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Respiratory Admissions Linked to Air Pollution in a Medium Sized City of the UK: A Case-crossover Study

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ABSTRACT

This study, from the Tayside Pollution Research Programme (TPRP), aims to investigate the effects of air pollution on respiratory hospital admissions in adults and children < 16 y of age, over a 14-year period, in Dundee, Scotland (population circa 148,270). We conducted a case-crossover study using routinely collected healthcare records from Ninewells Hospital, Dundee, Scotland from 2004 to 2017. Respiratory hospitalisation events were linked to daily nitric oxide gases (NO_x, NO_2, NO) extracted from publicly available data over this period. We used distributed lag models to allow for delayed effects of air pollutants up to 14 days. A total of 34,192 hospital admissions for a respiratory condition were included in this study (children = 9,501; adults = 24,691). Respiratory admissions in children were significantly associated with cumulative 14-day exposure to NO_x (RR for a 10 µg m^{-3} increase in concentration 1.020; 95% confidence interval 1.010–1.031), NO_2 (RR 1.086; 95% CI 1.036–1.139) and NO (RR 1.033; 95% CI 1.016–1.052). Similar estimates were observed for acute respiratory infection categories in children. Effects appeared to be somewhat delayed, with the largest estimates mostly observed around lag 6. No significant association was seen for respiratory admissions in adults. This study shows that both NO and NO_2 are associated with increased respiratory hospital admissions in children < 16 y of age, and that much more should be done to improve and enforce the established legal NO_x pollution limits in cities for the sake of our children's health.

Keywords: NO_x, Pollution, Respiratory disease, Children, Nitrogen oxide

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1 INTRODUCTION

The World Health Organisation (WHO) estimated that 7 million people die every year due to air pollution (Bălă *et al.*, 2021) with around 40,000 deaths per annum in the UK (Carvalho, 2019). Respiratory conditions make up a large proportion of the cause of these deaths, with the elderly, young children, and people with comorbidities at highest risk (Mannucci *et al.*, 2015). Nitrogen oxides (NO_x), made up of nitrogen dioxide (NO_2), nitrogen oxide (NO) and other smaller fractions of pollutants has been previously shown to be associated with various health conditions, such as asthma (Shima, 2017), bronchitis (Pershagen *et al.*, 1995), acute limb ischaemia (Fitton *et al.*, 2021), stroke (Andersen *et al.*, 2011), cardiovascular death (Duan *et al.*, 2019) and preterm birth (Ji *et al.*, 2019).

Currently, limits on air pollution in Scotland are set by the Scottish government, using the World Health Organization's (WHO) air quality guidelines (DEFRA, 2020). Limits have been set of 40 µg m^{-3} for NO_2, 30 µg m^{-3} for NO and 18 µg m^{-3} for particulate matter with an aerodynamic diameter smaller than 10 µm (PM_{10}) (DEFRA, 2020), with low emission zones recently introduced to larger cities to decrease air pollution from traffic. Despite this, in countries with moderate levels of air pollution, the health effects are often ignored or considered unimportant (Belch *et al.*, 2021). We have previously demonstrated that the air pollution levels in Dundee persisted in being above Scottish government limits and may have an impact on health (Belch *et al.*, 2021).

This study, from the Tayside Pollution Research Programme (TPRP), builds on previous work and aims to investigate the effects of air pollution on respiratory hospital admissions in adults and children (< 16 years), over a 14-year period, in Dundee, Scotland.

2 METHODS

2.1 Data and Consent for Study

Consent for the study was given by the Tayside Caldicott Guardian. Ethics approval and patient consent were not required as this data linkage study did not include patient participation. All data storage and analyses were carried out on anonymised data, held within the Safe Haven, the Tayside Health Informatics Centre (HIC). Hospital data is available from HIC with appropriate permissions. Air pollution data is publicly available from: https://uk-air.defra.gov.uk/data/data_selector.

