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## Ambient Air Pollution and Sudden Infant Death Syndrome: A case crossover study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-018341
Article Type:	Research
Date Submitted by the Author:	21-Jun-2017
Complete List of Authors:	Litchfield, Ian; University of Birmingham, Institute of Applied Health Research Ayres, Jon; University of Birmingham, Institute of Applied Health Research Jaakkola, Jouni; University of Oulu, Center for Environmental and Respiratory Health Research Mohammed, Nuredin; University of Birmingham, Institute of Applied Health Research
<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Occupational and environmental medicine, Paediatrics, Public health, Respiratory medicine
Keywords:	EPIDEMIOLGY, Community child health < PAEDIATRICS, Cot death < PAEDIATRICS, Paediatric thoracic medicine < PAEDIATRICS, PUBLIC HEALTH

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# Ambient Air Pollution and Sudden Infant Death Syndrome: A case crossover study

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Word count: 2460

Number of figures: 4

Number of tables: 4

## ABSTRACT

**Objectives:** Air pollution has been associated with increased mortality and morbidity in several studies with indications its effect could be more severe in children. This study examined the relationship between short-term variations in criteria air pollutants and occurrence of sudden infant death syndrome (SIDS). using data from the West Midlands region in the UK.

**Design:** We used a case-crossover study design. widely applied in air pollution studies and particularly useful for estimating the risk of a rare acute outcome associated with short-term exposure.

**Setting:** The study used data from the West Midlands region in the UK

**Participants:** We obtained daily time series data on SIDS mortality (ICD-9: 798.0 or ICD-10: R95) for the period 1996-2006 a total of 211 SIDS events.

**Primary outcome measures:** The association between short-term exposure to air pollution and the occurrence of SIDS events controlling for daily birth counts and average daily temperature.

**Results:** For an interquartile range increase in previous day pollutant concentration, the percentage increases (95% confidence interval) in SIDS were 16 (6, 28) for PM<sub>10</sub>, 1 (-7, 13) for SO<sub>2</sub>, 4 (-5, 13) for CO, -24 (-36, -5) for O<sub>3</sub>, 13 (0.1, 28) for NO<sub>2</sub>, and 1 (-4, 7) for NO. Results were qualitatively similar after additional control for index of multiple deprivation (IMD) scores for most of the lag structures investigated. PM<sub>10</sub> and NO<sub>2</sub> showed relatively consistent association which persisted across different lag structures and after adjusting for co-pollutants.

**Conclusions:** The results indicated ambient air pollutants, particularly PM<sub>10</sub> and NO<sub>2</sub>, were associated with increased SIDS mortality. Thus, future studies are recommended to

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2  
3 understand possible mechanistic explanations on the role of air pollution on SIDS incidence and  
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5 the ways in which we might reduce pollution exposure among infants.  
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10 **Clinical trial registration:** Not applicable.  
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## 14 **Article Summary**

### 15 **Strengths and limitations of this study**

- 16 • Sudden infant death is the leading cause of death in healthy infants between one  
17 month and one year old. The exact cause is unknown though evidence suggests a  
18 respiratory trigger may be involved.
- 19 • Our study is the first based on time series data from the UK to investigate the  
20 relationship between common air pollutants and SIDS.
- 21 • We used a case-crossover design which is widely applied in air pollution studies and  
22 particularly useful for estimating the risk of a rare acute outcome associated with  
23 short-term exposure.
- 24 • We investigated various lags and multi-pollutant models indicating delayed effects of  
25 pollutants that persisted after controlling for co-pollutants.
- 26 • Our study is limited in power due to the comparatively small number of daily SIDS  
27 events.  
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## INTRODUCTION

The quality of ambient air is an important factor in the health of adults and children. Ambient air quality is the second largest challenge facing public health in the UK.[1] According to the World Health Organisation (WHO), over 3.7 million premature deaths per annum may be attributed to the harmful effects of ambient air. Children it would seem are more vulnerable than any other group[2] and recent studies have indicated how even low-levels of traffic-related air pollution can have a negative impact on birth outcomes and perinatal health.[3, 4] A number of studies have also suggested a link between ambient air quality and the incidence of sudden infant death syndrome (SIDS).[5-10]

Sudden infant death is the leading cause of death in healthy infants between one month and one year old,[11] and the impact on the families is notably traumatic as the death is without warning or witness.[12] The exact cause is unknown though is likely the result of a combination of factors including susceptibility and environmental stressors such as lower social status of parents,[13] environmental tobacco smoke,[13, 14] the prone position[15] and the winter season.[5, 15] The impact of tobacco smoke suggests a respiratory trigger may be involved, however the evidence of an association between SIDS and air pollution warrant further research as findings from epidemiological studies have been inconsistent.[16, 17] and few have satisfactorily explore the impact of short-term exposure on SIDs. Our study is the first based on time series data from the UK to investigate the relationship between common air pollutants and SIDS. We have collated data from a ten-year period on concentrations of air pollution and onset of SIDS within the West Midlands one of the largest and most polluted conurbations in the UK.

## METHODS

### Data collection

We combined data on SIDS events with data on total births, air pollution, air temperature and a measure of deprivation.

