Association Between Short-term NO_x Exposure and Asthma Exacerbations in East London: A Time Series Regression Model

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Abstract

Background: There is strong interest in the relationship between short-term air pollution exposure and human health. Most studies in this field focus on serious health effects such as death or hospital admission, but air pollution exposure affects many people with less severe impacts such as exacerbations of respiratory conditions.

Method: We developed a time series regression model to quantify the relationship between daily NO_x concentration and asthma exacerbations requiring oral steroids from primary care settings. Explanatory variables include daily NO_x concentration measurements extracted from 8 available background and roadside monitoring stations in east London, and daily ambient temperature extracted for London City Airport, located in east London. Lags of NO_x concentrations up to 21 days (3 weeks) were used in the model.

Result: Results of the time series modelling showed a significant relationship between NO_x concentrations on each day and the number of oral steroid courses prescribed in the following three weeks. Atmospheric concentrations of NO_x measured at roadside stations are a more effective indicator of future prescriptions of oral steroid courses than are measurements at background stations. This relationship has two main components, one during the first week and the other towards the end of the second week. We find that an increase of 1 μgm^{-3} in atmospheric concentration of NO_x (mean 95.75 μgm^{-3}) leads to an increase of about 2.7% in the mean of 30.9 prescriptions of oral steroid courses per day in the study area. There is a negative correlation between ambient temperature and asthma exacerbation, with a reduction of $1\,C^{\circ}$ leading to an increase of about 1.4% in the mean number of prescriptions per day. We did not find any effects of daily precipitation or relative humidity additional to annual seasonal ones.

Keywords: asthma exacerbation, air pollution, time series modelling

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1. Introduction

Exposure to air pollution is a leading risk factor for human health, contributing to 3.4 million premature deaths in 2017 worldwide (Soriano et al., 2017; Stanaway et al., 2018). In cities such as London, a major source of air pollution is road transport and policies have been introduced to control air pollution from this sector such as establishing a low emission zone (LEZ) in 2008 that covers almost all of greater London and an ultra-low emission zone (ULEZ) in 2019 that covers a much smaller are in central London. However, concentrations of atmospheric pollutants such as Nitrogen dioxide (NO_2) still exceed the annual mean Euro Limit of 40 μgm^{-3} (European Comission, 2017) in several parts of London ("London Atmospheric Emissions Inventory (LAEI) 2016 - Methodology," 2020).

Studies show substantial detrimental health impacts even at low air pollution concentrations (Madaniyazi and Xerxes, 2021). A variety of studies focus on mortality and hospital admission as a result of long or short-term air pollution exposure (Chen et al., 2021; Fuinhas et al., 2021; Yin et al., 2020). However, less severe health effects such as respiratory conditions requiring primary care management are rarely considered in the literature (Ashworth et al., 2021), which may be the result of limited access to primary care clinical and prescribing data, despite the major health and economic burden resulting.

In the present study, the effects of short-term air pollution exposure on asthma exacerbations requiring oral steroid treatment are investigated. Asthma, a common chronic disease, affecting 235 million people worldwide (Soriano et al., 2017), results from multiple interacting factors including genetic predisposition, behavioural and environmental factors. In recent decades, the rising prevalence of asthma has been linked to changes in environmental factors, including air pollution (Huang et al., 2014). There is consistent evidence that air pollution is harmful in asthma and airways diseases: for example in a study in Brussels, (Casas et al., 2016) showed significant association between daily sales of asthma and Chronic obstructive pulmonary disease (COPD) medication and NO_2 exposure among adolescents. In addition, a study in Bradford, UK showed that air pollution, and in particular road transport air pollution, lead to a large childhood asthma burden. They estimated that between 15 - 33% of all annual childhood asthma cases in Bradford are associated with urban air pollution (Khreis et al., 2019).

The statistics emphasise the severity of asthma in the UK, notably in London ("Asthma facts and statistics | Asthma UK," 2020) and particularly in the east of the city, where hospitalisation for asthma is 14% higher than the London average (Hull et al., 2016). However, the relevant researches are very limited for London.

In the present study, the effects of short-term air pollution exposure on asthma exacerbations requiring oral steroid treatment for management in the community are investigated. We selected oral corticosteroid courses prescribed in general practice for patients with asthma as a marker for moderate to severe asthma exacerbation in this study. We selected 8 monitoring stations in east London and extracted daily Nitrogen oxides (NO_x) concentrations. NO_x refers to nitric oxide (NO) and nitrogen dioxide (NO_2). NO_x was chosen as the pollutant measure to be assessed in this study given its established toxic effects on the lungs (Glencross et al., 2020) and association with traffic related air pollution (Ehlers et al., 2016; Kelly et al., 2011). A lagged regression model was developed that used daily NO_x concentrations and daily ambient temperature as explanatory variables. This model estimates the association between the number of oral steroid courses prescribed on each day and measurements of air pollution on recent days and ambient temperature. To understand short-term effects of air pollution on asthma exacerbation, lags of NO_x concentrations up to 21 days (3 weeks) were included in this model. We found that an increase of 1 μgm^{-3} in NO_x leads to an increase of about 2.7% in the mean number of prescriptions whilst a reduction of $1\,C^{\circ}$ leads to an increase of about 1.4% . We found no statistically significant effect on prescriptions of departures from annual trends in relative humidity and precipitation.

2. Study Setting and Data Sources

The study was located in the three geographically contiguous east London Clinical Commissioning Groups (CCGs) of Newham, Tower Hamlets, and City & Hackney. In the 2011 UK Census, 48% of the population in these CCGs was recorded as being of non-White ethnic origin (*Nomis official labour market statistics, KS201EW - Ethnic group*, 2013), and the English indices of deprivation 2015 show that all three feature in the top decile of the most socially deprived boroughs in (Ministry of Housing Communities & Local Government, 2015). The study time frame is two years from February 2018 to January 2020.

