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Original Research

GENETIC AND DEVELOPMENTAL DISORDERS

Impact of Air Pollution on Cystic Fibrosis Pulmonary Exacerbations

A Case-Crossover Analysis

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Background: **Pulmonary exacerbations in cystic fibrosis (CF) contribute to the burden of disease, with a negative impact on quality of life, costs, and lung function. Our aim was to evaluate whether exacerbations, defined by antibiotic use, were triggered by daily fluctuations in air pollution.**
Methods: **In a case-crossover analysis, we evaluated 215 patients with CF and pollution data from January 1, 1998, to December 31, 2010. Exacerbation was defined as the start of IV or oral antibiotic use in a home or hospital setting. We calculated regional background levels of particulate matter with a diameter < 10 μm (PM_{10}), ozone, and nitrogen dioxide (NO_2) on the day of the event and on the 2 days prior to the event at each patient's home address. We matched for day of the week and controlled for temperature on the day of the event and the 2 preceding days. In the month where antibiotic treatment was started, all days with the same temperature ($\pm 2°C$) as the event day served as control days, excluding 3 days before and after the start of treatment.**
Results: **A total of 215 patients (male sex, 49%, mean age, 21 ± 13 years) had 2,204 antibiotic treatments (1,107 IV and 1,097 oral). Over a period of 12 years, an increase in risk of antibiotic use was associated with increasing concentrations of PM_{10}, NO_2, and ozone on the event day and for NO_2 on the day before. A tendency toward significance was seen the day before antibiotic use for PM_{10} and ozone. Overall, a rise in OR was seen from 2 days before until the day of the start of antibiotics.**
Conclusions: **In patients with CF and exacerbations, ambient concentrations of ozone, PM_{10}, and NO_2 play a role in triggering an exacerbation.** ***CHEST 2013; 143(4):946–954***

Abbreviations: CF = cystic fibrosis; NO_2 = nitrogen dioxide; $PM_{2.5}$ = particulate matter with a diameter < 2.5 μm; PM_{10} = particulate matter with a diameter < 10 μm

Air pollution is linked to a decrease in lung function in healthy adults and children.[1-3] The adverse impact of pollution has been implicated in different acute and chronic pulmonary diseases, such as pneumonia, COPD, and asthma.[4-6] Pollution can trigger cellular responses in the lung, resulting in cytotoxicity, inflammation, and mutagenesis. Kamdar et al[7] showed that bronchial epithelial cells from patients with cystic fibrosis (CF) were highly sensitive to airborne particulate matter-induced oxidative stress and apoptosis at a much lower dose than normal bronchial cells, suggesting that CF airways undergo an intense response to the oxidative stress induced by air

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pollution. Linking retrospective data from the Cystic Fibrosis Foundation National Patient Registry and the US Environmental Protection Agency Aerometric Information Retrieval System, Goss et al[8] showed that annual average levels of air pollution exposure were associated with lung function decrease and an increased likelihood of exacerbation in CF. Acute changes in air pollution have not been studied. Pulmonary exacerbations in CF contribute significantly to the burden of disease, with a negative impact on quality of life, costs, and lung function.[9-14] Our aim was to evaluate in a case-crossover analysis whether exacerbations, defined by antibiotic use, were associated with daily fluctuations in air pollution.