#### Data on SIDS mortality and total births

We obtained daily time series data on SIDS mortality (ICD-9: 798.0 or ICD-10: R95) for the period 1996-2006 from the Perinatal Institute (PI). This data consisted of the date of death and the first three digits of the postcode to avoid the possibility of identifying individual cases due to the rare nature of SIDS. This allowed us to explore the effects of short-term exposure. We obtained daily births data with West Midlands' postcodes from the Office of National Statistics (ONS) for the period 1996-2006.

#### Air pollution data

The daily time series data on air pollution were compiled from the UK air quality archive managed by Department for the Environment, Food and Rural Affairs (DEFRA). These include a total of ten monitoring stations in the West Midlands measuring PM<sub>10</sub>, SO<sub>2</sub>, NO<sub>2</sub>, NO, NO<sub>x</sub>, CO and O<sub>3</sub> including sites within Birmingham, Coventry, Walsall and Wolverhampton. Before 1996 the reliability of air quality data was inconsistent. Not all monitoring stations had measurements for the range of pollutants over the entire study period and the precise pollutants measured at each monitoring centre are described in Table 1.

Table 1: Pollutants measured and corresponding time period by monitoring stations

Name (postcode area)	Pollutants	Time period <sup>a</sup>
Birmingham Centre (B)	PM <sub>10</sub> , SO <sub>2</sub> , NO <sub>2</sub> ,NO, NO <sub>x</sub> , CO, O <sub>3</sub>	01/01/1996-31/12/2006
Birmingham East (B)	PM <sub>10</sub> , SO <sub>2</sub> , NO <sub>2</sub> ,NO, CO, O <sub>3</sub>	01/01/1996-03/08/2004
Birmingham Tyburn (B)	PM <sub>10</sub> , SO <sub>2</sub> , NO <sub>2</sub> ,NO, CO, O <sub>3</sub>	16/08/2004-31/12/2006
Oldbury (B)	PM <sub>10</sub> , SO <sub>2</sub> , NO <sub>2</sub> ,NO, NO <sub>x</sub> , CO, O <sub>3</sub>	27/06/1997-20/09/1998
West Bromwich (B)	PM <sub>10</sub> , SO <sub>2</sub> , NO <sub>2</sub> ,NO, NO <sub>x</sub> , CO, O <sub>3</sub>	04/11/1998-31/12/2006
Coventry Centre (CV)	PM <sub>10</sub> , SO <sub>2</sub> , NO <sub>2</sub> ,NO, NO <sub>x</sub> , CO, O <sub>3</sub>	19/02/1997-31/12/2006
Coventry Memorial (CV)	PM <sub>10</sub> , SO <sub>2</sub> , NO <sub>2</sub> ,NO, NO <sub>x</sub> , CO, O <sub>3</sub>	26/02/2001-31/12/2006
Walsall Alumwell (WS)	NO <sub>2</sub> , NO <sub>x</sub>	01/01/1996-31/12/2006
Walsall Willenhall (WS)	NO <sub>2</sub>	13/05/1997-31/12/2006
Wolverhampton Centre (WV)	PM <sub>10</sub> , SO <sub>2</sub> , NO <sub>2</sub> ,NO, NO <sub>x</sub> , CO, O <sub>3</sub>	19/12/1995-31/12/2006

<sup>a</sup>Period with at least one pollutant being measured and taking into account missing data between start and end dates.



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3 We aimed to examine the association between day-to-day variability in air pollution  
4 exposure and SIDS counts over the entire region rather than contrasting exposure and outcome  
5 between areas within the West Midlands region. Therefore the daily pollution data for West  
6 Midlands were calculated by averaging across all monitoring stations with available  
7 measurements.  
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#### 17 Temperature data

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19 Data on daily minimum and maximum temperature were compiled for weather monitoring  
20 stations in the West Midlands from the Meteorological Office British Atmospheric Data Centre  
21 (BADC).[18] We used the average daily temperature which was calculated by taking the average  
22 of the minimum and maximum temperature at each monitoring station for each day to obtain the  
23 daily average temperature for the entire West Midlands.  
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#### 33 Index of multiple deprivation (IMD) score

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35 The IMD score is a composite measure based on seven dimensions of deprivation  
36 including income deprivation, employment deprivation, health deprivation and disability,  
37 education deprivation, crime deprivation, barriers to housing and services deprivation and living  
38 environment deprivation. The data for the 2010 IMD at postcode level were downloaded from  
39 EDINA Digimap ShareGeo facility, an online spatial data repository.[19]  
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#### 49 **Statistical analysis**