We used data on respiratory hospital admissions in adults (16 years and over) and children (< 16 years) at Ninewells Hospital, Dundee, Scotland from January 1st, 2004, to December 31st, 2017. Unique personal identifier codes (CHI) were used to extract electronic medical records from the Scottish Morbidity record 01 (SMR01) database that documents all hospitalization events in Scotland.

Hospital admissions of interest were agreed a priori and were defined by ICD10 code (2016 addition) recorded on the SMR01. Hospital admissions of interest included: emergency admissions, outpatient and inpatient admissions. The following respiratory conditions were considered: acute upper respiratory tract infections (J00–J06); acute lower respiratory tract infections (J09–18, J20–22); and asthma admissions (J45) The full list of ICD10 codes used for these groups is listed in Supplementary Table S1. Only those with the appropriate ICD10 codes listed as a primary reason for hospital admission were included. Admissions were restricted to only those children who resided in Dundee in the following postcode districts: DD1, DD2, DD3, DD4, DD5, DD6, DD7.

2.2 Exposure Data

Pollution information is measured daily at urban background sites, throughout the UK, as part of the UK's Automatic Urban and Rural Network (AURN). Daily NO_x, NO_2 and NO concentrations measured in Seagate, Dundee, were used for the analysis. Data on mean air temperature and relative humidity were obtained from the UK Meteorological Office. Temperature data from Mylnefield, near Dundee, and humidity data from Leuchars, Fife, were used.

2.3 Statistical Analysis

The case-crossover design has been previously used to analyse associations of short-term exposures with acute outcomes (Nawrot *et al.*, 2011) and is a variation of a matched case-control study. Each subject serves as its own control, so that known and unknown time-independent confounders are inherently adjusted for by study design (Maclure, 1991). The case-crossover design 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 is avoided by applying a bidirectional time-stratified design (Levy *et al.*, 2001). Control days are taken from the same calendar month and year as the case day (the day of the hospital admission), both before and after the case, therefore controlling for long-term trends and season by design. Cases and controls were also matched by day of the week to control for any weekly patterns in air pollution or hospital admissions.

To investigate the association between respiratory hospital admissions and pollution exposure up to 14 days before the hospital admission (lag zero to 14), we combined the case-crossover design with distributed lag (non-linear) models (DL(N)M) (Gasparrini *et al.*, 2010; Armstrong, 2006), using separate models for NO_x, NO_2 and NO.

DL(N)Ms enable the investigation of the temporal pattern of the association, providing an estimate of the "overall" effect of the exposure, incorporating potential delayed and harvesting effects. A DL(N)M model is defined through a "cross-basis" function, a bi-dimensional space of functions describing simultaneously the shape of the relationship along the space of the predictor (exposure-response function), and its distributed lag effects (lag-response function). We used a linear exposure-response function for the association between air pollution exposure and hospital admissions. The number of days included in the cross-basis was chosen based on visual inspection of the 3D exposure-lag-response surfaces. The lag structure was modelled with a natural cubic spline with three degrees of freedom (df), placing the knots at equally spaced values on the log scale of lags to allow more flexible lag effects at shorter delays (Gasparrini, 2011). To account for the (potentially delayed) effects of meteorological factors on respiratory admissions (Law *et al.*, 2017), we also included DLNM cross-bases for mean temperature and for humidity in the model. In both cross-bases, the maximum lag was set to 14 days and natural cubic splines with three df were used to model the exposure-response and the lag-response functions.

Risk ratios (RR) of hospital admissions were calculated for a 10 $\mu g\ m^{-3}$ increase in air pollutant concentrations. Reported estimates, computed as the risk at day 0 (day of exposure), and the cumulative risk over the total lag period, are presented with corresponding 95% confidence intervals (CI). All analyses were performed with the statistical software R (R Foundation for Statistical Computing, Vienna, Austria) using the "dlnm" package (https://cran.r-project.org/web/packages/dlnm/index.html).