Materials and Methods

Patient Selection

We obtained clinical data from the CF patient database of the University Hospital Gasthuisberg, Leuven, Belgium, a CF referral center that cared for 285 patients at the time of this study. CF diagnosis was based on the presence of two known CF mutations or one known mutation with a positive sweat test or the absence of a known mutation but suggestive symptoms and a positive sweat test. Patients were excluded from analysis for the following reasons: no exacerbation or registered antibiotic use between January 1, 1998, and December 31, 2010 (n = 52), and no clear end dates of all antibiotic treatments so that start dates of new treatments were overlapping (n = 18). Exacerbation data from the remaining 215 patients were used for analysis. A pulmonary exacerbation was defined as the use of IV antibiotics at home or in the hospital or the use of oral antibiotics at home or in the hospital. All episodes of oral and IV antibiotic use mentioned in the clinical records for each patient were registered from September 1990 to March 2011. Clinical records included detailed registration of all oral antibiotic use on the basis of patient history obtained during clinic visits (outpatient visits at least quarterly) and information from the general practitioner. For the analysis, three end points were tested: (1) all episodes of IV antibiotic administration because of clinical or FEV_1 deterioration; (2) all oral antibiotic treatments because of clinical or FEV_1 deterioration; and (3) all IV or oral antibiotic treatments because of clinical or FEV_1 deterioration. For the definition of clinical or lung function deterioration, we used modified Fuchs criteria validated by the European consensus group (EuroCareCF Working Group).[15,16] In patients with long periods of oral antibiotic use and intermittent IV antibiotic use, the IV antibiotic events were registered as an event. Episodes of elective treatment with antibiotics, which has never been a routine practice at our center, were not registered. For the descriptive analysis, the least favorable status for patients with a change in *Pseudomonas* infection status was chosen (ie, chronic > intermittent > free > never). For the subanalysis on the effect of pollution between the different *Pseudomonas* infection status groups, each antibiotic treatment was allocated to the *Pseudomonas* infection status at that moment according to Leeds criteria.[17]

Air Pollution and Meteorologic Data

We calculated the residential background levels of particulate matter with a diameter < 10 μm (PM_{10}), ozone, and nitrogen dioxide (NO_2) on the day of the event (lag 0) and 2 days prior to the event (lag 1 and lag 2) for each patient's home address using a kriging interpolation method.[18,19] This model provides interpolated ozone, NO_2, and PM_{10} values from the Belgian regional telemetric air quality networks in 4×4-km grids. The interpolation was based on a detrended kriging interpolation model that uses land cover data obtained from satellite images (Corine land cover 2000 data set; European Environment Agency). The Royal Meteorological Institute (Brussels, Belgium) provided mean daily temperatures and relative humidity of the study region over the study period.

Statistical Analysis

We used data collected between January 1, 1998, and December 31, 2010, to estimate ORs associated with a 10-μg/m^3 increase of daily average PM_{10} and NO_2 concentrations and daily highest 8-h mean ozone on the day of CF exacerbation and the 2 preceding days. For ozone, only the months of May to September were considered. The daily highest 8-h ozone averages were used because ozone concentrations during the night are low and do not correctly represent acute exposure during day.

We applied a case-crossover design, which is widely used for analyzing short-term pollution exposure with acute outcomes.[20,21] It is a variant of the matched case-control design in which each subject serves as his or her own control.[22] As possible control days, we used all the days of the month of the event both before and after the day of the event. Additionally, to avoid short-term autocorrelation, the 3 days around the event day were excluded (Fig 1). This so-called bidirectional approach avoids selection bias[23] and overlap bias.[24] We matched for temperature by excluding control days that differed from the event day by > 2°C and adjusted the analyses for day of the week by inclusion of an indicator variable in the model. We also studied potential effect modification by season.

Because the day of the week may be a strong confounder for the type of event we investigated, we did an analysis where we matched for day of the week, controlling for temperature on the day of the event and the 2 previous days using restricted cubic splines with four knots.[25] Furthermore, we studied the effects stratified by *Pseudomonas* infection status. The conditional logistic regression models were fitted using the PROC PHREG procedure (SAS version 9.2; SAS Institute Inc).

Ethics Committee

Approval was obtained from the local ethics committee of the University Hospital Gasthuisberg (B51060-B32220084152).