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51 The case-crossover design was used to investigate the association between short-term  
52 exposure to air pollution and the occurrence of SIDS events controlling for daily birth counts and  
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3 average daily temperature. This design, introduced by Maclure,[20] has been widely applied in  
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5 air pollution studies and is particularly useful for estimating the risk of a rare acute outcome  
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7 associated with short-term exposure.[21-24] In case-crossover design each case acts as their own  
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9 control and like case-control studies[25] the distribution of exposure is compared between  
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11 ‘cases’ and ‘controls’. That is, exposure at the time just prior to the event (‘case’ or ‘index’ time)  
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13 is compared with a set of ‘control’ times that represent the expected distribution of exposure for  
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15 non-event follow-up times. The design helps primarily to control for confounding by subject-  
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17 specific factors which remain static over time such as ethnicity and gender.  
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24 We applied the time stratified case-crossover approach where the strata are matching days  
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26 based on the same day of the week, calendar month and year. That is, control days were selected  
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28 from the same day of the week, within the same calendar month and year as the event day. We  
29  
30 applied a conditional Poisson regression model which has been shown to give equivalent  
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32 estimates as the conditional logistic model but with the advantage of readily allowing for  
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34 overdispersion and autocorrelation.[26] All our models assume a linear effect for air pollution  
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36 reported in previous studies[27-29] while temperature effects are likely to be non-linear and were  
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38 modelled using natural splines with 3 degrees of freedom.[30, 31]  
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#### 44 Sensitivity analyses

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47 The primary aim was to investigate the risk of SIDS events in relation to air pollution on  
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49 the previous day in single pollutant models. To examine sensitivities to our *a priori* model  
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51 specification, additional lag structures were explored including single lags of 0,1,2,...,6 days and  
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53 also the corresponding average of lags 0-1, 0-2, 0-3,..., 0-6. Moreover, the association between  
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3 SIDS and air pollution was examined after adjusting for the effect of each of the pollutants PM<sub>10</sub>,  
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5 SO<sub>2</sub>, NO<sub>2</sub>, NO, CO and O<sub>3</sub> as a second pollutant in turn. The aim of this two-pollutant modelling  
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7 approach was to account for potential confounding effect of co-pollutants. Further control for  
8  
9 potential confounding effect of the IMD scores was made in both single and multi-pollutant  
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11 models after categorising the scores into five groups (quintiles). We excluded NO<sub>x</sub> from the  
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13 sensitivity analyses as it showed very strong correlation particularly with NO (r=0.96).  
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19 Results are presented as percentage increases in mortality with 95% confidence intervals  
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21 (CIs) for an interquartile range (IQR) increase in pollutant concentration. Hypothesis tests were  
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23 two-sided with a significance level of 0.05. All analyses were performed using the R statistical  
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25 package.[32]  
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## RESULTS

### Descriptive statistics

Over the study period (1996–2006), there were 211 SIDS events across the four postcode areas (B, CV, WS and WV) included in the analyses which accounted for about approximately 5% of the days within the study period (Table 2). In the same period and location, a total of 943,937 live (single) births were registered.

Table 2: Average air pollution, temperature and IMD scores for selected West Midlands postcode areas with SIDS and birth counts, 1996-2006

Post town (area)	PM <sub>10</sub>	SO <sub>2</sub>	CO	O <sub>3</sub>	NO <sub>2</sub>	NO	NO <sub>x</sub>	Temp. (Min- Max)	IMD score	SIDS event event (%)	Birth count count (%)
Birmingham (B)	23.8	6.8	0.4	38.	33.9	17.5	60	7.2-12.8	36.6	118 (55.9)	75384 4 (79.9)
Coventry (CV)	18.3	11.3	0.3	32. 4	22.5	9.2	36.2	7.7-13.5	23.7	43 (20.4)	91393 (9.7)
Walsall (WS)					41.5		89.4	6.4-14.0	25.2	24 (11.4)	53532 (5.7)
Wolverhampton (WV)	23.8	9.3	0.5	38. 9	29.5	18.9	59.5	8.4-12.3	33.4	26 (12.3)	45168 (4.8)
Total										211 (100)	94393 7 (100)

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3 The daily average air pollution concentrations and their standard deviations are presented  
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5 in Table 3 and show that average concentrations tended to be below UK air quality limits.  
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Table 3: Descriptive statistics for daily SIDS mortality counts, air pollution, temperature and birth counts for West Midlands, 1996-2006

Variable	Mean	SD	Median	IQR	Min	Max
SIDS count	0.1	0.3	0.0	0-0	0.0	2.0
Average temperature	10.2	5.4	10.2	6.2-14.5	-4.2	25.0
Max temperature	13.1	6.0	12.9	8.5-17.6	-2.1	29.6
Min temperature	7.4	5.1	7.5	3.6-11.4	-7.5	20.7
PM <sub>10</sub>	23.4	11.6	20.2	15.7-28.2	4.0	128.9
SO <sub>2</sub>	8.5	6.9	7.2	4.4-10.2	0.0	70.8
CO	0.4	0.2	0.4	0.3-0.5	0.1	3.5
O <sub>3</sub>	38.1	18.2	38.0	25.4-50.4	1.3	115.8
NO <sub>2</sub>	33.2	14.3	31.2	22.3-41.8	5.9	113.0
NO	16.9	23.8	9.0	5.4-17.9	0.4	314.9
NO <sub>x</sub>	64.5	49.3	51.1	35.2-76.4	7.9	569.2
Birth count <sup>a</sup>	289.8	33.9	295.0	266.0-314.0	183.0	387.0
IMD score	32.3	12.6	31.7	21.3-40.5	7.2	54.9