2.1. Asthma prescribing data

The study population included all patients (5-80 years old) with a diagnosis of asthma and who were prescribed asthma medication in the previous year, registered at the 157 general practice (GP) in the three study clinical commissioning groups (CCGs). All study patients were registered at least one year before the data extraction period. Anonymised prescribing data were extracted for the study period (February 2018 to January 2020). Data were extracted on secure N3 terminals from EMIS Web, all data was anonymous and managed according to UK NHS information governance requirements.

The daily number of oral steroid courses prescribed for the asthma population was used as a marker of asthma exacerbations. A minority of patients received more than one prescription for oral steroids within one month because of continuing asthma symptoms - for these patients only the first prescription has been included, with the subsequent ones removed from the dataset.

The population of the study area of east London (the Boroughs of Newham, Tower Hamlets, Hackney, and the City of London) in 2018 was 958,081 (ONS, 2020) and 33,672 had diagnosis of asthma at the end of January 2020. Among those, 9,111 (27%) patients requested at least one oral corticosteroid course during the 2-year study time frame, February 2018 – January 2020, and the average number of separate courses prescribed to those who requested them was 2.48. Age group and gender information of these patients are presented in Table 1 along with the population distribution for the study are and for the whole of London. This shows that in the study area compared with London as a whole, within the age range (5 – 80 years) of the present study the proportion of adults was about 5% greater and that of elderly persons about 5% less. This gives a mean age of the population in the study area in the range of patient ages of 34.5 years, which is about 2 years younger than the corresponding mean age of 37.4 years in this age range for the whole of London. However, the age distribution of patients who requested oral corticosteroid courses was substantially different, with a smaller proportion (14%) of child compared with the population of the study area (17.4%), a much smaller proportion (45%) of adults (*cf* 73.8%) and a much larger proportion of elderly (41% *cf* 8.9%). The mean age of the patients at 48.2 years was more than 13 years older than the mean of the corresponding age groups in the study area population, 34.5 years. Males were more frequent among these patients (61%) than in the population of the study area (52%).

Table 1: Age group and gender information for patients who requested oral corticosteroid course and population of that age

	Category (Age, years)	Patients (%)	Population (%)	
			Study area	London
Age Group	Child (5-17)	1270 (14)	151,452 (17.4)	1,406,140 (17.5)
	Adults (18-60)	4,062 (44)	642,933 (73.8)	5,531,987 (68.9)
	Elderly (61-80)	3,779 (42)	77,271 (8.9)	1,094,130 (13.6)
Gender	Male	5,554 (61)	453,601 (52.0)	4,029,453 (50.2)
	Female	3,557 (39)	418,028 (48.0)	4,002,804 (49.8)

2.2. Daily NO_x concentrations

NO_x daily concentration measurements were extracted from London Air Quality Network (LAQN) (Environmental Research Group Kings College London, 2016) for the two years (February 2018 - January 2020) .

In London, road transport is the largest source of NO_x emissions. NO_x is primarily made up of two pollutants - nitric oxide (NO) and nitrogen dioxide (NO_2). While NO_2 is of greater concern due to its impacts on health, NO converts readily to NO_2 in the air. Emissions from road transport have fallen by 34% between 1990 and 2000, mainly because of improvements in engine design and fitting three-way catalysts to petrol vehicles.

Each of the 8 monitoring stations is categorized as either urban background or roadside (Table 2). Background stations are those not dominated by a single nearby pollution source, such as road transport, construction site or petrol stations, and located at least 50 metres away of any large sources of air pollution and 30 metres from busy roads. Roadside monitoring stations are those located within 1-5 metres of a busy road and ideally located at breathing height (Greater London Authority, 2018). The monitoring stations should be at least 10 metres apart for zero overlap (Greater London Authority, 2012) , which was considered in selecting the 8 monitoring stations.

The atmospheric concentrations of NO*x* varied substantially among the stations, irrespective of their location as background or roadside. At each of the 8 stations, the mean concentration was greater during weekdays than on weekend days (Saturday and Sunday), and varied relatively little within these two groupings of days.

Table 2: details of monitoring stations, mean and standard deviation of NOx concentrations during weekday and weekends

			NO_x (μgm^{-3})					
			Weekday		Weekend		All	
Station	Type*	Location	Mean	SD	Mean	SD	Mean	SD
1	R	Newham Cam Road	42.7	1.2	31.57	1.98	39.51	33.51
2	B	Newham Wren Close	51.0	1.9	38.46	3.05	47.46	35.08
3	R	Hackney - Old Street	107.0	4.5	82.40	8.55	100.02	43.30
4	R	City of London - Beech Street	173.0	11.4	89.73	20.94	149.27	88.20
5	R	City of London - Wall Brook Wharf	222.6	14.5	154.07	31.52	203.08	94.46
6	B	City of London - the Aldgate School	120.2	2.3	81.92	6.67	109.28	55.85
7	R	Tower Hamlets - Blackwall	86.93	1.90	67.22	1.37	81.31	50.66
8	R	Tower Hamlets - Mile End Road	50.9	1.3	37.43	4.33	47.07	30.71
All			106.8	4.3	72.85	9.80	97.09	17.40

*R= roadside, B=background

Figure 1 shows the time series of the daily number of oral steroid courses prescribed by GPs together with the NO_x concentrations (μgm^{-3}) averaged over the 8 monitoring stations. These time series are smoothed by 28-day rolling average so that four instances of each day of the week are included in each value. This shows clear annual trends in each of the NO_x and oral steroid series, which could be due to patterns in human location and activity as well as susceptibility to asthma due to seasonal illness.