Results

Patient Characteristics

The 215 patients (male sex, 49%; mean age, 21 ± 13 years) had a total of 2,204 treatments, including 1,107 IV antibiotic treatments and 1,097 oral antibiotic

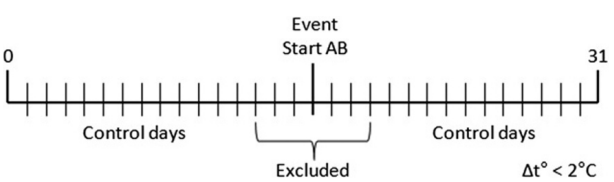

Figure 1. Case-crossover control days, using a bidirectional approach. All the days of the month where AB treatment was started serve as control days, with the exception of 3 days before and after the start of treatment. Control days with the same temperature (± 2°C) as the event day were selected. AB = antibiotic.

treatments. In analyses with matching for temperature, a total of 2,147 treatments (1,075 IV and 1,072 oral) remained for further analysis after excluding treatments that had no possible control day according to study criteria. Pancreatic insufficiency was noted in 85% of the patients. CF genotype distribution encompassed 55% homozygous DF508/DF508, 35% heterozygous DF508/other, and 10% other mutations. *Pseudomonas* infection status according to Leeds criteria showed chronic infection in 30%, intermittent infection in 14%, free of infection in 13%, and never infected in 43%.[17]

Pollution Results

The exposure indicators and temperature on the days of the events are shown in Table 1. Median (interquartile range) values of pollution on the days of the events were 72.4 (57.3-90.3) $\mu g/m^3$ for ozone, 24 (17.6-32.1) $\mu g/m^3$ for PM_{10}, and 23.9 (17.2-31.9) $\mu g/m^3$ for NO_2 (Table 1).

For the three end points, we found an increase in the risk of exacerbation by increasing concentrations of PM_{10}, NO_2, and ozone on the day antibiotic treatment was started (lag 0) (Fig 2A-2C). For every 10-$\mu g/m^3$ increase of NO_2, we observed an 11.6% increase of the odds to start oral or IV antibiotics, an 11.4% increase of the odds of IV antibiotic treatment, and a 14.2% increase of the odds of oral antibiotic treatment. One day before the start of antibiotic treatment, NO_2 showed the highest odds of the three pollutants (IV or oral antibiotic treatment odds increase by 6.3%, IV odds increase by 6.7%, and oral odds increase by 6.5%) (Figs 2A-C). Overall, a rise in OR can be seen for all three pollutants throughout the 3 measured days, with highest odds on the day of the start of treatment.

Stratification by oral or IV antibiotic administration revealed no differences in risk magnitudes of exacerbations in association with exposure of PM_{10} and NO_2 on the day of the event. However, ozone was not associated with exacerbations defined as intake of oral antibiotics.

We also averaged the exposure of the case day and the day before. This revealed a significant result for all pollutants. Estimates calculated per 10-$\mu g/m^3$ increase resulted in an increase of the risk for exacerbation by 4.3% (95% CI, 1.004-1.084; $P = .03$) for PM_{10}, of 10.6% (95% CI, 1.05-1.166; $P < .001$) for NO_2, and of 3.4% (95% CI, 1.003-1.067; $P = .03$) for ozone for both IV and oral antibiotic treatments.

As expected, daily variation in NO_2 and PM_{10} were strongly correlated ($r = 0.67$, $P < .0001$), whereas the association between ozone and either NO_2 or PM_{10} was less evident ($r = -0.43$ and -0.22, respectively, $P < .0001$). Analysis of all events (both oral and IV antibiotics) showed in multiple pollution models a significant association with NO_2 on the day of the event (OR, 1.169 per 10-$\mu g/m^3$ increase; 95% CI, 1.081-1.264; $P < .001$) but not with PM_{10} (OR, 0.972 per 10-$\mu g/m^3$ increase; 95% CI, 0.92-1.027; $P = .31$) or ozone (OR, 1.022 per 10-$\mu g/m^3$ increase; 95% CI, 0.99-1.054; $P = .18$). Estimates from analyses with control days matched for day of the week were comparable to those from analyses with control days matched for temperature, with significance at lag 0 and no significance at lag 1 and 2 (data not shown).

Analysis of chronic *Pseudomonas* vs nonchronic colonization showed no significant differences in exacerbations induced by air pollution between both groups because there was an overlap in the 95% CIs. However, based on both effect size and significance, the effect seems to be stronger in the *Pseudomonas* chronic colonization group (Table 2).

