



Early View

Original article

The impact of acute air pollution fluctuations on bronchiectasis pulmonary exacerbation. A case-crossover analysis

C. Pieter Goeminne, Bianca Cox, Simon Finch, Michael R. Loebinger, Pallavi Bedi, Adam T Hill, Tom C Fardon, Kees de Hoogh, Tim S. Nawrot, James D. Chalmers

Please cite this article as: Goeminne CP, Cox B, Finch S, *et al.* The impact of acute air pollution fluctuations on bronchiectasis pulmonary exacerbation. A case-crossover analysis. *Eur Respir J* 2018; in press (<https://doi.org/10.1183/13993003.02557-2017>).

This manuscript has recently been accepted for publication in the *European Respiratory Journal*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJ online.

Copyright ©ERS 2018

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

Goeminne Pieter C^{1,2}, Cox Bianca³, Finch Simon⁴, Loebinger Michael R⁵, Bedi Pallavi⁶, Hill Adam T⁷, Fardon Tom C⁴, de Hoogh Kees^{8,9}, Nawrot Tim S^{3,10}, Chalmers James D⁴

1. Department of respiratory Medicine, AZ Nikolaas, Sint-Niklaas, Belgium
2. Department of respiratory Medicine, UZ Leuven, Leuven, Belgium
3. Centre for Environmental Sciences, Hasselt University, Diepenbeek, Belgium
4. Scottish Centre for Respiratory Research, University of Dundee, Dundee, United Kingdom
5. Royal Brompton Hospital and National Heart and Lung Institute, Imperial College London, London, UK.
6. University of Edinburgh/MRC Centre for Inflammation Research, Queen's Medical Research Institute, Edinburgh, UK
7. Department of Respiratory Medicine, Royal Infirmary of Edinburgh, Edinburgh, UK; University of Edinburgh/MRC Centre for Inflammation Research, Queen's Medical Research Institute, Edinburgh, UK.
8. Swiss Tropical and Public Health Institute, Basel, Switzerland
9. University of Basel, Basel, Switzerland
10. Department of Public Health and Primary Care, Leuven University, Leuven, Belgium

Author contribution:

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.

Author contact:

Name: Pieter C Goeminne
Street + n°: Moerlandstraat 1
Postal code: B-9100
City and country: St-Niklaas, Belgium
e-mail: pieter.goeminne@aznikolaas.be
tel: +32 (0)3 760 23 27

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 PM₁₀ was based on 6741 exacerbations from 430 patients and for NO₂ it included 6248 exacerbations from 426 patients. For each 10µg/m³ increase in PM₁₀ and NO₂, 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/m³ increase in air pollutant concentration was 11.2% (95%CI:6.0-16.8) for PM₁₀ and 4.7% (95%CI:0.1-9.5) for NO₂. Subanalysis showed significant higher relative risks during spring (PM₁₀ 1.198, 95%CI 1.102-1.303;NO₂ 1.146, 95%CI:1.035-1.268) and summer (PM₁₀ 2.142, 95%CI:1.785-2.570;NO₂ 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 FEV₁ 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 PM₁₀ (particulate matter with a diameter smaller than 10 µm) and NO₂ 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, Mylnfield, Kinross, Dalwhinnie, and Tyndrum for the postcode areas Aberdeen, Dundee, Kirkcaldy, Perth, and Falkirk, respectively. As humidity data are not available for Mylnfield 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 PM₁₀ and NO₂. 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 $10 \mu\text{g}/\text{m}^3$ increase in air pollutant concentrations. In our analysis, this accords 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) $\mu\text{g}/\text{m}^3$ and 25.5 (1.7 to 85.7) $\mu\text{g}/\text{m}^3$

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 PM₁₀ and NO₂ was 0.35. The correlation with mean temperature was 0.05 for PM₁₀ and -0.30 for NO₂.