Percent reduction in admissions over the study period was calculated using the RR estimates and P5–P95 pollution levels over the period. Risk estimates were converted into percentage increase in admissions per 10 $\mu g\ m^{-3}$. P5 and P95 were used as the range of pollution for this calculation. Risk percentage was then calculated for P5–25 and P25–95 and subtracted from each other resulting in a total percentage of excess admissions.

3 RESULTS

A total of 9,501 and 24,691 respiratory hospital admissions in 6,175 children and 11,192 adults respectively were included in this study, over the 14-year period. The number of control days per case was 3–4 with a total of 31,829 and 100,288 of control days for children and adults respectively, in this case-crossover design. Table 1 details the mean, median and percentiles of pollutants over the study period.

Fig. 1 shows the pollution trend for NO_2 over the total study period. NO_2 pollution has largely stayed stable over the study period, often exceeding the 40 $\mu g\ m^{-3}$ limit set by regulations. The peaks in pollution occur during winter periods. NO_x and NO follow the same trends as seen in Fig. 1 for NO_2.

3.1 Respiratory Hospital Admissions in Children

All Respiratory admissions in children (< 16 years) taken together were significantly associated with cumulative (14-day) exposure to NO_x (RR 1.018; 95% CI 1.009–1.028), NO_2 (RR 1.086; 95% CI 1.036–1.139) and NO (RR 1.033; 95% CI 1.016–1.052), although same-day (lag 0) estimates were not significant (Table 2).

Fig. 2 shows the lag-response function plots for all respiratory hospital admissions in children. Fig. 2 show an initial increase in risk ratios on day 0 of exposure, followed by a dip in risk on days

Table 1. Descriptive statistics of air pollution concentrations ($\mu g\ m^{-3}$) measured in Dundee from 2004–2017. P5 = 5th percentile; P25 = 25th percentile; P75 = 75th percentile; P95 = 95th percentile.

Measure	NO_x	NO_2	NO
Mean	172.3	50.4	79.8
Median	165.0	49.7	75.0
P5	61.3	26.0	21.6
P25	123.0	39.8	44.1
P75	212.0	60.2	84.2
P95	313.3	76.1	138.7

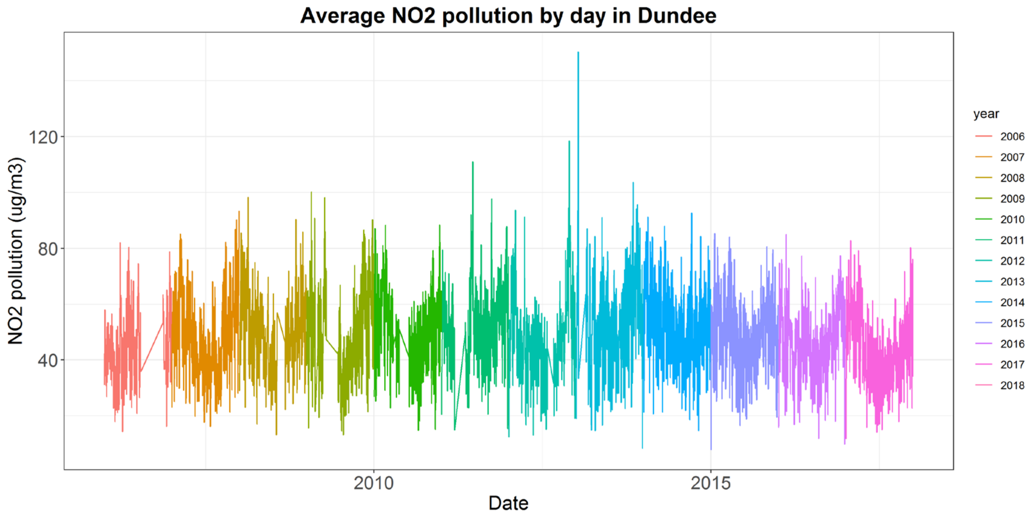

Fig. 1. Average NO_2 pollution by day, over the total study period in Dundee.