Although the number of exacerbations did not differ among seasons, a stronger effect of air pollution on exacerbations was seen during warmer months. For every 10-$\mu g/m^3$ increase of NO_2 or PM_{10}, a significant increase in the odds to start antibiotic treatment was seen during the months of April to September. This effect was seen for the day therapy was started up to 2 days prior to treatment (Table 3).

Discussion

This case-crossover analysis in 215 patients with CF showed that the risk of having an exacerbation increased significantly on days with higher air pollution. Independent of temperature, the risk for antibiotic therapy increased by 11.6% and 6.3% for each 10-$\mu g/m^3$ increase in ambient NO_2 at the same or previous day, respectively. Significant results were also seen for ozone and PM_{10}.

Table 1—*Distribution of the Exposure Indicators and Temperature on the Days of the Events*

Pollutant	5th Percentile	Lower Quartile	Median	Upper Quartile	95th Percentile
PM_{10}, $\mu g/m^3$	11.7	17.6	24	32.1	53.3
NO_2, $\mu g/m^3$	10	17.2	23.9	31.9	47.3
Ozone, $\mu g/m^3$[a]	39	57.3	72.4	90.3	132.4
Temperature, °C	−2.9	3.1	8.8	14.7	20.8

NO_2 = nitrogen dioxide; PM_{10} = particulate matter with a diameter < 10 μm.
[a]For ozone, only events between May and September were considered and the daily highest 8-h mean used.