Effects of air pollution on exacerbation risk

The three-dimensional plots show the association between bronchiectasis and PM₁₀ and NO₂ 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 µg/m³ increase in air pollutant concentrations. Significant RR were observed at lag 0 and 1 for PM₁₀, and at lag 0 for NO₂. 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 µg/m³ increase in same-day (lag 0) PM₁₀ and NO₂, 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 µg/m³ increase in air pollutant concentration was 11.2% (95% CI 6.0 to 16.8) for PM₁₀ and 4.7% (95% CI 0.1 to 9.5) for NO₂. 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 µg/m³ increase in PM₁₀ was 1.115 (95% CI: 0.989 – 1.257) and for NO₂ 1.046 (95% CI: 0.937 – 1.169). In *P. aeruginosa* naïve patients relative risks for bronchiectasis exacerbations associated with a 10 µg/m³ increase in PM₁₀ was 1.114 (95% CI 1.056 – 1.175) and for NO₂ 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 (PM₁₀ 1.198, 95% CI 1.102 – 1.303; NO₂ 1.146, 95% CI 1.035 – 1.268) and especially during summer (PM₁₀ 2.142, 95% CI 1.785 – 2.570; NO₂ 1.352, 95% CI 1.140 – 1.602) as compared to autumn (PM₁₀ 0.922, 95% CI 0.828 – 1.027; NO₂ 1.035, 95% CI 0.927 – 1.156) and winter (PM₁₀ 0.984, 95% CI 0.891 – 1.086; NO₂ 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 PM₁₀, 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 NO₂, 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 PM₁₀ (11.1, 95% CI -9.2 to 36.0) but resulted in an increase in the estimate for NO₂ (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 PM₁₀ and NO₂, 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/m³ increase in air pollutant concentration was much higher, reaching 11.2% for PM₁₀ and 4.7% for NO₂.

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 PM₁₀ and NO₂, 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 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. PM₁₀ 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 PM₁₀ 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 PM₁₀ and PM_{2.5} correlation coefficient of 0.86. Moreover, we added NO₂ as black carbon is the particulate matter fraction that correlates best with NO₂.³⁵ NO₂ 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 PM₁₀ 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 existence 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 PM₁₀ by 10 µg/m³ would

potentially lead to a reduction of 11.2% exacerbations. This means that during the study period of 5384 days, a reduction of PM₁₀ 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.

Acknowledgements

Funded by the British Lung Foundation through the GSK/British Lung Foundation Chair of Respiratory Research to JDC and by the European Respiratory Society through the EMBARC (European Multicentre Audit and Research Collaboration) Project.

We acknowledge the support of the Health Informatics Centre (HIC), University of Dundee and the Farr Institute Scotland for managing and supplying the anonymised data and NHS Tayside, the original data source.

References

1. Chalmers JD, Goeminne PC, Aliberti S, McDonnell MJ, Lonni S, Davidson J, Poppelwell L, Salih W, Pesci A, Dupont LJ, Fardon TC, De Soyza A, Hill AT. The Bronchiectasis Severity Index: an international derivation and validation study. *Am J Respir Crit Care Med.* 2014;189(5):576-585
2. Chalmers JD, Aliberti S, Filonenko A, Shteinberg M, Goeminne PC, Hill AT, Fardon TC, Obradovic D, Gerlinger C, Sotgiu G, Operschall E, Rutherford RM, Dimakou K, Polverino E, De Soyza A, McDonnell MJ. Characterisation of the "Frequent Exacerbator Phenotype" in Bronchiectasis. *Am J Respir Crit Care Med.* 2018; doi: 10.1164/rccm.201711-2202OC.
3. Polverino E, Goeminne PC, McDonnell MJ, Aliberti S, Marshall SE, Loebinger MR, Murriss M, Cantón R, Torres A, Dimakou K, De Soyza A, Hill AT, Haworth CS, Vendrell M, Ringshausen FC, Subotic D, Wilson R, Vilaró J, Stallberg B, Welte T, Rohde G, Blasi F, Elborn S, Almagro M, Timothy A, Ruddy T, Tonia T, Rigau D, Chalmers JD. European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur Respir J.* 2017;50:1700629.
4. Chalmers JD, Haworth CS, Johnson C, Aliberti S, Goeminne PC, Ringhausen F, Boersma W, De Soyza A, Murriss M, Polverino E, Vendrell M. Management of bronchiectasis in Europe: Data from the European bronchiectasis registry (EMBARC). *Abstract presented at the European Respiratory Society Congress 2016 London.*
5. McCreanor J, Cullinan P, Nieuwenhuijsen MJ, Stewart-Evans J, Malliarou E, Jarup L, Harrington R, Svartengren M, Han IK, Ohman-Strickland P, Chung KF, Zhang J. Respiratory Effects of Exposure to Diesel Traffic in Persons with Asthma. *N Engl J Med.* 2007;357(23):2348-2358.