<sup>a</sup>Counts are for single births only

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3 Table 4 shows that there was generally a strong correlation between the levels of pollutants  
4 investigated with the exception of the weaker correlation between O<sub>3</sub> and PM<sub>10</sub> (r=-0.26) and  
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6 with SO<sub>2</sub> (r=-0.34).  
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Table 4: Pairwise Pearson correlations coefficients ( $r$ ) for pollutants and temperature

	PM <sub>10</sub>	SO <sub>2</sub>	CO	O <sub>3</sub>	NO <sub>2</sub>	NO	NO <sub>x</sub>
SO <sub>2</sub>	0.53						
CO	0.56	0.59					
O <sub>3</sub>	-0.26	-0.34	-0.56				
NO <sub>2</sub>	0.66	0.56	0.76	-0.62			
NO	0.54	0.48	0.87	-0.58	0.73		
NO <sub>x</sub>	0.59	0.56	0.90	-0.62	0.86	0.96	
Temperature	-0.08	-0.24	-0.39	0.40	-0.40	-0.38	-0.40

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3 Comparing the four postcode areas, Birmingham had the highest SIDS mortality (about  
4 56%) and births rates (about 80%). Air pollution concentrations were more or less similar for  
5 Birmingham and Wolverhampton except slightly lower levels of NO<sub>2</sub> and higher levels of SO<sub>2</sub>  
6 observed for the latter. Coventry had the lowest pollution level with respect to all pollutants  
7 except SO<sub>2</sub>. Walsall had measurements for NO<sub>2</sub> and NO<sub>x</sub> only which were very large compared  
8 to the other postcode areas (Table 2). Similarly, Birmingham and Wolverhampton had higher  
9 average deprivation scores compared to Coventry and Walsall (Table 2). Also, SIDS counts and  
10 pollution levels tended to be larger in highly deprived areas and near motorways and A-road  
11 networks which may be a reflection of population density (Figure 1; see Supplementary File:  
12 Figure S1).  
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28 Looking at the temporal distribution of SIDS occurrence over the study period, the highest  
29 proportions of deaths were recorded in 1997 (about 14%), 1999 (about 13%) and 2003 (about  
30 12%). There was also indication of seasonal pattern for SIDS occurrence; the highest proportions  
31 of SIDS were observed in January and February (about 10%) and among the relatively colder  
32 months and in July (about 14%) among the warmer months (see Supplementary File: Table S1).  
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### 42 **Case-crossover analysis**

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44 Figure 2 shows the estimated odds ratio (OR) (95% CI) for the association of SIDS events  
45 with each of the pollutants considered based on the conditional Poisson model. For an  
46 interquartile range increase in previous day pollutant concentration, the percentage increase  
47 (95% confidence interval) for the risk of SIDS death was 16 (6, 28);  $p = 0.001$  for PM<sub>10</sub>, 1 (-7,  
48 13);  $p = 0.84$  for SO<sub>2</sub>, 4 (-5, 13) ;  $p = 0.43$  for CO, -24 (-36, -5) ;  $p = 0.01$  for O<sub>3</sub>, 13 (0.1, 28)  
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3 ;  $p = 0.048$  for  $\text{NO}_2$ , 1 (-4, 7) ;  $p = 0.65$  for NO and 7 (-2, 17) ;  $p = 0.12$  for  $\text{NO}_x$ . Therefore,  
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5 considering pollutant levels at lag 1, significant association with increased risk of SIDS was  
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7 indicated only for  $\text{PM}_{10}$  and  $\text{NO}_2$  while a protective effect was apparent for  $\text{O}_3$  before controlling  
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9 for IMD. These results were similar at least qualitatively after adjusting for IMD but with  
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11 decreased OR for  $\text{PM}_{10}$  and increased OR for  $\text{NO}_2$ .  
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### 17 **Sensitivity analyses**

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19 Lag structures: Analyses exploring relationships between SIDS and air pollution for other  
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21 lag structures (lags 0, 2, 3, ..., 6 and corresponding average of lags 0-1, 0-2, 0-3, ..., 0-6)  
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23 indicated associations were somewhat sensitive to the choice of lag (Figure 3). In the single lag  
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25 models, there was an impression of stronger delayed effects for CO,  $\text{NO}_2$ ,  $\text{O}_3$ ,  $\text{PM}_{10}$  and  $\text{SO}_2$   
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27 compared to relatively recent lags (lag 0 and lag 1). The effect of NO appeared to remain  
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29 comparatively flat across lags. Relatively more consistent association across lags was observed  
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31 for  $\text{NO}_2$  and  $\text{PM}_{10}$  and to some extent for CO. Likewise, in average lag models, ORs tended to  
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33 increase with averaging over more lags with exception of NO where such an effect was not  
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35 observed. However, only  $\text{PM}_{10}$ ,  $\text{NO}_2$  and  $\text{O}_3$  showed association across several lags after  
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37 additional control for IMD (see Supplementary File: Figure S2).  
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45 Multi-pollutant models: Further investigation using two-pollutant models also showed  
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47 associations were sensitive to control of other pollutants. In general, adjusting for co-pollutants  
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49 appeared to attenuate ORs towards the null except for  $\text{NO}_2$  and  $\text{PM}_{10}$  where effects remained to  
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51 persist (Figure 4). Interestingly, after controlling for  $\text{PM}_{10}$ , the protective effect of  $\text{O}_3$  and the  
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53 adverse effect of  $\text{NO}_2$  observed in the single pollutant models were not apparent for most of the  
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3 lag choices. Similarly, none of the other pollutants showed marked association with SIDS after  
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5 controlling for PM<sub>10</sub> effects. The estimates from the multi-pollutant model should, however, be  
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7 interpreted with caution as most of the pollutants were correlated.  
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## COMMENTS