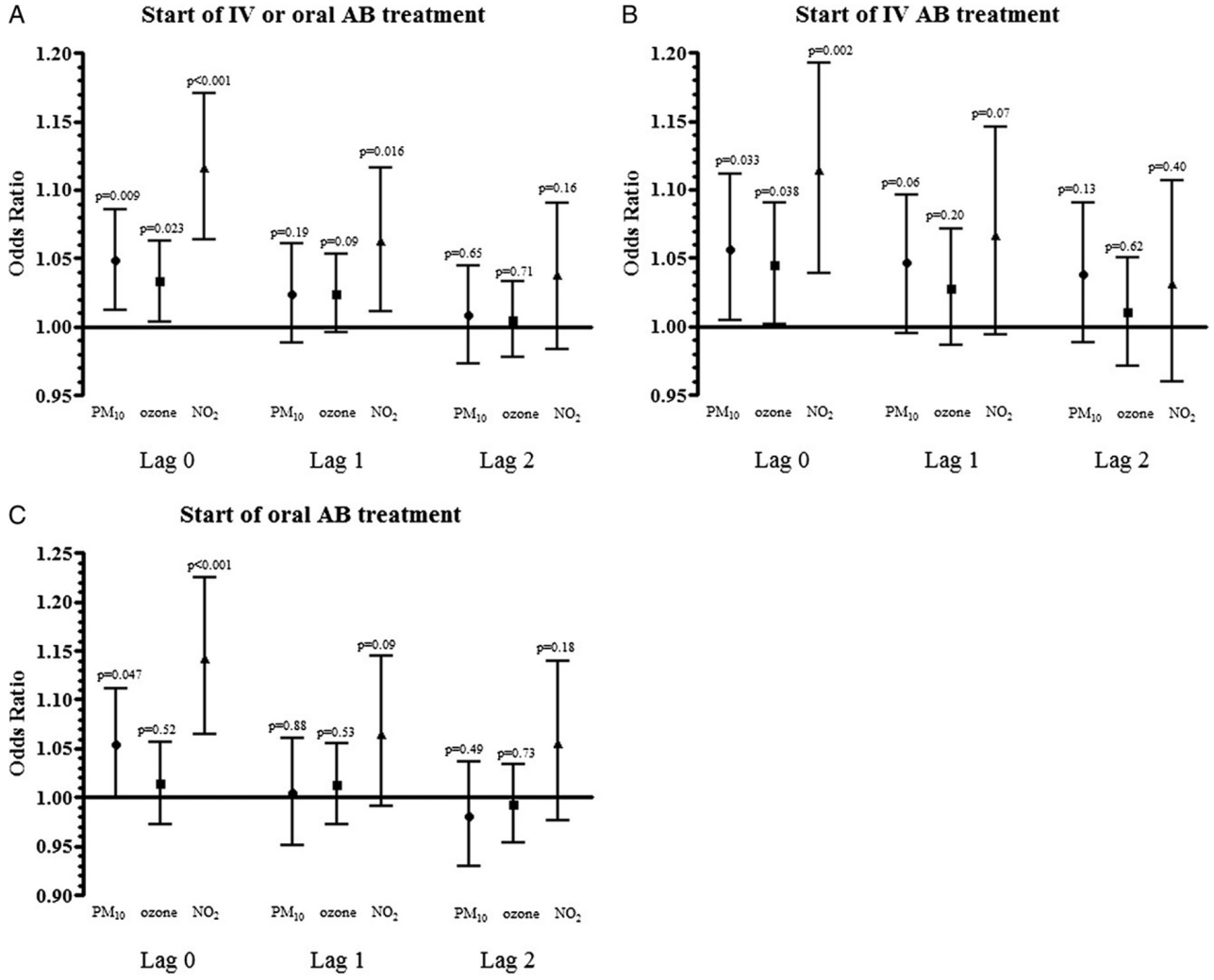

FIGURE 2. Assessment of oral and IV AB treatment per 10-$\mu g/m^3$ increase of three pollutants. When analyzed together and separately, a rise in OR can be seen from 2 d before antibiotic start until the day antibiotics were started. A, Assessment of all events at the start of either oral or IV AB treatment. There is an overall significance at lag 0. At lag 1, only NO_2 showed significance over the other two pollutants. B, Assessment of start of IV AB treatment. There is an overall significance at lag 0. C, Assessment of start of oral AB treatment. There is an overall significance at lag 0, except for ozone. lag 0 = the day of the start of antibiotic treatment; lag 1 = the day before the start of antibiotic treatment; lag 2 = 2 days before the start of antibiotic treatment; NO_2 = nitric dioxide; PM_{10} = particulate matter with a diameter < 10 μm. See Figure 1 legend for expansion of other abbreviation.

Previous research on CF and pollution showed a significant association between annual average exposure to PM_{10} and ozone and exacerbation rate.[8] In addition to these data, the present results show for the first time to our knowledge that exacerbations in patients with CF that are associated with exposure to air pollution. The major advantage of this study is its case-crossover design, reducing the influence of confounding covariates because each crossover patient serves as his or her own control. Compared with the chronic exposure study by Goss et al,[8] there was a difference in the definition of exacerbation. Goss et al[8] defined an exacerbation as a hospital admission or as hospital or home IV antibiotic use. Use of oral antibiotics was not registered. In the present study, hospital admissions for other reasons than antibiotic treatment were not registered, and administration of oral antibiotics because of respiratory deterioration was noted as an exacerbation; this is in line with the European consensus group, which defined an exacerbation as the need for additional antibiotic treatment as indicated by a recent change in clinical parameters.[15]

NO_2, mainly emitted by combustion processes, such as engines of vehicles and heating and power generation, is a good proxy for the global mixture of traffic-related air pollution. In the present study, the highest OR for antibiotic treatment initiation was found for NO_2 levels. There was a less pronounced effect of particulate matter. It is known that PM_{10} and particulate matter with a diameter < 2.5 μm ($PM_{2.5}$) also contain pollution particles that are not produced locally by combustion processes but are the result of

Table 2—*Effect of Pollutants on Patients With or Without Chronic Pseudomonas Colonization*

Pollutant	Colonized With *Pseudomonas* (613 Events)		Not Colonized With *Pseudomonas* (1,534 Events)	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
PM_{10}				
0	1.073 (1.004-1.146)	.037	1.038 (0.995-1.083)	.086
1	1.084 (1.017-1.156)	.013	0.998 (0.956-1.043)	.941
m	1.095 (1.020-1.175)	.012	1.022 (0.975-1.070)	.371
NO_2				
0	1.146 (1.049-1.251)	.003	1.103 (1.042-1.169)	< .001
1	1.132 (1.033-1.241)	.008	1.036 (0.977-1.100)	.240
m	1.167 (1.059-1.287)	.002	1.083 (1.017-1.153)	.013
Ozone				
0	1.051 (0.999-1.105)	.053	1.024 (0.989-1.061)	.170
1	1.041 (0.992-1.093)	.105	1.015 (0.981-1.050)	.400
m	1.055 (1.000-1.114)	.052	1.023 (0.986-1.063)	.230