6. Angrill J, Agustí C, De Celis R, Fillela X, Rañó A, Elena M, De La Bellacasa JP, Xaubet A, Torres A. Bronchial inflammation and colonization in patients with clinically stable bronchiectasis. *Am J Respir Crit Care Med.* 2001;164(9):1628-1632.
7. Goeminne PC, Kiciński M, Vermeulen F, Fierens F, De Boeck K, Nemery B, Nawrot TS, Dupont LJ. Impact of air pollution on cystic fibrosis pulmonary exacerbations: a case-crossover analysis. *Chest.* 2013;143(4):946-954
8. Farhat SC, Almeida MB, Silva-Filho LV, Farhat J, Rodrigues JC, Braga AL. Ozone is associated with an increased risk of respiratory exacerbations in patients with cystic fibrosis. *Chest.* 2013;144(4):1186-1192
9. Jassal MS, Yu AM, Bhatia R, Keens TG, Davidson Ward SL. Effect of residential proximity to major roadways on cystic fibrosis exacerbations. *Int J Env H Res.* 2013;23(2):119-131
10. Goss CH, Newsom SA, Schildcrout JS, Sheppard L, Kaufman JD. Effect of ambient air pollution on pulmonary exacerbations and lung function in cystic fibrosis. *Am J Respir Crit Care Med.* 2004;169(7):816-821
11. Goeminne PC, Bijmens E, Nemery B, Nawrot TS, Dupont LJ. Impact of traffic related air pollution indicators on non-cystic fibrosis bronchiectasis mortality: a cohort analysis. *Respir Res.* 2014;15:108
12. Short PM, Anderson WJ, Elder DH, Struthers AD, Lipworth BJ. Impact of left ventricular hypertrophy on survival in chronic obstructive pulmonary disease. *Lung.* 2015;193(4):487-495.

13. Short PM, Lipworth SI, Elder DH, Schembri S, Lipworth BJ. Effect of beta-blockers in treatment of chronic obstructive disease: a retrospective cohort study. *BMJ*. 2011;342:d2549.
14. Schembri S, Williamson PA, Short PM, Singanayagam A, Akram A, Taylor J, Singanayagam A, Hill AT, Chalmers JD. Cardiovascular events following Clarithromycin use in lower respiratory tract infections: analysis of two prospective cohort studies. *BMJ*. 2013;346:f1235.
15. Ye X, Wolff R, Yu W, Vaneckova P, Pan X, Tong S. Ambient temperature and morbidity: a review of epidemiological evidence. *Environ Health Perspect*. 2012;120(1):19-28.
16. Nawrot TS, Perez L, Kunzli N, Munters E, Nemery B. Public health importance of triggers of myocardial infarction: a comparative risk assessment. *Lancet*. 2011;377(9767):732-740.
17. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. *Am J Epidemiol*. 1991;133:144-153.
18. Levy D, Lumley T, Sheppard L, Kaufman J, Checkoway H. Referent selection in case-crossover analyses of acute health effects of air pollution. *Epidemiology*. 2001;12(2):186-192.
19. Luo X, Sorock GS. Analysis of recurrent event data under the case-crossover design with applications to elderly falls. *Stat Med*. 2008;27:2890-2901.
20. Gasparrini A. Modeling exposure-lag-response associations with distributed lag non-linear models. *Stat Med*. 2014;33(5):881-899.
21. Gasparrini A. Distributed lag linear and non-linear models in R: the package dlnm. *J Stat Softw*. 2011;43(8):1-20.
22. Scottish Government. The Scottish Index of Multiple Deprivation. <http://www.gov.scot/Topics/Statistics/SIMD/>

23. Dickie C. Guidance on the definition of SIMD quintiles. <http://www.gov.scot/Resource/0043/00439496.pdf>
24. Schwartz J. The distributed lag between air pollution and daily deaths. *Epidemiology*. 2000;11(3):320-326.
25. Luo X, Sorock GS. Analysis of recurrent event data under the case-crossover design with applications to elderly falls. *Stat Med*. 2008;27(15):2890-2901.
26. Kunzli N, Schindler C. A call for reporting the relevant exposure term in air pollution case-crossover studies. *J Epidemiol Community Health*. 2005;59(6):527-530.
27. Tramuto F, Cusimano R, Cerame G, Vultaggio M, Calamusa G, Maida CM, Vitale F. Urban air pollution and emergency room admissions for respiratory symptoms: a case-crossover study in Palermo, Italy. *Environ Health*. 2011;10:31.
28. Hetland RB, Cassee FR, Låg M, Refsnes M, Dybing E, Schwarze PE. Cytokine release from alveolar macrophages exposed to ambient particulate matter: heterogeneity in relation to size, city and season. *Part Fibre Toxicol*. 2005;2:4.
29. Sørensen M, Loft S, Andersen HV, Raaschou-Nielsen O, Skovgaard LT, Knudsen LE, Nielsen IV, Hertel O. Personal exposure to PM_{2.5}, black smoke and NO₂ in Copenhagen: relationship to bedroom and outdoor concentrations covering seasonal variation. *J Expo Anal Environ Epidemiol* . 2005; 15: 413-422.
30. Collaco JM, McGready J, Green DM, Naughton KM, Watson CP, Shields T, Bell SC, Wainwright CE; ACFBAL Study Group, Cutting GR. Effect of temperature on cystic fibrosis lung disease and infections: a replicated cohort study. *PLoS ONE*. 2011;6: e27784 .