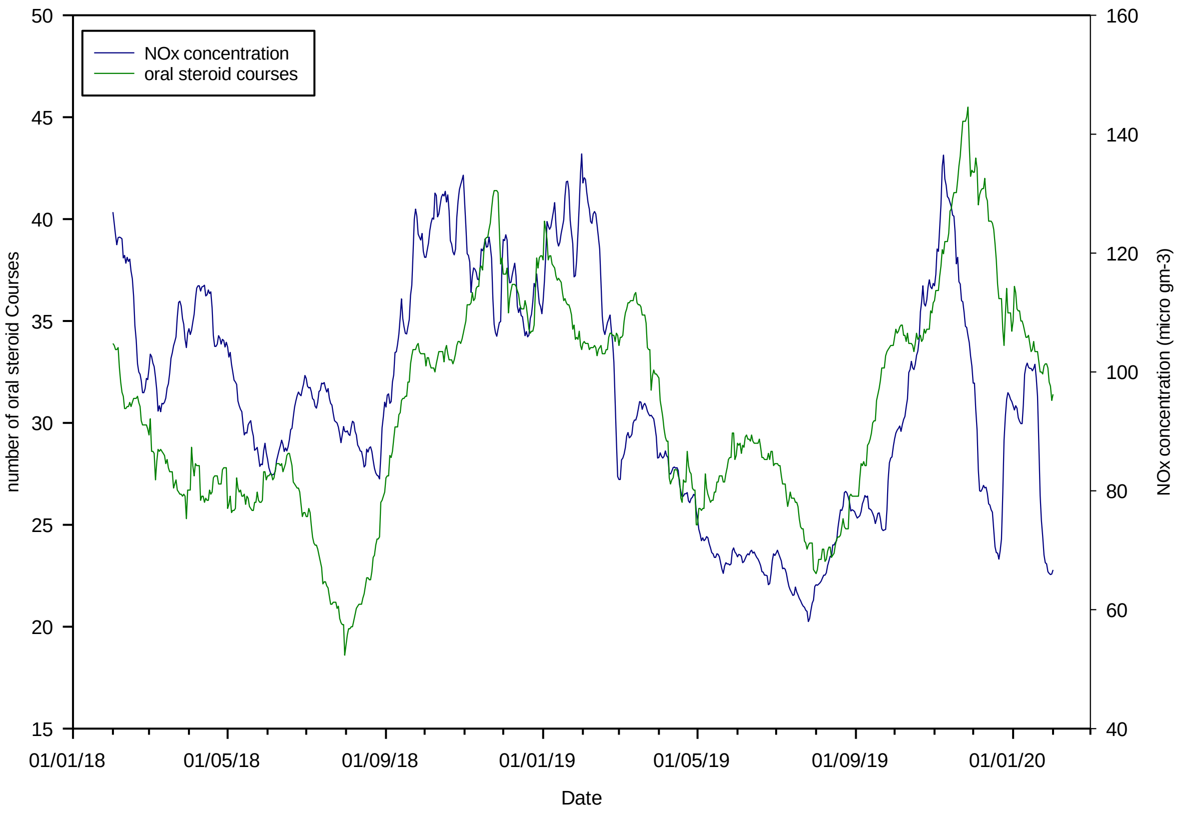

Figure 1: time series of NO_x concentrations (average of 8 stations) and number of oral steroid courses

2.3. Temperature

Daily ambient temperature (C°), daily average relative humidity and precipitation were extracted from records at London City Airport, which is also located in east London. This dataset was provided by the National Centres for Environmental Information (NOAA) (National Oceanic and Atmospheric Administration, 2019).

3. Statistical Modelling

To investigate the dynamic relationship between the time series of oral steroid courses and NO_x concentrations along with daily temperature, a time series regression model (Box, 2008; Wei et al., 2013) was developed. In this model, the dependent variable is oral steroid courses prescribed on each day and explanatory variables are NO_x concentrations at each of the 8 monitoring stations and daily temperature. In this model, the NO_x concentrations at the same day plus previous days (lags) were used. In addition, because most general practices are close on bank holidays, oral steroid courses would not normally be prescribed on these days; to accommodate this effect, a binary covariate vector (1 for bank holidays, 0 otherwise, data from Gov.UK, 2021) was included in the model.

3.1. Imputation of missing values

Around 4.5% of the daily averaged concentrations at 8 monitoring were not available (missing data). For this study, multiple imputation by chained equation (MICE) (Resche-Rigon and White, 2018; van

Buuren and Groothuis-Oudshoorn, 2011; Zhang, 2016) was used to impute missing values. The MICE method adopts a joint distribution function of the multivariate time series at each time t. The results of comparing this method with other common imputation approaches showed that MICE works substantially better, particularly for air pollution datasets (Hajmohammadi and Heydecker, 2021).

3.2. Seasonal and day-of-week effects

Seasonality in time series represents variations in measured values that repeat regularly over a time interval with duration m. The most likely causes in the present study were respiratory infections and influenza in winter, and hay fever in spring.

To accommodate these trends, an annual differencing technique was used on both explanatory and outcome variables. In this present study, $m = 364$, so that the NO_x and oral steroid time series used in the model are the differenced observations between corresponding days of the week almost exactly one year apart.

3.3. A Time Series Regression Model

In the present time series regression model, the number of oral steroid courses at day t is S_t, NO_x concentration (μgm^{-3}) at monitoring station i and day t is $N_{i,t}^b$ or $N_{i,t}^r$ (for background and roadside monitoring stations, respectively), the daily temperature is T_t, and bank holiday is H_t coded as a binary indicator. This model can be formulated in 364-day differenced variables as:

$$S_t = \sum_{i=1}^{2}\sum_{l=0}^{L}\varphi_{i,l}^{b}B^{l}\left(N_{i,t}^{b}\right) + \sum_{i=1}^{6}\sum_{l=0}^{L}\varphi_{i,l}^{r}B^{l}\left(N_{i,t}^{r}\right) + \tau T_t + \gamma H_t + \varepsilon_t \tag{1}$$

where φ^b and φ^r are the coefficient of NO_x concentrations at background and roadside stations, respectively, τ and γ are the effect of temperature and bank holiday, respectively; and ε is a random error term with Normal distribution ($\varepsilon \sim N(0,\sigma^2)$). In Equation (1), the lagged variables are defined by the backshift operator $B: B^l x_t = x_{t-l}$. Hence, the lagged variable at each station ranges from $l = 0$ (same day) up to L days previously, which allows for delayed effects of atmospheric pollution on the number of prescriptions.

The parameter L in equation (1) determines the number of lags used in the model. To decide the value of this parameter, the cross-correlation function (CCF) between NO_x and number of oral steroid courses time series is used. The CCF is the set of sample correlations between x_{t+r} (independent variable, in this case N_t) and y_t (dependent variable, in this case S_t) with positive and negative values of r (Chatfield and Xing, 2019).