Chronic colonization status was defined according to the Leeds criteria.[17] The patients not chronically colonized encompass all other patients. Each event per patient was allocated to the colonization status at that moment. 0 = lag 0 or the day antibiotic treatment was started; 1 = lag 1 or the day before antibiotic treatment was started; m = mean of lag 0 and 1 or the mean of the day the antibiotic therapy was started and the day before. See Table 1 legend for expansion of other abbreviations.

the formation of secondary aerosols and a transport of particles from a distant origin. The particulate matter fraction that correlates best with the traffic-related NO_2 is black carbon, and its correlation with NO_2 was much higher than with PM_{10} or $PM_{2.5}$.[26] Therefore, we hypothesize that traffic-related air pollution is responsible for the observed relation between NO_2 levels and CF exacerbations.

The association between exposure to higher NO_2 levels and risk of CF exacerbations in the present study corroborates previous studies relating NO_2 to poor health outcomes. The World Health Organization acknowledged that traffic-related air pollution is linked to an increasing risk of respiratory symptoms and morbidity and suggested that inflammatory processes are related to exposure to this type of pollution.[27] In children, neighborhood traffic-related air pollution gives rise to reduced ventilatory function and increased respiratory symptoms,[28] even at low levels of exposure.[29] Short-term exposure will trigger hospital admission for asthma[30] and respiratory disease in general.[31] In CF, a correlation between FEV_1 decline and annual average rates of exposure to $PM_{2.5}$ has been shown.[8] Even in healthy children, lung function follow-up over an 8-year period showed a growth deficit in FEV_1 that was associated with exposure to NO_2 and $PM_{2.5}$.[2] Important effects were also established in other lung diseases. COPD incidence was associated with the 35-year mean NO_2 level,[32] and hospitalization for community-acquired pneumonia was significantly related to long-term exposure to NO_2 and $PM_{2.5}$.[4] For mortality, NO_2 was the most important effect modifier, with a higher increase in daily mortality with a 10-$\mu g/m^3$ increase in PM_{10} in cities with high long-term average NO_2 concentration.[33]

In combined pollution models (on the day of event) and based on results in single pollution models with exposures of the day before (Fig 2A), it appears that

Table 3—*Estimated OR of CF Exacerbations During Warm and Cold Periods Associated With a 10-$\mu g/m^3$ Increase in the Daily Average of PM_{10} and NO_2 Concentrations*

Pollutant	April-September (1,004 Events)		October-March (1,143 Events)	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
PM_{10}				
0	1.151 (1.071-1.236)	< .001	1.010 (0.968-1.055)	.639
1	1.056 (0.984-1.132)	.128	1.006 (0.964-1.051)	.774
2	1.057 (0.991-1.128)	.094	0.981 (0.938-1.025)	.396
m	1.114 (1.022-1.214)	.003	1.006 (0.953-1.062)	.680
NO_2				
0	1.356 (1.225-1.501)	< .001	1.037 (0.972-1.106)	.274
1	1.180 (1.063-1.311)	.002	1.003 (0.939-1.072)	.920
2	1.132 (1.016-1.261)	.024	0.978 (0.915-1.045)	.511
m	1.217 (1.080-1.370)	< .001	1.046 (0.969-1.129)	.501

2 = lag 2 or the day before antibiotic treatment was started; CF = cystic fibrosis. See Table 1 and 2 legends for expansion on other abbreviations.

the results for NO_2 levels were the most robust. Compared with particulate matter and NO_2, ozone level is much more strongly related to temperature because this is the driver for photochemical ozone formation in ambient air. Because ozone peaks occur only during the warm period of the year, this might result in lower power compared with the other pollutants. Secondly, in urban areas with high NO_x emissions, ozone concentration will be lower because of titration with NO ($O_3 + NO \rightarrow O_2 + NO_2$).