Table 2. Association between nitric oxide air pollution exposure and hospital admissions for respiratory diagnoses in children (< 16 years). Results given as RR with 95% confidence intervals for a 10 µg m^{-3} increase in air pollutant concentrations.

Exposure	Lag 0	Cumulative (lag 0–14)
All child respiratory admissions n = 9501		
NO_x	1.002 (0.997–1.006)	1.018 (1.009–1.028)
NO_2	1.007 (0.984–1.030)	1.086 (1.036–1.139)
NO	1.004 (0.995–1.012)	1.033 (1.016–1.052)
Acute respiratory infections n = 7940		
NO_x	1.003 (0.998–1.007)	1.020 (1.010–1.031)
NO_2	1.014 (0.990–1.040)	1.111 (1.056–1.169)
NO	1.003 (0.998–1.007)	1.020 (1.010–1.031)
Acute upper respiratory infections n =4336		
NO_x	1.001 (0.995–1.008)	1.020 (1.006–1.035)
NO_2	0.989 (0.957–1.023)	1.105 (1.029–1.186)
NO	1.003 (0.991–1.015)	1.035 (1.008–1.063)
Acute lower respiratory infections n =3605		
NO_x	1.003 (0.997–1.010)	1.020 (1.006–1.034)
NO_2	1.043 (1.006–1.082)	1.119 (1.039–1.204)
NO	1.005 (0.992–1.017)	1.035 (1.008–1.062)
Asthma n = 958		
NO_x	0.999 (0.985–1.014)	1.020 (0.988–1.053)
NO_2	0.951 (0.883–1.024)	1.011 (0.865–1.181)
NO	1.002 (0.976–1.028)	1.043 (0.983–1.107)

1–2, again followed by an increased risk. Fig. 2 indicate a significantly increased risk over days 6–10 following exposure to pollution.

Hospital admissions for acute respiratory infections in children were significantly associated with cumulative (lag 0–14) exposure to NO_x (RR 1.020; 95% CI 1.010–1.031), NO_2 (RR 1.111; 95% CI 1.056–1.169) and NO (RR 1.020; 95% CI 1.010–1.031) (Table 2). Again, acute respiratory admissions were not significantly associated with pollutant concentrations on the day of exposure (Table 2).

Acute respiratory infections were split into upper (J00–06) or lower (J09–18, J20–22) tract infections. The majority of upper respiratory infections were: acute tonsilitis (n = 2,161); acute obstructive laryngitis (n = 1,083); and unspecified upper respiratory infections (n = 4,436). Lower