In this model, daily averaged NO_x at each monitoring station and daily average ambient temperature in east London were used as explanatory variables. First the model was developed with both roadside and background stations (with separate coefficients), then to investigate the contribution of measurements at each of the monitoring station types, two separate models were developed: one with just roadside stations and one with just background stations. We also investigated inclusion of relative humidity and precipitation as explanatory variables.

4. Results

The results of fitting the time series regression model are presented in this se*ction. Three models were developed based on the type of monitoring station:

- Model *R*: explanatory variables are six roadside monitoring stations (station 1, 3,4,5,7 and 8) plus daily temperature and bank holiday
- Model *B*: explanatory variables are two background monitoring stations (station 2 and 6) plus daily temperature and bank holiday
- Model *M*: explanatory variables are all stations 1-8 plus daily temperature and bank holiday.

Figure 2 shows the average for each day of the week of each of the number of oral steroid courses prescribed and the NO_x concentrations (μgm^{-3}) averaged over the 8 monitoring stations. This shows clear day of week dependence in each of these series. This could be due to patterns in human location and activity, leading to weekly variations in generation of NO_x and exposure to it as well as weekly variations in patients' attendance at GP surgeries and hence prescriptions.

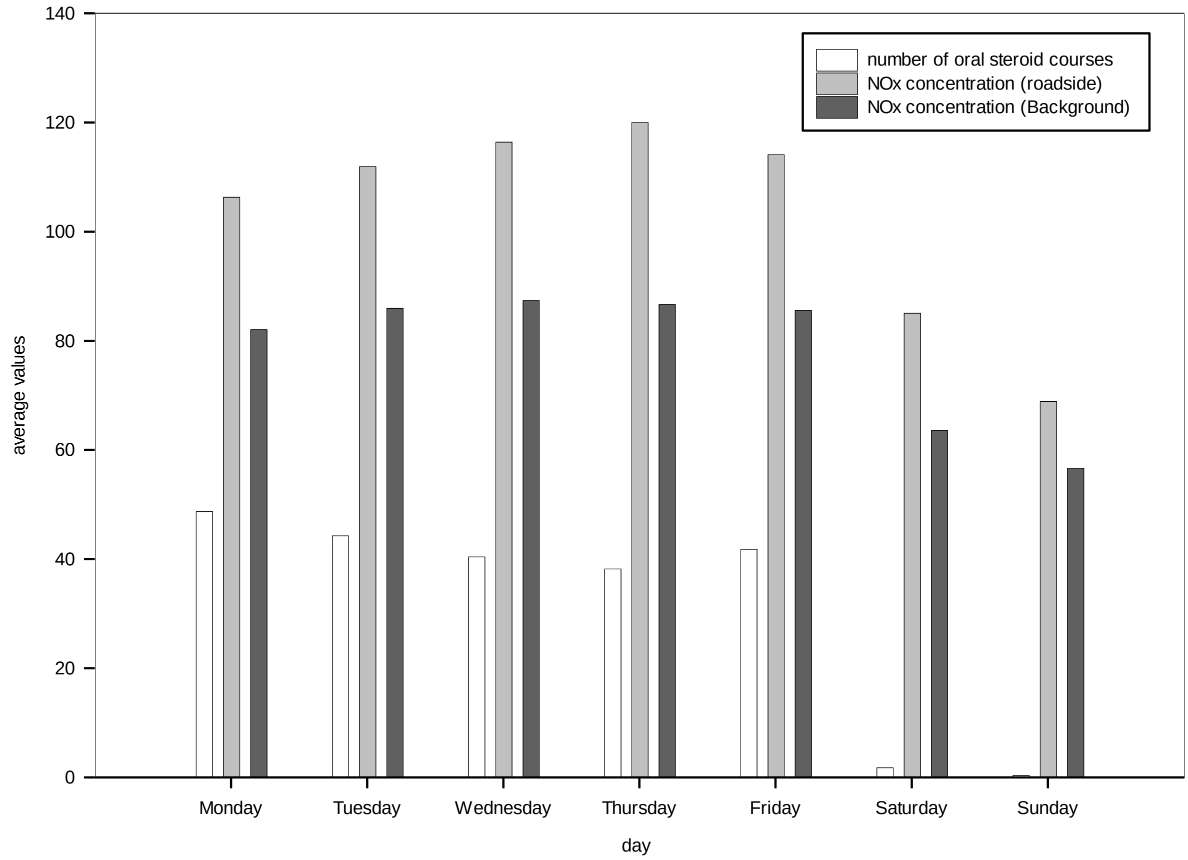

Figure 2: Average values for NOx (μgm^{-3}) roadside and background, and average number of oral steroid courses by day of the week

4.1. Cross-Correlation Function (CCF)

To decide on parameter *L* (number of lags) to be used in the statistical models, CCF plots of the raw data (NO_x concentrations at the 8 stations and number of oral steroid courses) were used. The CCF plot of station 1 is presented in Figure 3; the CCFs of the other 7 stations are similar.

This CCF plot shows statistically significant correlations repeating every 7 days, with both positive and negative lags. This is a direct consequence of the systematic weekly cycles in each of the two series. To accommodate this phenomenon in modelling the relationships between the series, each of them was differenced at an interval of m=364 (=52×7) days to align the day of the week and so cancel this effect. Differencing over this interval also aligned the time of year, so cancelling any effects associated with annual seasonal variations in NO_x generation and in climatic conditions on health.