### Summary of findings

In this study we hypothesised a delayed effect (lag 1) of air pollution on SIDS incidence and investigated additional lags in sensitivity analyses both before and after controlling for IMD and in single and multi-pollutant models. We found evidence suggesting association of SIDS mortality with PM<sub>10</sub> and NO<sub>2</sub> exposure. Compared to other pollutants, their effects persisted after controlling for IMD, in multi-pollutant models and across the various lag structures investigated.

Though controlling for O<sub>3</sub> and IMD in the same model did attenuate the risk estimates observed for both PM<sub>10</sub> and NO<sub>2</sub>. There were no consistent associations observed with exposure to the remaining pollutants investigated (CO, SO<sub>2</sub>, NO, NO<sub>x</sub>). An exception was the protective effect observed in relation to O<sub>3</sub> exposure.

### Strengths and limitations

Previously studies had focused on relatively longer-term exposure to air pollutants.[33-35] Our study is one of the first to show the potential adverse effects of relatively short-term exposure to air pollution on SIDS occurrence. One of its key strengths is the investigation of various lags and multi-pollutant models indicating delayed effects of pollutants that persisted after controlling for co-pollutants. We acknowledge that our case-crossover study is limited in power due to the small number of daily SIDS events. Other epidemiological studies use data from ambient monitoring stations have shown a good level of correlation between daily personal exposure and daily ambient air pollution measurements,[36, 37] though there is the potential for measurement error that can attenuate regression coefficient estimates.

## Detailed discussion

Previous studies reported mixed results on the relationship between SIDS and air pollution. An earlier study using visibility as a surrogate for the level of air pollution in Taiwan reported adjusted rate ratio (ARR) of 3.8 (2.8–5.1) on the day of SIDS event comparing lowest versus highest visibility. The ARR increased to 5.1 (3.2–8.1) for visibility comparison during 9 days before SIDS occurrence.[5] Later studies with actual air pollution measurements also reported increased risk for SIDS mortality but with much reduced effect sizes. Woodruff et al. and Lipfert et al. found ORs (95% CI) of 1.12 (1.07–1.17) and 1.15 (1.07–1.24) respectively per 10  $\mu\text{g}/\text{m}^3$  increase in  $\text{PM}_{10}$ . [6, 38] A multi-city study from Canada reported about 17.7% increase in SIDS occurrence for an interquartile range increase in  $\text{SO}_2$  (lag 0) and  $\text{NO}_2$  (lag 2) that persisted in more rigorous models adjusting for weather and seasonality. They did not find associations for  $\text{O}_3$  and particulate pollution and the effect of  $\text{CO}$  was not robust to models choice; [8] Ritz et al. had also found such a negative association for  $\text{O}_3$  reporting ORs (95% CI) of 0.89 (0.82–0.96) and 0.93 (0.84–1.02) for single and multi-pollutant models respectively.[33] Similar to our results they highlighted that OR estimates were attenuated in multi-pollutant models. One possible reason for the negative association of  $\text{O}_3$  might be its negative correlation with other pollutants and it could also be confounded by season. For example, Woodruff et al. analysed  $\text{O}_3$  effect for different seasons and found adverse  $\text{O}_3$  effects in the summer season only [34] while Samet et al. reported similar effect for the summer but protective effect in the winter season.[39] However, Sarnat et al. argued that the negative association observed for  $\text{O}_3$  can be explained by its negative correlation with fine particulate matter pollution.[40]

## Conclusion

In conclusion, our findings suggest that air pollution exposure may increase risk of SIDS mortality. Thus, future studies are recommended to help understand possible mechanistic explanations on the role of air pollution on SIDS incidence and the ways in which we can reduce pollution exposure among infants.

For peer review only

## ACKNOWLEDGMENTS

**Funding:** This work was supported by The Lullaby Trust, grant number 260.

**Competing interests:** All authors declare: grants from The Lullaby Trust; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years and no other relationships or activities that could appear to have influenced the submitted work.

**Author contributions statement:** NIM contributed to the research design, performed the data management, data analysis and interpretation, and drafted the initial manuscript; JGA contributed to the conceptualisation of the study, data interpretation and critically reviewed the manuscript; JJKJ contributed to the conceptualisation of the study, data interpretation and critically reviewed the manuscript; IJL contributed to the conceptualisation of the study, initial draft manuscript and supervised the research project at all stages. All authors approved the final manuscript as submitted.

**Transparency:** As lead author, I can confirm that the manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects have been omitted and there are no discrepancies from the planned study.

**Ethics committee approval:** Ethical approval was given by the University of Birmingham, Life and Health Sciences Ethical Review Committee.