31. Wong C, Jayaram L, Karalus N, Eaton T, Tong C, Hockey H, Milne D, Fergusson W, Tuffery C, Sexton P, Storey L, Ashton T. Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2012;380(9842):660-667.
32. Serisier DJ, Martin ML, McGuckin MA, Lourie R, Chen AC, Brain B, Biga S, Schlebusch S, Dash P, Bowler SD. Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non-cystic fibrosis bronchiectasis: the BLESS randomized controlled trial. *JAMA*. 2013;309(12):1260-1267.
33. Hill AT, Haworth CS, Aliberti S, Barker A, Blasi F, Boersma W, Chalmers JD, De Soyza A, Dimakou K, Elborn JS, Feldman C, Flume P, Goeminne PC, Loebinger MR, Menendez R, Morgan L, Murris M, Polverino E, Quittner A, Ringshausen FC, Tino G, Torres A, Vendrell M, Welte T, Wilson R, Wong C, O'Donnell A, Aksamit T; EMBARC/BRR definitions working group. Pulmonary exacerbations in adults with bronchiectasis: a consensus definition for clinical research. *Eur Respir J* 2017;49(6).
34. Brook RD, Rajagopalan S, Pope CA 3rd, Brook JR, Bhatnagar A, Diez-Roux AV, Holguin F, Hong Y, Luepker RV, Mittleman MA, Peters A, Siscovick D, Smith SC Jr, Whitsel L, Kaufman JD; American Heart Association Council on Epidemiology and Prevention, Council on the Kidney in Cardiovascular Disease, and Council on Nutrition, Physical Activity and Metabolism. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. *Circulation*. 2010 Jun 1;121(21):2331-2378.
35. Vanderstraeten P , Forton M , Brasseur O , Offer ZY. Black carbon instead of particle mass concentration as an indicator for the traffic related particles in the Brussels capital region. *JEP*. 2011;2:525-532 .

36. Janssen NA, Lanki T, Hoek G, Vallius M, de Hartog JJ, Van Grieken R, Pekkanen J, Brunekreef B. Associations between ambient, personal, and indoor exposure to fine particulate matter constituents in Dutch and Finnish panels of cardiovascular patients. *Occup Environ Med.* 2005 ;62(12):868-877
37. Williams R, Suggs J, Zweidinger R, Evans G, Creason J, Kwok R, Rodes C, Lawless P, Sheldon L. The 1998 Baltimore Particulate Matter Epidemiology-Exposure Study: part 1. Comparison of ambient, residential outdoor, indoor and apartment particulate matter monitoring. *J Expo Anal Environ Epidemiol.* 2000;10(6pt1):518-532 .
38. Scheers H, Mwalili SM, Faes C, Fierens F, Nemery B, Nawrot TS. Does air pollution trigger infant mortality in Western Europe? A case-crossover study. *Environ Health Perspect.* 2011;119(7):1017-1022.
39. Roberts ME, Lowndes L, Milne DG, Wong CA. Socioeconomic deprivation, readmissions, mortality and acute exacerbations of bronchiectasis. *Intern Med J.* 2012; 42: e129–e136
40. Mao B, Yang JW, Lu HW, Xu JF. Asthma and bronchiectasis exacerbation. *Eur Respir J.* 2016 Jun;47(6):1680-6.
41. Guarneri M, Balmes JR. Outdoor air pollution and asthma. *Lancet* 2014;383:1581-92
42. Goeminne PC, Nawrot TS, Ruttens D, Seys S, Dupont LJ. Mortality in non-cystic fibrosis bronchiectasis: a prospective cohort analysis. *Respir Med.* 2014 Feb;108(2):287-96.
43. Gatheral T, Kumar N, Sansom B, Lai D, Nair A, Vlahos I, Baker EH. COPD-related bronchiectasis; independent impact on disease course and outcomes. *COPD.* 2014 Dec;11(6):605-14.