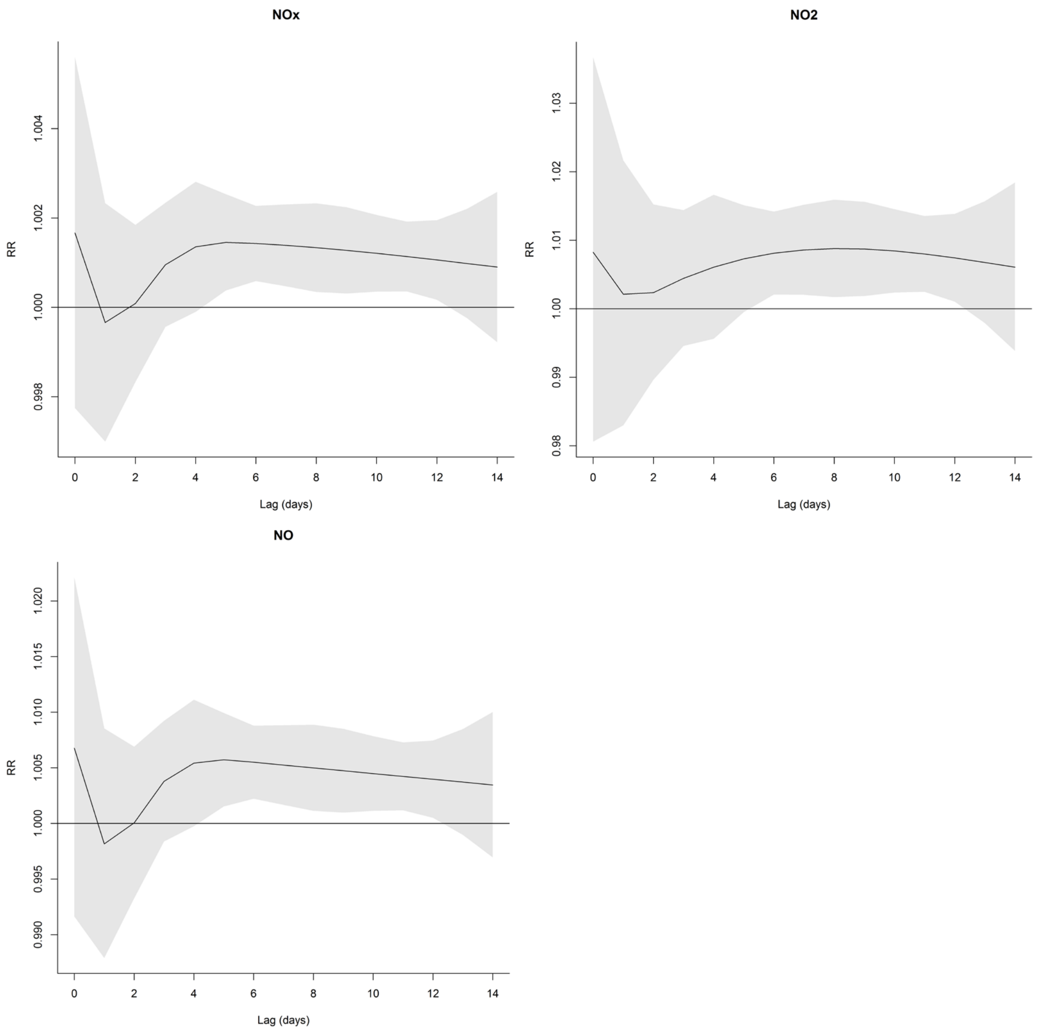

Fig. 2. Lag-response function plots for NO_x, NO_2 and NO pollution over the study period for children.

tract infections were largely the following conditions: influenza/pneumonia (n = 790); acute bronchiolitis (n = 3,138); and unspecified lower respiratory infections (n = 1,367). See supplementary Table S1 for list of ICD10 codes.

Upper tract infections were significantly associated with cumulative exposure to NO_x, NO_2 and NO, but not with pollution on the day of exposure (Table 2).

Hospital admissions for lower respiratory tract infections were significantly associated with the day of exposure to NO_2, but not NO_x or NO (Table 3). Lower tract infections were associated with cumulative NO_x, NO_2 and NO exposure (Table 2).

Asthma hospital admissions were not associated with exposure on the day (lag 0) or cumulative exposure (lag 0–14) to NO_x, NO_2 or NO (Table 2).

3.2 Respiratory Hospital Admissions in Adults

All respiratory admissions in adults were not significantly associated with same-day (lag 0) or cumulative (0–14 day) exposure to NO_x, NO_2 and NO (Table 3).

Fig. 3 shows the lag-response function plots for all respiratory hospital admissions in adults. Fig. 3 show an initial increase in risk ratios on day 0 of exposure, followed by a significant dip in risk on days 2–4, again followed by an increased risk.

Acute respiratory infections and asthma admissions were not significantly associated with same-day (lag 0) or cumulative (0–14 day) exposure to NO_x, NO_2 and NO (Table 3).

Table 3. Association between nitric oxide air pollution exposure and hospital admissions for respiratory diagnoses in adults. Results given as RR with 95% confidence intervals for a 10 µg m^{-3} increase in air pollutant concentrations.

