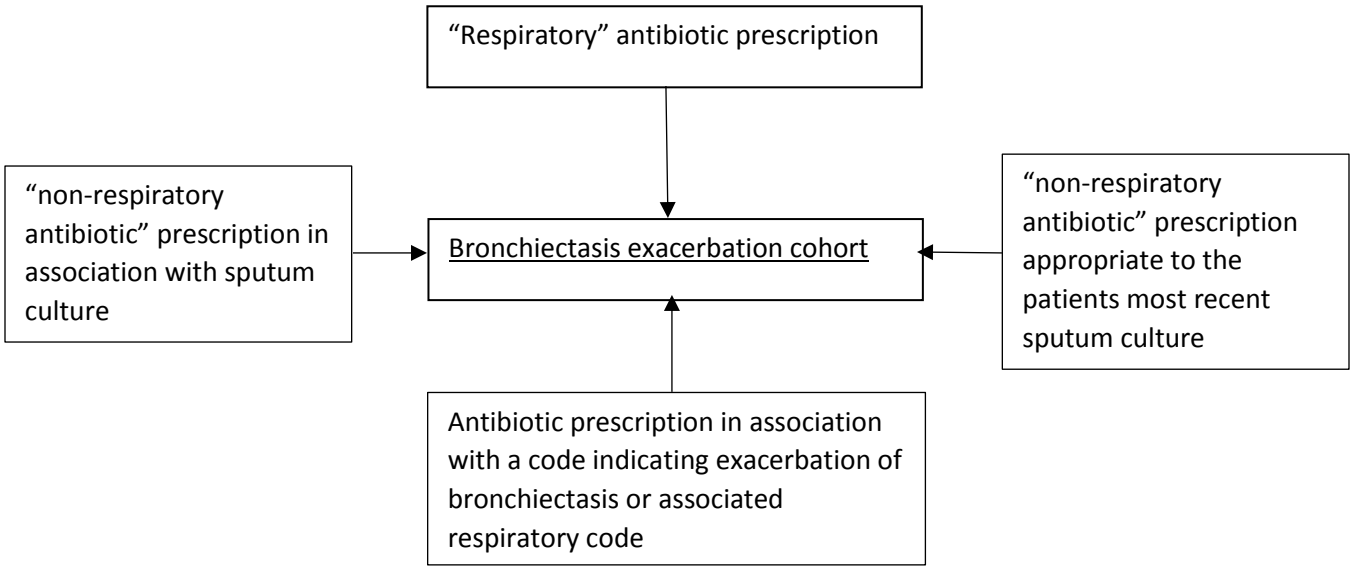


Figure E1: this figure shows the assignment of exacerbations status.

Diagnostic codes used to identify hospitalization for respiratory causes were J10 J11 J12 J15 J16 J17 J18 J44 J45 J47 which encompass lower respiratory tract infections and exacerbations of bronchiectasis, asthma and COPD. Multiple codes are used because of historical miscoding of bronchiectasis as asthma and COPD which is common in clinical practice. Only the primary diagnostic code was used.

Validation of the assignment of exacerbation events was performed using data from a prospective cohort of patients with bronchiectasis. [4] Fifty exacerbations that were prospectively diagnosed and confirmed and 38 non-respiratory events for which antibiotics were prescribed (predominantly urinary tract infections) were compared to the linked electronic medical records.

The above algorithm had successfully identified all 50 exacerbation events as being exacerbations of bronchiectasis giving a sensitivity of 100%. The algorithm also identified 5 out of 38 non-respiratory events as exacerbations of bronchiectasis giving a specificity of 87%.

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