44. Gan WQ, FitzGerald JM, Carlsten C, Sadatsafavi M, Brauer M. Associations of ambient air pollution with chronic obstructive pulmonary disease hospitalization and mortality. *Am J Respir Crit Care Med*. 2013 Apr 1;187(7):721-7.
45. World Health Organization. Health Risks of Particulate Matter from Long-range Transboundary Air Pollution. Copenhagen, World Health Organization Regional Office for Europe, 2006. Available from http://www.euro.who.int/_data/assets/pdf_file/0006/78657/E88189.pdf Accessed July 12, 2017.

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	<i>Haemophilus influenzae</i> : 136 (31.6) <i>Staphylococcus aureus</i> : 34 (7.9) <i>Moraxella catarrhalis</i> : 53 (12.3) <i>Enterobacteriaceae</i> : 59 (13.7) <i>Pseudomonas aeruginosa</i> : 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 (µg/m ³) ^a	15.8	9.4	1.0	82.6
NO ₂ (µg/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 (µg/m ³) ^a	7.2	7.1	0.0	62.8
NO ₂ (µg/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.

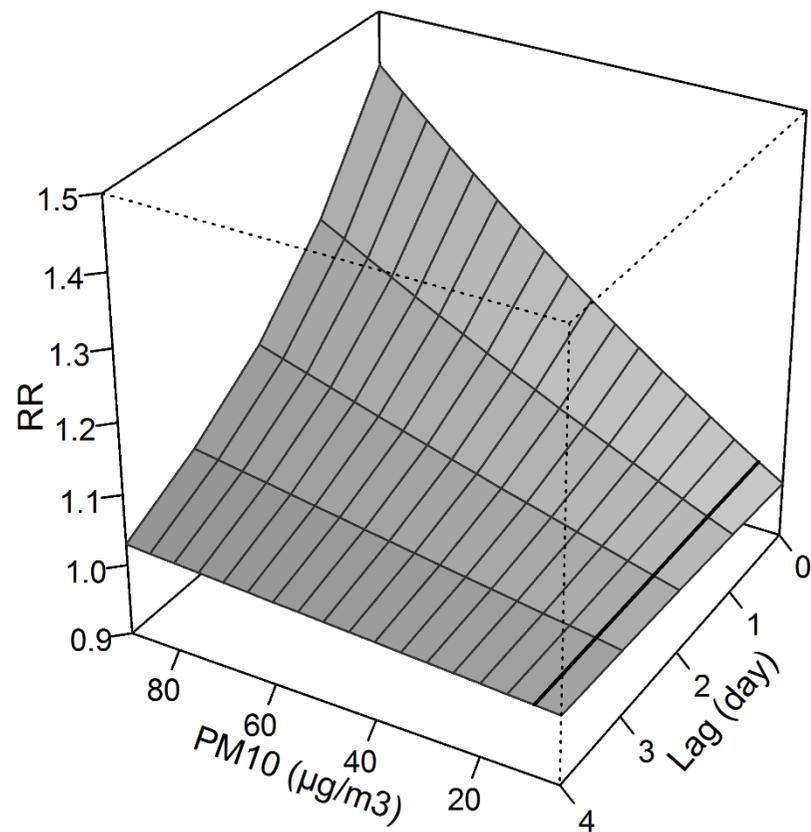
^aSummary statistics for cases with PM₁₀ data available (N exacerbations = 6741; Total number of patients = 430).

^bSummary statistics for cases with NO₂ data available (N exacerbations = 6248; Total number of patients = 426).