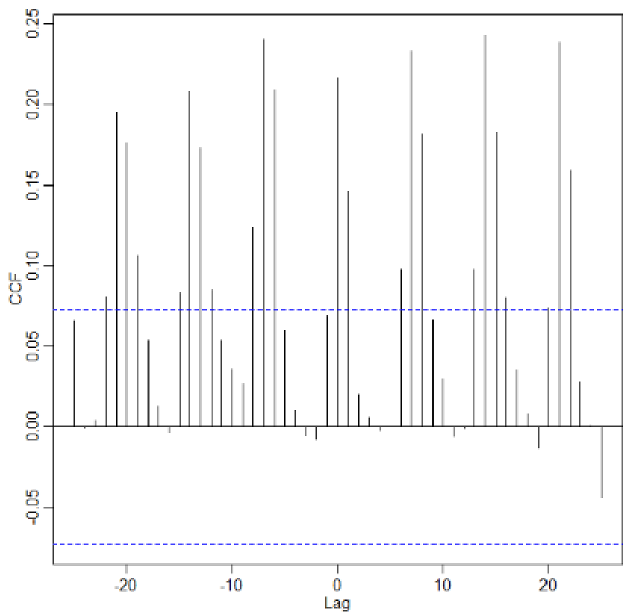

Figure 3: Cross-correlation function (CCF) of NO_x concentration at station 1 and oral steroid courses

4.2. Model Development and Evaluation

Based on the CCF plot in Figure 3, we investigated each of Model *R*, *B* and *M* with up to 28 lags *L*=28 (1 month), 21, 14 and 7 days, then selected the best one.

The performance of these models was evaluated using the Bayes Information Criterion (BIC) (Pandis, 2016):

$$\mathrm{BIC} = -2LogL + \log_e(n)p \tag{2}$$

where p is the number of free parameters in the model, n is the number of observations and $LogL$ is the log-likelihood of the fitted model. Models with smaller values of BIC are preferred, with the use of additional parameters justified by sufficient improvement in the likelihood of the fitted model. This criterion provides a balance between improvement in fit (represented by increased log-likelihood) and model complexity (represented by the number of parameters used) whilst respecting the scaling effect of the dataset size (Pandis, 2016).

The BIC values for Model *R*, *B* and *M* with lags up to 7, 14, 21 and 28 days are presented in Figure 4, denoted as *R*(*L*) etc. These results (ordered from smallest to largest) show that Model R (roadside stations only) performs better than Model M (roadside and background stations) and Model B (background stations only). Model *R*(21) with lags up to 21 days (three weeks) to perform better than Model *B*(14) and Model *M*(14). That shows removing background stations from Model *M* and including one more week in lags (*L*=21) will improve the efficiency of the model.

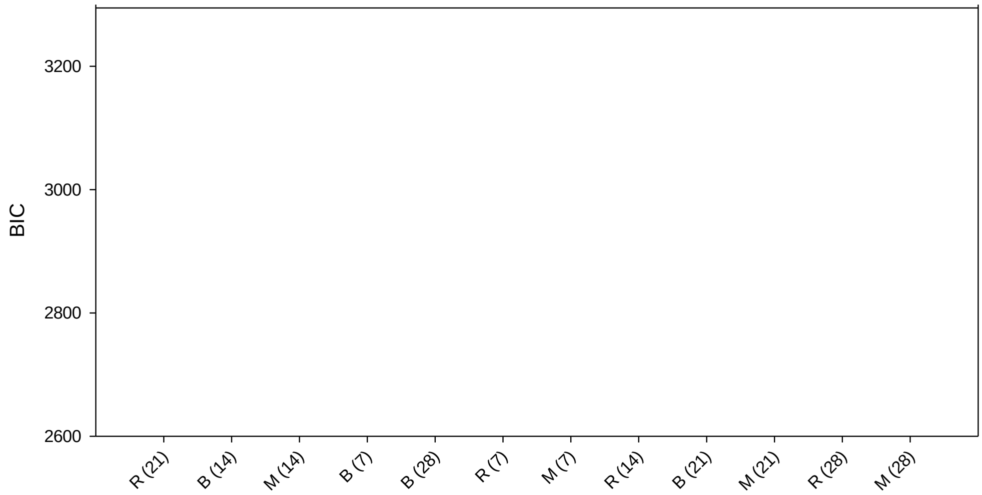

Figure 4: BIC values for Model R, B and M with L= 7, 14, 21 and 28

Adjusted R^2 values of these models (ordered from highest to lowest) are presented in Table 3. Simillary to the BIC values, Model $R(21)$ with the highest adjusted R^2 performas better than the other models.

Table 3: Adjusted-R^2 for Model R, B and M with L= 7, 14, 21 and 28

Model	**Adjusted- R^2**
R(21)	0.845
B(14)	0.814
M(14)	0.724
B(7)	0.722
B(28)	0.702
R(7)	0.654
M(7)	0.631
R(14)	0.615
B(21)	0.552
M(21)	0.541
R(28)	0.498
M(28)	0.447

We investigated the effects of including each of daily average relative humidity and precipitation (differenced at m=364) as additional explanatory variables. In this differenced form, these variables represent deviation from values at that time of year. We found that these variables did not improve performance of model R(21) as quantified by the BIC (the BIC value for model R(21) is 2616 while it increased by 9.5 to 2625 when we added these further meteorological variables to the model. We conclude that these meteorological variables do not enhance performance of the model after annual seasonal effects are accommodated.

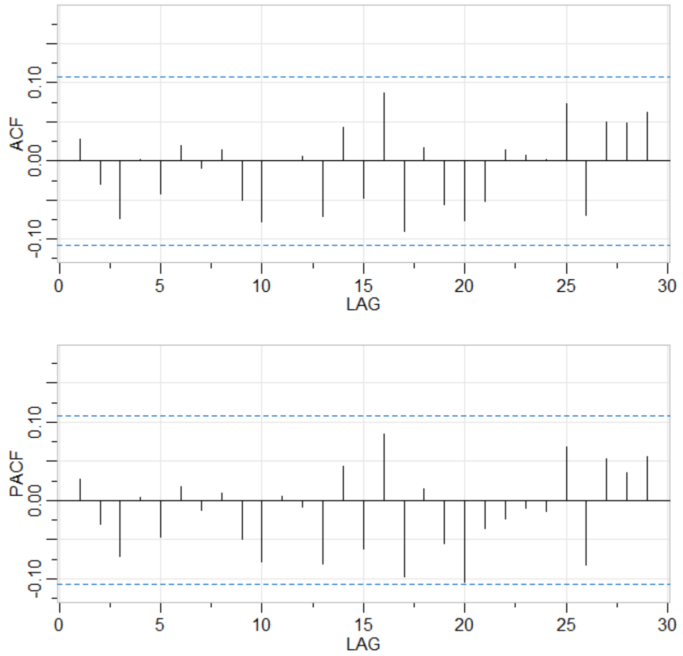

Figure 5: ACF and PACF of the residuals in Model R(21)