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**Data sharing:** No additional data available.

For peer review only

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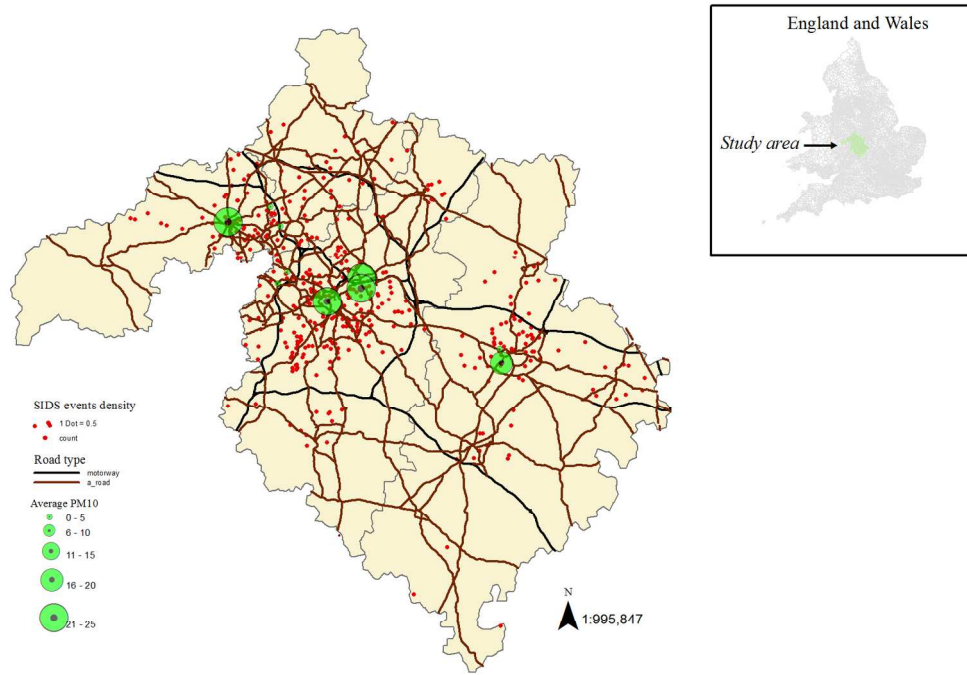
## 24 **FIGURE LEGENDS**

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28 **Fig. 1** Air pollution monitoring sites with road networks (motorways and A-roads) and SIDS events in the  
29 study area. We used ArcGIS Desktop 10.2 (<http://www.esri.com/software/arcgis>) to create the map  
30 combining shapefiles for postcode areas and motorways and overlaying air pollution and SIDS data.  
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37 **Fig. 2** Estimated risk of SIDS for an IQR increase in lag 1 pollutant concentration before and after  
38 controlling for quintiles of IMD scores  
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43 **Fig. 3** Risk of SIDS associated with an IQR increase in pollution for selected lags and average of lags  
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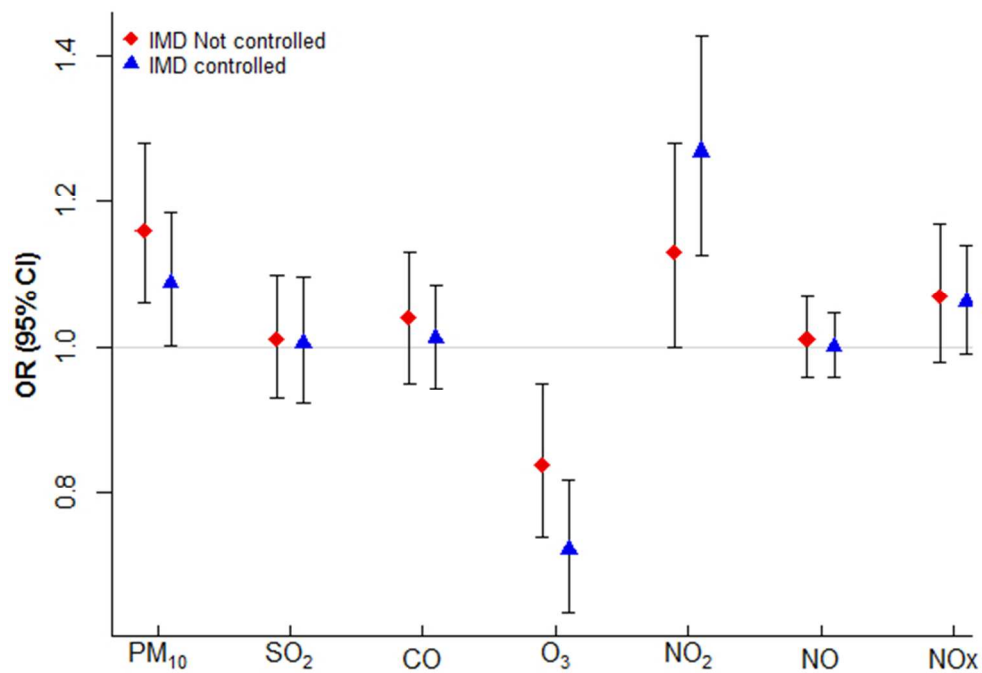
47 **Fig. 4** Risk of SIDS associated with an IQR increase in air pollution after controlling for co-pollutants  
48 (panel titles indicate: main and co-pollutant respectively)  
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Air pollution monitoring sites with road networks (motorways and A-roads) and SIDS events in the study area. We used ArcGIS Desktop 10.2 (<http://www.esri.com/software/arcgis>) to create the map combining shapefiles for postcode areas and motorways and overlaying air pollution and SIDS data.