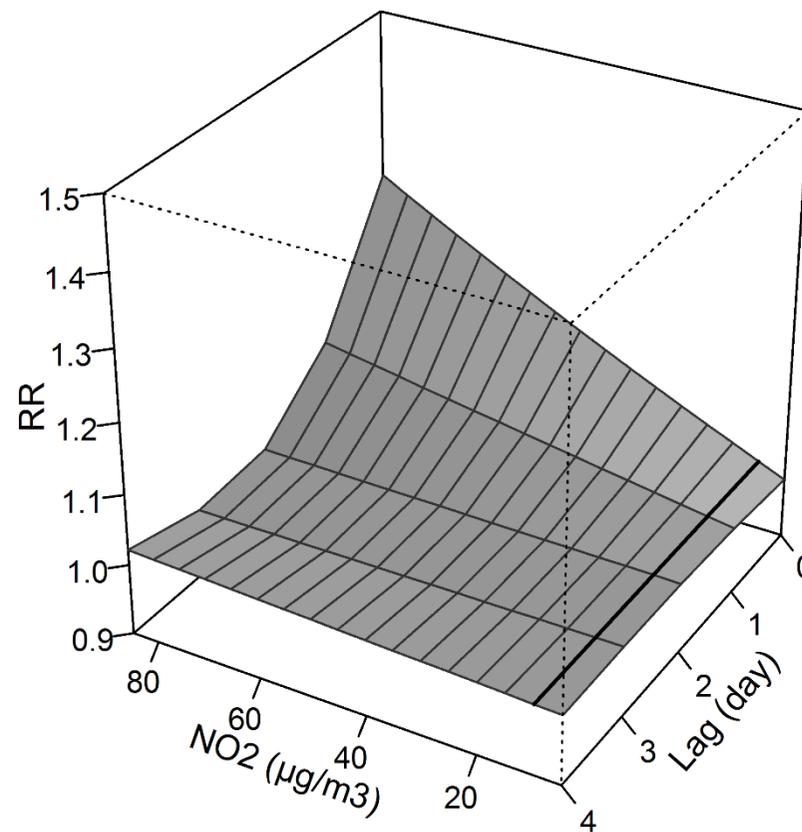
^cThe relevant exposure term in a case-crossover design (23). Min indicates minimum; Max, maximum.