Exposure	Lag 0	Cumulative (lag 0–14)
All adult respiratory admissions n = 24,691		
NO_x	1.002 (0.999–1.004)	1.000 (0.994–1.005)
NO_2	1.007 (0.994–1.020)	0.999 (0.972–1.026)
NO	1.003 (0.998–1.007)	0.999 (0.989–1.010)
Acute respiratory infections n = 15,680		
NO_x	1.000 (0.996–1.004)	1.001 (0.993–1.009)
NO_2	0.996 (0.978–1.014)	1.001 (0.964–1.039)
NO	1.000 (0.994–1.007)	1.002 (0.987–1.016)
Acute upper respiratory infections n = 719		
NO_x	1.000 (0.984–1.016)	1.010 (0.974–1.047)
NO_2	1.041 (0.958–1.131)	1.091 (0.915–1.300)
NO	0.996 (0.967–1.026)	1.013 (0.948–1.083)
Acute lower respiratory infections n = 14,961		
NO_x	1.000 (0.996–1.004)	1.000 (0.993–1.008)
NO_2	1.000 (0.998–1.002)	1.000 (0.996–1.004)
NO	1.001 (0.994–1.007)	1.001 (0.987–1.016)
Asthma n = 3468		
NO_x	1.005 (0.990–1.021)	1.011 (0.978–1.045)
NO_2	1.018 (0.941–1.102)	0.999 (0.848–1.178)
NO	1.010 (0.981–1.039)	1.026 (0.964–1.091)

Table 4 shows the percentage decrease in children's respiratory hospital admissions if pollution was kept at the P25 measures we recorded in this study. Between 38–53% of admissions could have been avoided over the study period.

4 DISCUSSION

This study showed significant associations of NO_x, NO, and NO_2 with respiratory hospital admissions among children in Dundee, Scotland, but not adults, with significant effects observed around 6–7 days after the exposure. Our findings indicate that children may be at a higher risk of hospitalization at lower levels of NO_x pollution exposure than adults. Reasons for this may be increased susceptibility of immature lungs to toxins, and children tend to be outside more frequently than adults, and thus more exposed (Saadeh and Klaunig, 2014).

NO_x is measured as NO and NO_2 with smaller other particles (e.g., SO_2), however only the NO and NO_2 gases that make up NO_x are measured separately in Dundee at this time. NO_2 is linked to increased pulmonary mucous production making a fertile ground for infection (Ciampi *et al.*, 2022). Inflammatory cell adhesion molecules are stimulated by both NO and NO_2, as are inflammatory cytokines such as interleukin 8 (Channell *et al.*, 2012). Further endothelial damage and vasoconstriction can also occur reducing oxygen transport (Xu *et al.*, 2022). Thus, there are many mechanisms where by damage is caused. Air pollution is a special concern for children as their lungs and immune system are not fully developed when exposure begins, raising the possibility of different responses than seen in adults. In addition, children spend more time playing outside, where the concentrations of pollution from traffic are higher (Schwartz, 2004).

We report a slight increased risk of respiratory admissions in adults, particularly acute upper respiratory infections, however these results did not reach significance. Our results indicate that NO_2 may have the greatest effect on adults developing respiratory issues requiring hospital admission. Previous literature has confirmed that nitrogen oxides increase risk of developing respiratory conditions in adults (Kelly and Fussell, 2011), leading to hospital admission (Çapraz *et al.*, 2017).