152x114mm (300 x 300 DPI)

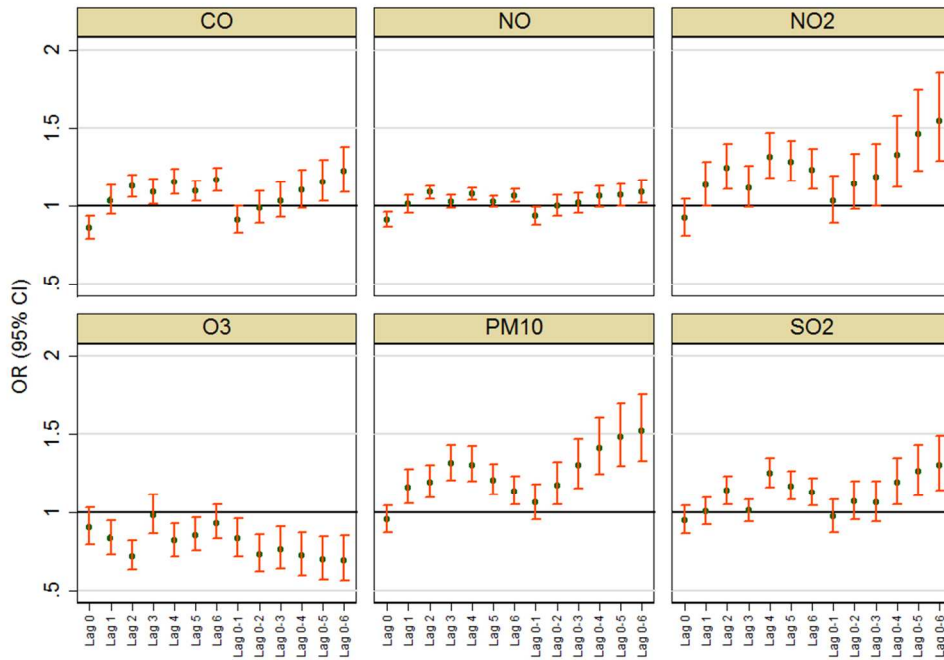
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Estimated risk of SIDS for an IQR increase in lag 1 pollutant concentration before and after controlling for quintiles of IMD scores

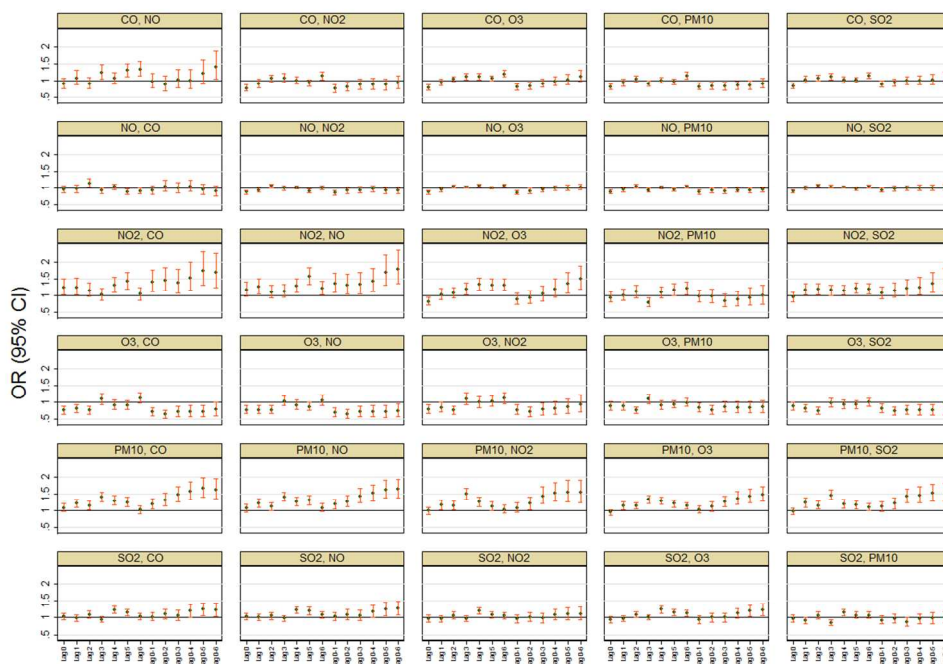
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Risk of SIDS associated with an IQR increase in pollution for selected lags and average of lags