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

PM10



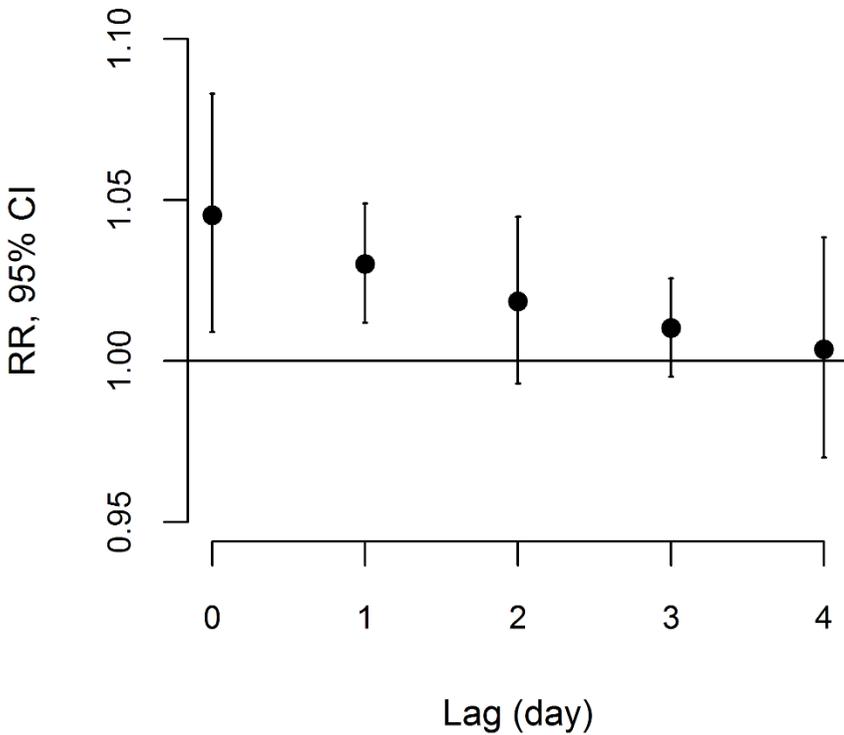
NO2



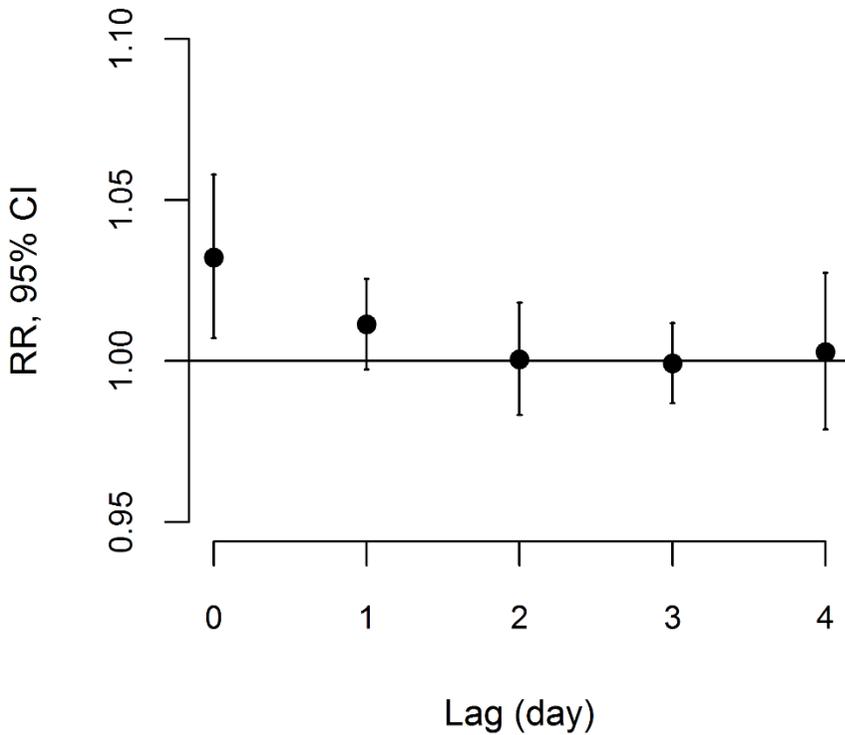
Exposure-lag-response surfaces for the association between bronchiectasis exacerbations and exposure to PM₁₀ (left) and NO₂ (right). Relative risks (RR) are relative to the reference value of 10 µg/m³ (bold line). Lag 0 is the day of exacerbation. Lag 1 is the day before the exacerbation. Lag 2, Lag 3 and Lag 4 are 2, 3 and 4 days before the exacerbation. RR = relative risk; PM₁₀ = particulate matter with a diameter smaller than 10 µm.

Figure 2. Lag-specific relative risks for bronchiectasis exacerbations

PM10



NO2



Lag-specific relative risks (RR, with 95% confidence interval) for bronchiectasis exacerbations associated with a 10 $\mu\text{g}/\text{m}^3$ increase in PM₁₀ (left) and NO₂ (right).

Table 3. Cumulative effects of PM₁₀ and NO₂ on bronchiectasis exacerbations along the lag days.

Lag (day)	PM₁₀	NO₂
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)

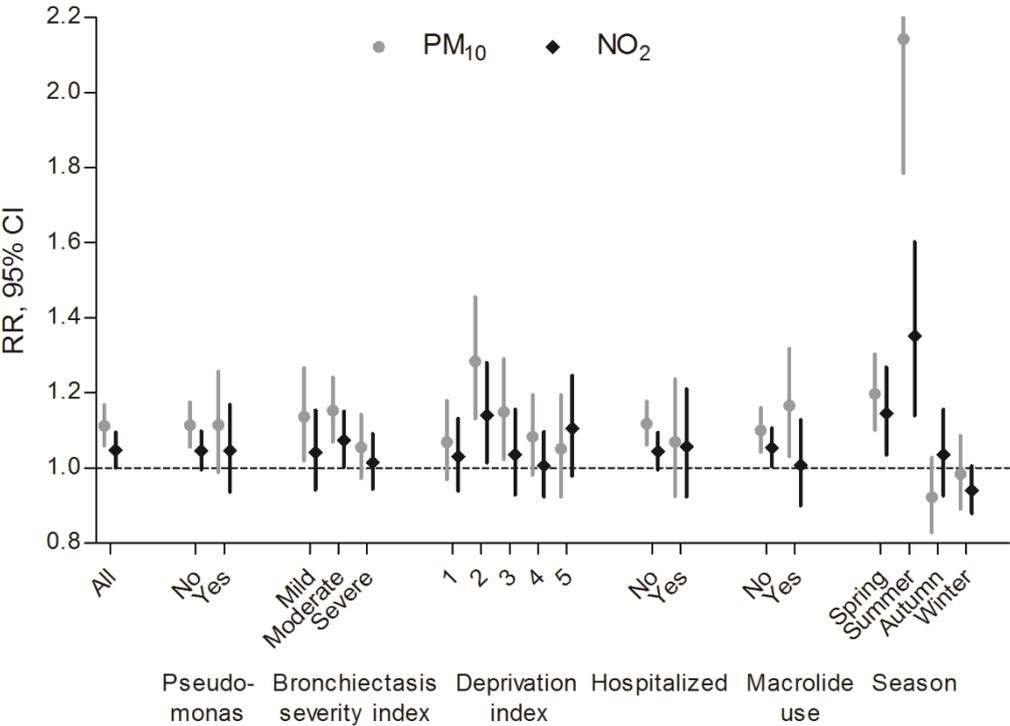
Estimates represent the percent change (95% confidence interval) in bronchiectasis exacerbations for a 10 µg/m³ increase in air pollutant concentration.