For a statistical model to fit time series data of the present kind appropriately, the residuals should be serially uncorrelated (Washington et al., 2020). Failure of this weakens the model because of lack of independence in the residuals and can be symptomatic of inadequate modelling. Two diagnostics that can be used to check the residuals are the autocorrelation function (ACF) and the partial autocorrelation function (PACF): these are shown in Figure 5 for Model R (21) . Based on these plots, Model R(21) is successful in representing all the variations in the observations, with no statistically significant lagged correlation remaining in the residuals. In addition, the CCF of the residuals of oral steroid courses and NO_x at Station 1 is plotted in Figure 6. This is clear from any trends, and notably from the 7-day (weekly) one that is apparent in the CCF of the oral steroid course prescriptions and NO_x shown in Figure 3. The CCFs of the other stations are also similar. This establishes that all temporal associations in the data have been represented adequately in the statistical model (1).

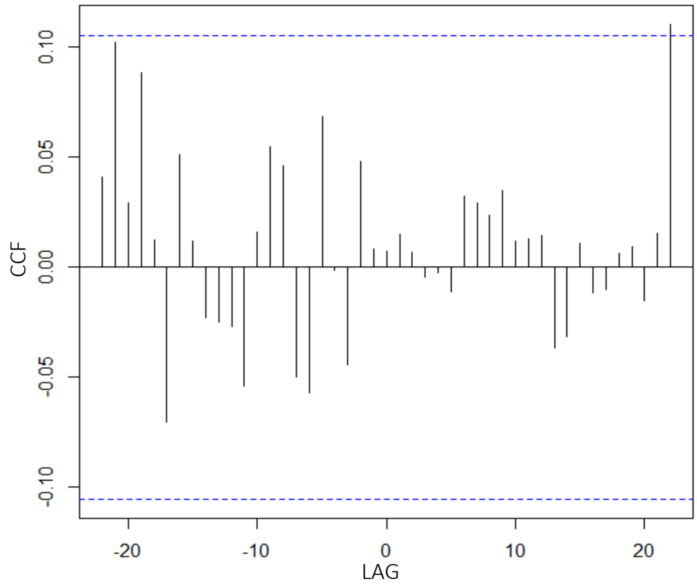

Figure 6: CCF of Model R(21) residuals of oral steroid courses and NO_x at station 1

The fitted values from Model *R*(21) are plotted in Figure 7 against differenced (*m*=364) number of oral steroid course prescriptions from the health record. The red reference line indicates the case in which the observed values from health records would be identical to the fitted ones.

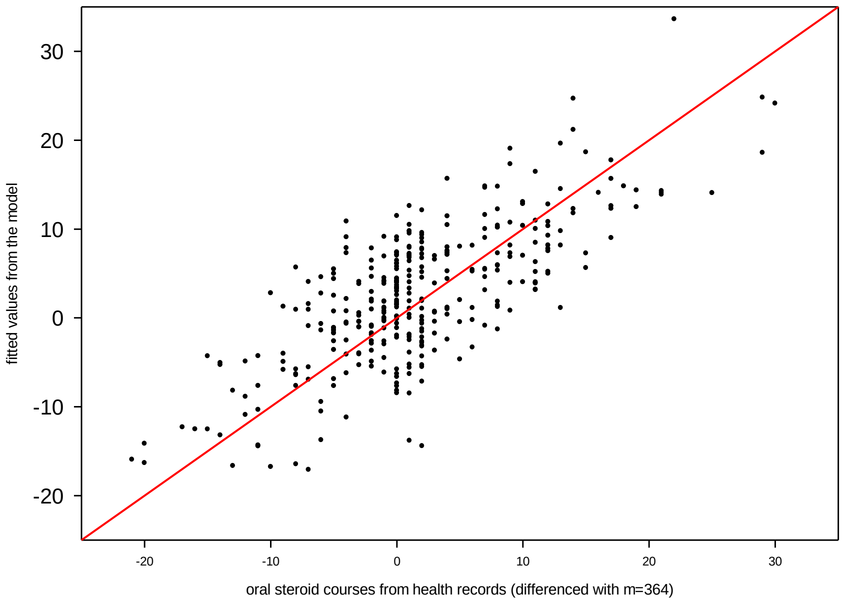

Figure 7: scatter plot of fitted values from Model R(21) vs differenced oral steroid courses from health records

The points are spread along the reference line, which shows that estimations from Model *R*(21) are close to the health records.

4.3. Specifications of the Model *R*(21)

The coefficients of roadside stations (φ_i^r , $i = 1, 2, ..., 6$) at different lags together with the coefficients of ambient temperature, τ, and bank holiday, γ , along with their *P*-values (*Pr*) of the Model *R*(21) are presented in Table 4 and 5, respectively. In this table, the statistically significant parameter values ($P < 0.05$) are highlighted.

From these results, the lags with significant *Pr* vary from road-side station to station, but they appear from the first lag (previous day) to the 21st lag (three weeks), which are analysed in the next subsection. The coefficients of these lags include both positive and negative values, with sums at the stations ranging from 0.110 to 0.199 (mean 0.139, standard deviation 0.032). The sum of these coefficients, $\sum_{i=1}^{6} \varphi_i^r$, is +0.835, which means that an increase of 1 (μgm^{-3}) in roadside NO_x concentration uniformly across the area including 6 stations would lead to an estimated increase in the daily number of prescribed oral steroid courses in the study area of 0.835 . This represents a proportional increase in oral steroid prescriptions of 2.7% for each increase of 1 (μgm^{-3}) in roadside NO_x above the typical value for that day of the week and time of year. Each of the coefficients of ambient temperature (τ) and bank holiday (γ) is negative and statistically significant which is as expected. The coefficient of temperature of -0.435 $/\mathrm{C}^{\circ}$ shows that a decrease of $1\,\mathrm{C}^{\circ}$ in daily average temperature below typical value for the time of year would lead to an estimated proportional increase in daily number of prescribed oral steroid courses of 1.4%.