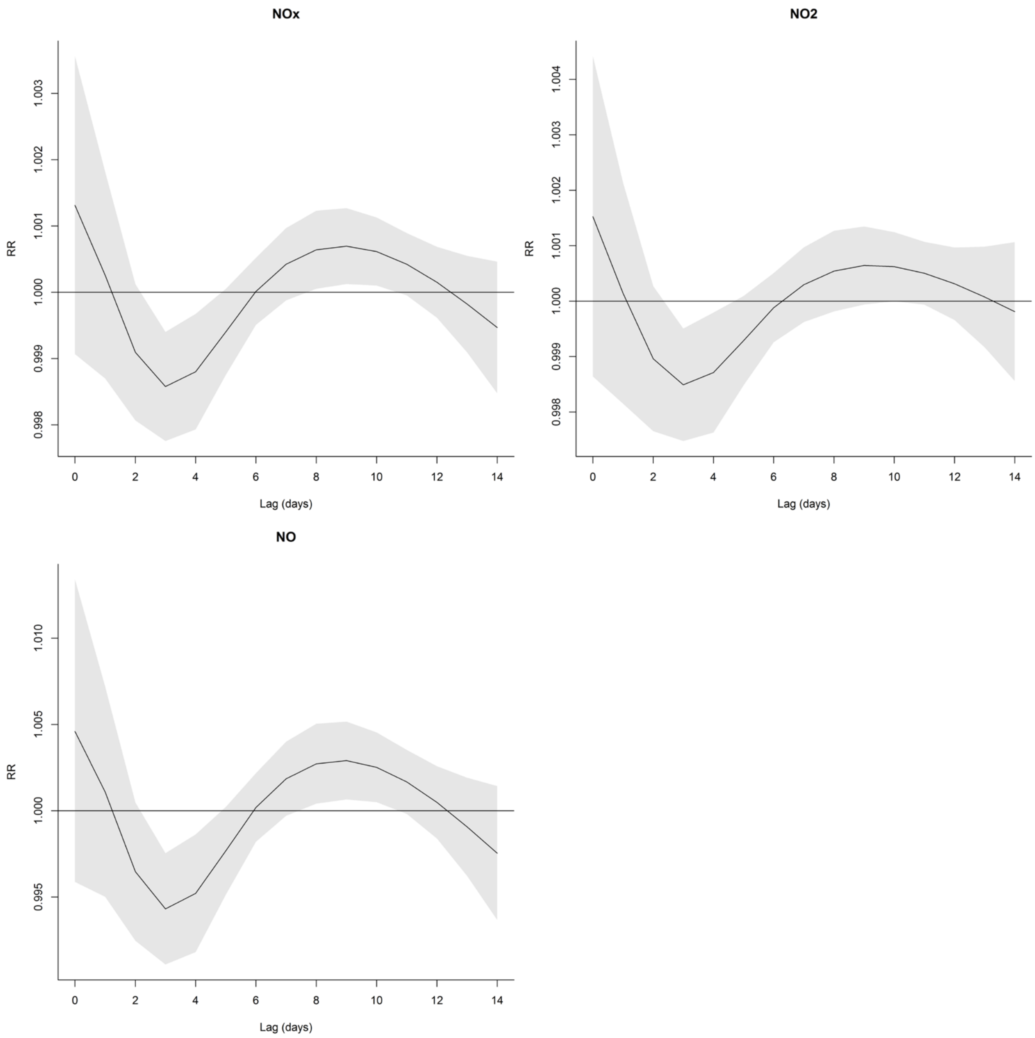

Fig. 3. Lag-response function plots for NO_x, NO_2 and NO pollution over the study period for adults.

Table 4. Potential percentage reduction of respiratory hospital admissions in children, if pollution were limited to P25 limits.

Pollutant	% decrease in admissions over study period
NO_x	45.2
NO_2	53.6
NO	38.3

While the literature supports an increased risk of respiratory conditions in adults, we can only suggest an increased risk in Dundee. One reason we theorize why adults were not found to be significant is that adults usually visit secondary care in the community, such as general practice rather than hospital for respiratory issues. This may mean we are underestimating the total respiratory distress associated with air pollution. Furthermore, adults may have a better control over their treatment in conditions such as exacerbated asthma due to pollution, whereas parents may be more likely to resort to emergency services when their child is having respiratory problems.