Table 4 Sensitivity analysis estimates for the cumulative lag 0-4 effects of PM₁₀ and NO₂ on bronchiectasis exacerbations.

Change in main model^b	PM₁₀	NO₂
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 µg/m³ 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 PM₁₀ and NO₂ air pollution, overall and by subpopulation



Cumulative relative risks (RR, with 95% confidence interval) for bronchiectasis exacerbations associated with a 10 µg/m³ increase in PM₁₀ (grey circles) and NO₂ (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.

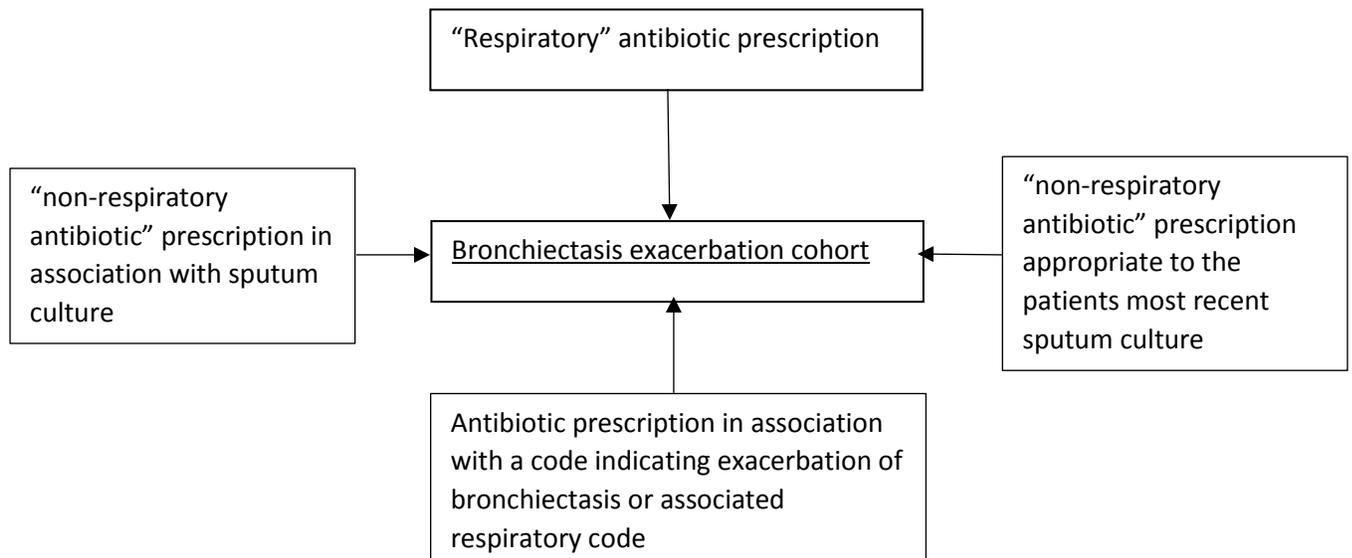


Figure E1: this figure shows the assignment of exacerbations status.

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%.

References

1. Rothnie KJ, Müllerová H, Hurst JR, Smeeth L, Davis K, Thomas SL, Quint JK. et al, Validation of the Recording of Acute Exacerbations of COPD in UK Primary Care Electronic Healthcare Records. PLoS One. 2016; 11(3): e0151357
2. Navaratnum V, Root AA, Douglas I, Smeeth L, Hubbard RB, Quint JK., Cardiovascular Outcomes after a Respiratory Tract Infection among Adults with Non-Cystic Fibrosis Bronchiectasis: A General Population-based Study. Ann Am Thorac Soc. 2018 Mar;15(3):315-321.
3. Mullerova H, Shukla A, Hawkins A, Quint J., Risk factors for acute exacerbations of COPD in a primary care population: a retrospective observational cohort study. BMJ Open. 2014 Dec 18;4(12):e006171.
4. Chalmers JD, Moffitt KL, Suarez-Cuartin G, Sibila O, Finch S, Furrrie E, Dicker A, Wrobel K, Elborn JS, Walker B, Martin SL, Marshall SE, Huang JT, Fardon TC. Neutrophil Elastase Activity Is Associated with Exacerbations and Lung Function Decline in Bronchiectasis. Am J Respir Crit Care Med. 2017 May 15;195(10):1384-1393)