Table 4: NOx coefficients with their P-values

Lag	station 1 φ_1^r	station 1 *Pr*	station 3 φ_2^r	station 3 *Pr*	station 4 φ_3^r	station 4 *Pr*	station 5 φ_4^r	station 5 *Pr*	station 7 φ_5^r	station 7 *Pr*	station 8 φ_6^r	station 8 *Pr*
0	0.001	0.972	0.000	0.996	-0.004	0.685	0.006	0.292	0.000	0.495	-0.006	0.088
1	0.043	0.150	-0.011	0.506	0.004	0.670	0.000	0.342	-0.032	0.002	0.091	0.029
2	0.032	0.292	0.008	0.961	0.064	0.530	0.050	0.085	0.025	0.020	-0.083	0.037
3	0.077	0.050	-0.018	0.434	0.010	0.318	-0.008	0.004	0.012	0.935	0.010	0.911
4	-0.069	0.024	0.008	0.847	-0.006	0.516	-0.004	0.051	-0.003	0.282	0.096	0.254
5	-0.014	0.649	-0.016	0.049	-0.011	0.025	0.010	0.736	0.048	0.116	-0.013	0.234
6	0.027	0.382	-0.013	0.763	0.020	0.045	-0.005	0.587	-0.033	0.271	0.039	0.301
7	0.012	0.007	0.034	0.049	-0.012	0.002	0.003	0.007	-0.001	0.051	-0.030	0.024
8	-0.009	0.050	0.003	0.645	-0.014	0.172	-0.001	0.048	-0.001	0.062	0.041	0.015
9	0.027	0.402	-0.004	0.443	0.093	0.359	0.029	0.953	-0.017	0.756	-0.047	0.073
10	0.013	0.677	0.011	0.753	0.000	0.843	0.000	0.456	0.017	0.591	-0.015	0.913
11	-0.017	0.577	0.017	0.616	-0.006	0.579	0.065	0.846	0.019	0.512	-0.014	0.742
12	0.007	0.832	0.012	0.320	0.009	0.373	-0.001	0.080	-0.017	0.509	0.039	0.998
13	-0.035	0.270	0.019	0.078	0.005	0.618	-0.006	0.886	0.071	0.012	-0.029	0.420
14	-0.022	0.473	-0.001	0.269	-0.017	0.101	0.014	0.034	0.023	0.071	0.051	0.007
15	-0.003	0.913	0.018	0.477	-0.002	0.873	-0.001	0.937	-0.002	0.961	0.033	0.055
16	-0.033	0.293	0.000	0.488	0.030	0.008	-0.002	0.904	0.021	0.268	-0.017	0.034
17	0.006	0.009	0.021	0.019	0.028	0.049	-0.006	0.980	0.002	0.040	-0.016	0.770
18	0.051	0.095	-0.008	0.050	-0.016	0.137	0.002	0.251	0.016	0.959	-0.015	0.858
19	-0.008	0.008	0.009	0.466	0.016	0.134	0.009	0.342	-0.001	0.342	0.025	0.632
20	0.021	0.048	0.005	0.913	-0.009	0.371	-0.007	0.049	-0.028	0.049	0.022	0.045
21	0.027	0.342	0.017	0.010	0.016	0.050	-0.013	0.019	-0.006	0.442	-0.016	0.507
Total	0.133	-	0.110	-	0.199	-	0.133	-	0.113	-	0.148	-

Table 5: Coefficients in Model R(21) of temperature and Bank Holiday with their P-values

Temperature (C°)		Bank holiday	
τ	*Pr*	γ	*Pr*
-0.435	0.046	-24.4	<0.001

4.4. The mixed distribution model for significant lags

From Table 3, around on third of lags (in all roadside stations) in the Model $R(21)$ are statistically significant: when added together, they give an estimate of the total effect of variations in roadside NO_x concentrations. To understand better how these significant lags are distributed over the 21 days, a mixed distribution model was fitted to them. The mixed distribution model can describe sub-groups of observations, known as model-based clustering (Bishop, 2006).

In the present study, a mixed distribution model with two components was fitted to the statistically significant lags, s. Each of these components is represented as a normal distribution. These two components combine with a mixing coefficient, λ. Hence, the mixed distribution model is defined as:

$$\begin{aligned}&\mathrm{Md}(s)=\lambda_1\,\mathrm{N}\left(s;\mu_1,\sigma_1^2\right)+\lambda_2\,\mathrm{N}\left(s;\mu_2,\sigma_2^2\right)\\&\lambda_1+\lambda_2=1\end{aligned} \tag{3}$$

where $\mathrm{N}\left(s;\mu,\sigma^2\right)$ is a normal distribution with parameters mean, μ, and variance, σ^2.

The results show that the first component of the mixed distribution model has mean of 3.2 (days) and standard deviation of 2.99 (days) showing a short-term effect of atmospheric NO_x. The second component mean is 16.14 (days) with standard deviation of 2.99 (days), showing a delayed effect after 2 weeks. The mixing coefficients of these components, λ_1 and λ_2, are 0.46 and 0.54, respectively, showing similar strength of effect between the two groups of time lags. Figure 8 shows the result of fitting this mixed distribution model together with these two components.