Limitations of this study are that we used a single monitoring station in Dundee to estimate personal exposure to air pollution, which may result in effect estimates being an underestimation of the actual impact, due to non-systematic exposure misclassification (Zeger *et al.*, 2000). Furthermore, as the pollutants are modelled separately, we cannot say whether they provide an additive effect, as NO_x, NO_2 and NO are highly correlated. This is also extended to other pollutant types, such as particulate matter. While PM_{10} measured in Dundee has been largely kept within Scottish guideline limits (Belch *et al.*, 2021), we cannot say whether this in combination with nitrogen oxides and other unmeasured pollutants have an additive effect, or whether the true association is due to these unmeasured pollutants rather than nitrogen oxides.

There has been a focus on improving air quality in the UK for the past 20 years, which has largely centred on the reduction of PM_{10} pollution. However, more needs to be done in Tayside and elsewhere where these results might be extrapolated, to address the high NO_x and NO pollution levels still being allowed, particularly considering the increased risks reported here, and in other studies. This study shows that both NO and NO_2 are associated with increased respiratory hospital admissions in children, and that more should be done to improve and enforce NO_x pollution restrictions in city centres. The burden on the health service is likely to be greater than estimated here, as a majority of people present to primary care rather than hospital for respiratory issues (Dowell *et al.*, 2017; Uijen *et al.*, 2010).

The major contributors to air pollution in Dundee are traffic pollution and agriculture. There are no other large industries within Dundee contributing to air pollution. Traffic air pollution is a mixture of particulate matter, NO_x and volatile compounds. The main components of air pollution from agriculture are ammonia (NH_3) and nitrous oxide (N_2O), with the other components being other nitrogen containing compounds (NO_x) (DEFRA, 2018). While pollutants such as NH_3, $PM_{2.5}$ and O_3 are increasingly important, they were not measured in Dundee over the study period.

As road traffic is responsible for 28% of NO_2 air pollution in the UK (GOV.UK, 2022), we are pleased to report the establishment of a Low Emission Zone in Dundee in 2022, although only in a small part of the city. Scotland generally has one of the toughest anti-pollution legislation in Europe, however our study, and others (Fitton *et al.*, 2021; Shah *et al.*, 2013), show this legislation is not cascading down at local level.

5 CONCLUSIONS

This study, from the Tayside Pollution Research Programme (TPRP), aimed to investigate the effects of air pollution on respiratory hospital admissions in adults and children, over a 14-year period, in Dundee, Scotland. Using routinely collected data, we conducted a case-crossover study from 2004 to 2017. Respiratory hospitalisation events were linked to daily nitric oxide gases (NO_x, NO_2, NO) extracted from publicly available data over this period. Respiratory admissions in children were significantly associated with cumulative 14-day exposure to NO_x, NO_2 and NO, particularly for acute respiratory infections. No significant association was seen for respiratory admissions in adults. This study shows that both NO and NO_2 are associated with increased respiratory hospital admissions in children $<$ 16 y of age, and that much more should be done to improve and enforce the established legal NO_x pollution limits in cities for the sake of our children's health.

ADDITIONAL INFORMATION AND DECLARATIONS

Ethics Approval and Consent to Participate

As all data were anonymised such that the researchers had no access to patient information, and the linkage was done in the Health Informatics Safe Haven. It was thus considered by the Institution's Research Governance Team that Caldicott Approval was sufficient to carry out this research.

Availability of Data and Materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing Interests

All Authors declare that they have no conflicts of interest/competing interests to declare for this work.

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Authors' Contributions

JJFB wrote the protocol, obtained funding, wrote first draft of paper; CF contributed to the protocol, did the analyses, contributed to the paper; BC developed the statistical methods, oversaw their implementation, contributed to the paper; JC contributed to the concept, contributed to the paper; SM contributed to the paper.

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Supplementary Material

Supplementary material for this article can be found in the online version at https://doi.org/10.4209/aaqr.230062

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