The association with pollution was most pronounced on the day of the start of the antibiotic treatment. Patients at our center receive a self-management plan and are instructed to start oral antibiotics, to contact us, or to visit the outpatient clinic or ED as soon as an increase in respiratory symptoms is noted. The increasing OR seen from 2 days before the start of antibiotic treatment onward indicates that increases on the day of the event and the day before are important in triggering treatment with antibiotics. This was confirmed when we calculated the average of lag 0 and lag 1, showing significant effects of all three pollutants on the start of antibiotic treatment. We hypothesize that patients undergoing a CF exacerbation may experience increasing inflammation and symptoms the days before, but the additional effect of pollution might be the trigger for the start of antibiotic treatment. Although the end point was different, Tramuto et al[34] showed a similar acute effect of air pollution. There was a positive association between ED visit for respiratory symptoms and ambient exposure to motor vehicle pollutants such as PM_{10}, NO_2, SO, and CO. A similar increase in OR on the preceding days was found, with significance for the day of the ED visit and the day before for PM_{10} and NO_2.[34] Acute effects of air pollution have been shown for other diseases as well. Nawrot et al[20] determined that air pollution is an important trigger for acute myocardial infarction.

Subanalysis by *Pseudomonas* infection status revealed that patients with chronic colonization represent a subset of those with CF exacerbations where the effect of pollution on the risk of receiving antibiotic therapy seems stronger than in patients with no chronic colonization. We speculate that the reason for this difference might be the higher inflammatory or infectious state in patients with chronic *Pseudomonas* colonization. This might lower the threshold for receiving antibiotic treatment when a trigger, such as a rise in air pollution, occurs.

We noticed effect modification by season on association between air pollution and exacerbations, with a more pronounced effect during the warmer period of the year, until 2 days prior to the exacerbation. The stronger association between exacerbations and air pollution during warmer periods are in line with previous observations on mortality.[35] We can only speculate about the mechanisms underlying the stronger observed effects in the summer. The component-specific toxicity of PM_{10} may differ across the temperature range. A recent study where isolated macrophages of rats were exposed to ambient particulate matter collected during winter, spring, and summer (in Amsterdam, The Netherlands; Lodz, Poland; Oslo, Norway; and Rome, Italy), showed that PM_{10} samples collected in summer were more potent at inducing inflammatory cytokines (IL-6 and tumor necrosis factor-α).[36] Other studies reported correlations between indoor and outdoor PM_{10}, ranging from 0.40 to 0.79, in general, with lower correlations in the colder periods of the year.[37-39] It is also known that ambient temperature is associated with prevalence of *Pseudomonas aeruginosa* and lower lung function in patients with CF,[40] and that might form a biologic mechanism to explain the higher relative effects observed during the warmer periods.

Continuous awareness of the impact of traffic-related air pollution on health is needed to decrease traffic-related air pollution. Cesaroni et al[41] showed that local policy to reduce the number of vehicles resulted in a decrease of NO_2 and PM_{10}, which resulted in a gain of 921 years of life per 100,000 for NO_2 reduction. In view of the present results, one could argue that a patient alert is needed when pollution concentrations are going to rise by > 10 $\mu g/m^3$, although prospective research is needed not only to address other particulate matter compounds but also to determine threshold values and assess preventive measures with their possible effect on exacerbations.

This study has some limitations. First, data from the patients with CF who did not report an exacerbation or antibiotic use during the study period were not used for analysis. The lack of reported exacerbations could also be due to missing data in those patients, as stated in the "Material and Methods" section. However, the case-crossover design only allowed for inclusion of cases of antibiotic treatment for a CF exacerbation to investigate the relationship between pollution and the use of antibiotic treatment. Although antibiotic treatment is most often given in case of an exacerbation, one can only extrapolate these results to actual exacerbations, bearing in mind that antibiotics are also administered for bacterial pathogens (eg, *P aeruginosa*). However, eradication antibiotics represent a minority of antibiotic use in patients with CF in our center (4.5%), and the application of a case-crossover design with a high number of patients and antibiotic events should partly overcome this problem.[42]

Second, we had insufficient access to patient socioeconomic status data. We do not believe, however, that this is a major limitation because of the case-crossover design, and adequate access to the health-care system

in Belgium is provided even for patients with a low socioeconomic status.