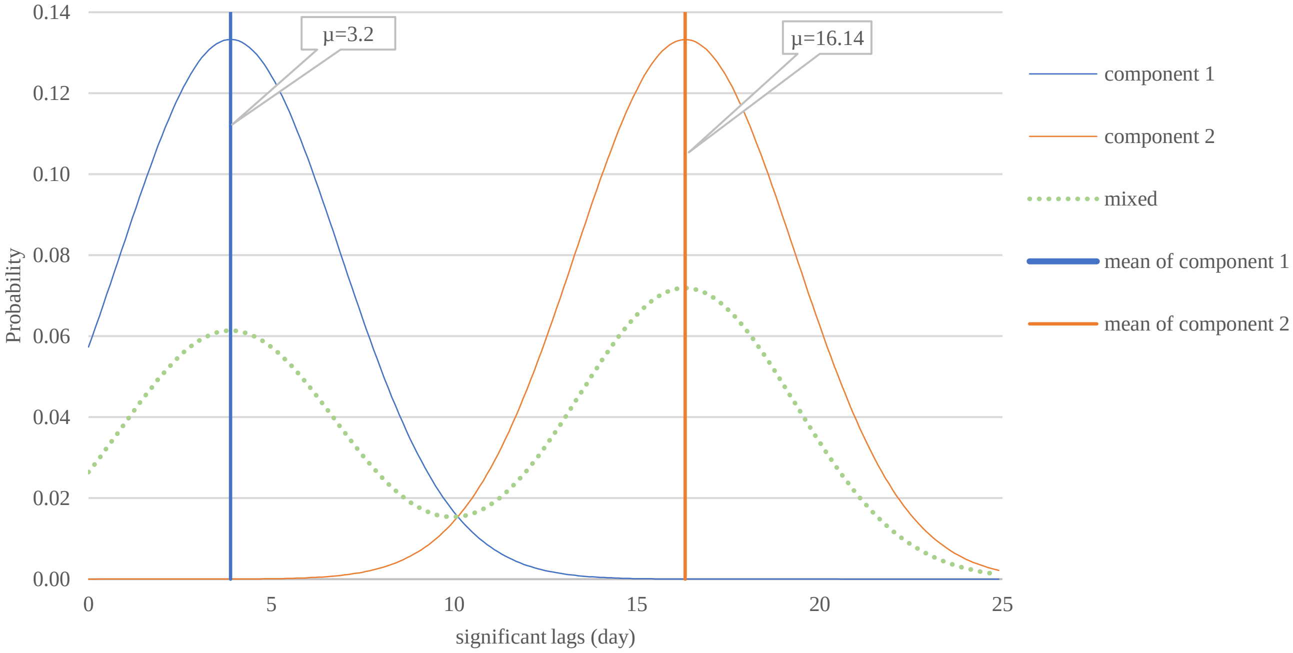

Figure 8: Mixed distribution model for significant lags

5. Discussion

The time series regression model was developed based on the monitoring station type (roadside, background and mixture of two) and number of lags (L). These models are evaluated by their BIC values, adjusted-R^2 and ACF/PACF of the residuals. Based on these criteria, Model $R(21)$ with lags up to 21 days performed better than any of the models with background stations (Model B), or those that used observations at both roadside and background stations (Model M).

The ACF and PACF (Figure 5), and CCF (Figure 6) were used to assess the residuals in Model $R(21)$. These plots show that the residuals have no temporal structure, and that the weekly pattern is represented adequately by this model.

That road-side models performed better is consistent with use of NO_x as a tracer for traffic-related pollutants. It is important to note that the individuals in the population studied would likely not have consistently travelled along the roads with the road-side monitors used in this study. The associations in this study therefore represent the toxic effects of road-side air pollution in general across a broad population irrespective of whether they lived or travelled along the most polluted roads in east London.

The coefficients of Model $R(21)$ (Table 3) show that around a third of the lags are statistically significant in this model ($P \leq 0.05$). This means considering temporal lags of NO_x concentrations in modelling asthma exacerbations is vital. The significant lags are distributed over three weeks (21 days), hence a mixed distribution model was fitted to them to explain their distribution. This model has two components which mean there are two main responses to the NO_x concentrations: the first one happens during the first week with a mean of 3.2 days, and the second happens within the third week with mean of 16.14 days (Figure 8). Ambient temperature is also statistically significant in this model with a negative coefficient, which shows a correlation of colder days with asthma exacerbation. The effect of bank holidays is substantial and negative as expected, as there were few prescriptions of oral steroid courses on bank holidays.

A lag of 3-4 days between NO_x exposure and airways exacerbation is consistent with previous studies. For example in the London COPD cohort a lag of 2-4 days has been reported for viral-type exacerbations following elevated NO_x exposure (Pfeffer et al., 2019), with similar lags reported in other studies (Mehta et al., 2012; Wong et al., 1999). Few previous studies have investigated lags beyond 2 weeks.

Limitations

This study has several limitations, which are listed in this section. We used fixed monitoring stations across east London (2 background and 6 roadside) for NO*x* measurements and London City airport (located in east London) for ambient temperate and other meteorological data. We assumed that these variables represent the air pollution exposure and temperature at the locations of cases. The resulting measurement error in explanatory variable will lead to attenuation bias (systematic reduction in magnitude) of the associated model coefficients.

PM measurements are available in only 3 and Ozone measurements in just 1 of these stations, so we were not able to use them in the model. Because of this, the effects of these omitted variables will be represented through that of NO_x where that is correlated. We used asthma registered patients (COPD excluded) and assumed the prescription of oral steroid for this population is related to their asthma conditions, while it is possible that this prescription is for some other conditions in a few cases though the majority of short-course oral steroid prescriptions are known to be prescribed for airways exacerbations.

6. Conclusion

While other current researchers have a focus on mortality or hospital admission due to long-term air pollution exposure, the present research has the advantage of using clinical data to quantify less severe impacts of short-term air pollution exposure on patients with asthma. This will help the primary care sector to understand better the pattern of asthma exacerbation related to daily air pollution exposure.

This report investigates the relationship between Nitrogen Oxides (NO_x) and the number of oral steroid courses using a time series regression model. The results of this model show that there is a significant relationship between short-term NO_x measurements at roadside stations in east London and asthma exacerbation in the same part of London for which oral steroids were prescribed. This model shows that these detrimental impacts of NO_x exposure are distributed over 21 days afterwards, with two main components, one during the first following week and the other during the third week. Another outcome of this model is significant negative correlation between ambient temperature and asthma exacerbation, which means more oral steroid prescription on colder days.

Future work on this topic will involve using measures of other types of air pollution such as particulate matter (PM), to investigate their relationship with asthma exacerbations. In addition, adding clinical data from other Clinical Commissioning Groups (CCGs) will improve the accuracy of the model.

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