Third, stress could also be a confounding factor because it might be associated with air pollution through noise or stagnant meteorology, but this will have had little impact on the results because the case-crossover design controls for nontime-varying confounders. We matched the control days for temperature and in sensitivity analysis, by day of the week, showing robust results. Stress induced by differences in weekday stressors or variation in noise exposure, therefore, were controlled for in the analysis. Nevertheless, an influence of stress cannot be ruled out completely because daily variation in stress was not measured in this patient group.

Fourth, we used the patients' current home addresses and could have included patients who previously lived elsewhere. However, we do not believe that this influenced the results because temporal differences in air pollution are much more determining than spatial differences in air pollution.[21]

Fifth, PM_{10} consists of $PM_{2.5}$ and larger particles of mainly crustal or biologic origin. On the basis of epidemiologic and laboratory studies, the smaller $PM_{2.5}$ fraction appears to be more potent for respiratory disease effects than PM_{10}.[43] In the present study, area $PM_{2.5}$ was only measured in enough monitoring stations from 2009 onward to make interpolation possible; thus, we could not assess this over the whole study period. However, very strong correlations between daily variations in PM_{10} and $PM_{2.5}$ ($r = 0.94$-0.98) have been observed, indicating that PM_{10} reflects the same time-varying trends.

Sixth, we used outdoor measurements of air pollution with interpolations at the residential level in grids of 4×4 km to partly estimate indoor personal exposures. However, recent studies comparing personal and ambient exposure reported good correlations among day-to-day changes in central measurement stations of particulate matter and personal exposure.[44,45] Previously, we found very high correlations ($r = 0.87$-1) among different grids (4×4 km) for the interpolated PM_{10} levels, showing the strong temporal correlation over the study area.[21] In other words, spatial variability in PM_{10} (which is rather low in the present small study area) appeared to be less important than temporal variability, which is driven largely by weather conditions. During stable meteorologic conditions with low wind speeds and in the presence of a temperature inversion, locally produced pollution accumulates in the lower parts of the atmosphere, which results in peak concentrations of particulate matter or other related atmospheric pollutants, such as NO_2.

Finally, one could argue that patients will spend more time indoors when there are media alerts of high pollution. We doubt that this had an effect on the results. The media only alert peak concentrations, and we studied continuous exposure distribution and the effect of 10-$\mu g/m^3$ increases in pollutant concentration. Studies have shown a good correlation between indoor and outdoor variation in pollution and exposure (with higher outdoor concentrations), and good correlations among day-to-day changes in central measurement stations of pollution and personal exposure were seen.[44,45]

In conclusion, the results show that ozone, PM_{10}, and NO_2 are associated with the use of oral and IV antibiotics in patients with CF exacerbations, with significance at the day of the start of therapy. A rise in OR can be seen for ozone, PM_{10}, and NO_2 on the days before the start of treatment. In patients with CF and exacerbations, ambient concentrations of ozone, PM_{10}, and NO_2 play a role in triggering an exacerbation.

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Author contributions: Drs Goeminne and Dupont had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Dr Goeminne: contributed to the study design, data acquisition, database construction, and writing of the first draft of the manuscript.
Mr Kiciński: contributed to the statistical analysis and study design.
Dr Vermeulen: contributed to the data acquisition and critical revision of the manuscript.
Mr Fierens: contributed to the interpolated air pollution concentrations based on the measured pollutant concentration from the Belgian regional telemetric air quality networks and critical revision of the manuscript.
Dr De Boeck: contributed to the study design and critical revision of the manuscript.
Dr Nemery: contributed to the study design and critical revision of the manuscript.
Dr Nawrot: contributed to the study design, statistical analysis, and critical revision of the manuscript.
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