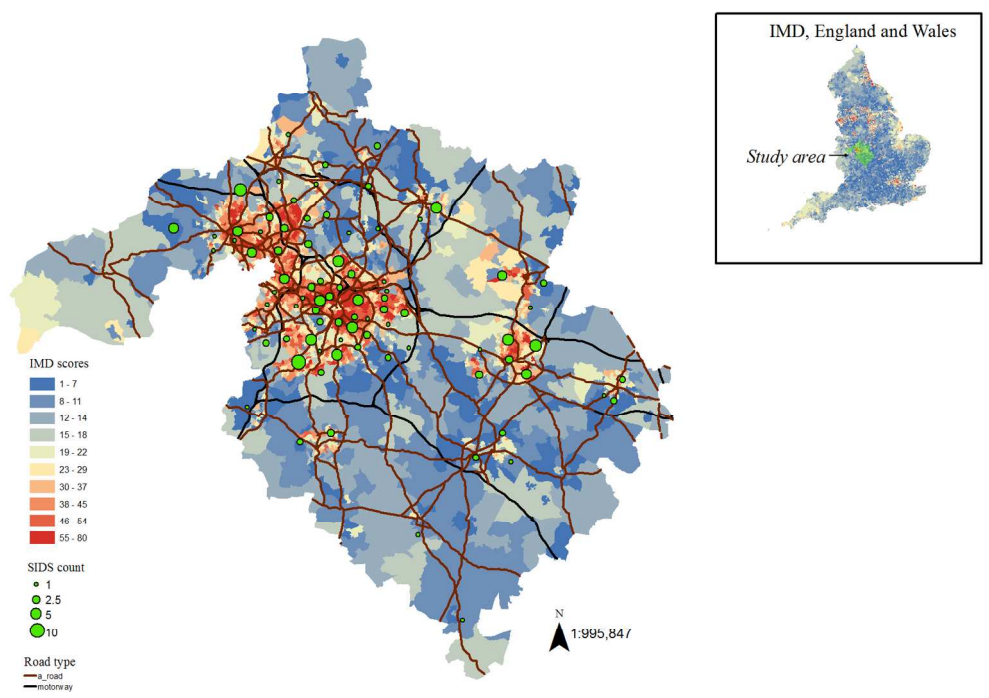
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Risk of SIDS associated with an IQR increase in air pollution after controlling for co-pollutants (panel titles indicate: main and co-pollutant respectively)

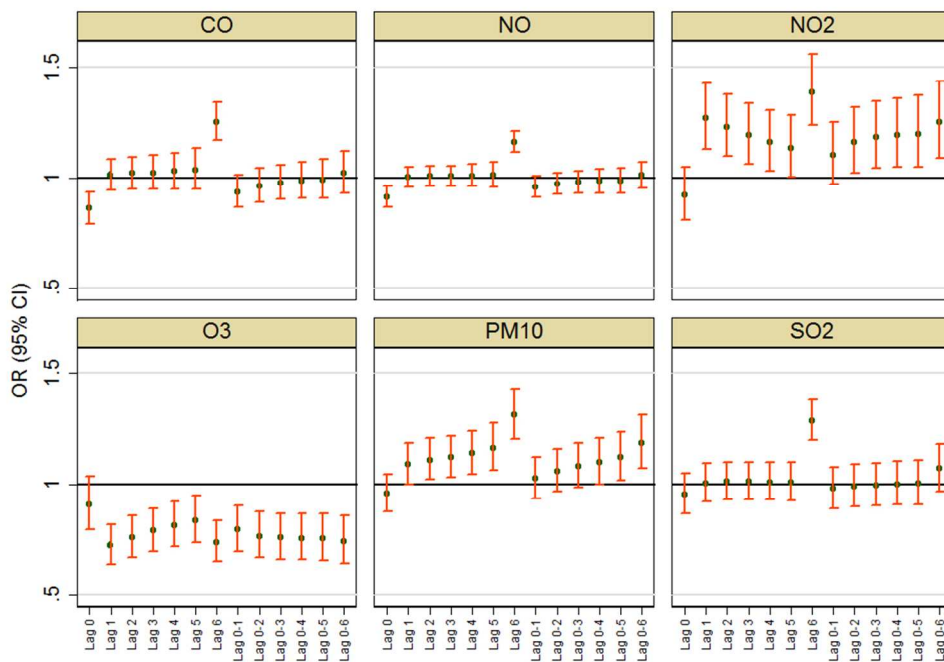
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Peer review only



352x256mm (72 x 72 DPI)

Peer Review Only

## STROBE Statement—checklist of items that should be included in reports of observational studies

	<b>Item No</b>	<b>Recommendation</b>
<b>Title and abstract</b>	1	Ambient Air Pollution and Sudden Infant Death Syndrome: a case crossover study Page 2
<b>Introduction</b>		
Background/rationale	2	Page 4
Objectives	3	Page 4
<b>Methods</b>		
Study design	4	Page 5
Setting	5	Page 5
Participants	6	Page 5
Variables	7	Page 6
Data sources/ measurement	8*	Page 5-7
Bias	9	Page 5-7
Study size	10	Page 5
Quantitative variables	11	Page 7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding Page 5-7 (b) Describe any methods used to examine subgroups and interactions Page 7 (c) Explain how missing data were addressed Page 5 (e) Describe any sensitivity analyses Page 8

Continued on next page

**Results**

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Page 9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Page 9
Outcome data	15*	Page 10-11
Main results	16	Page 10-11
Other analyses	17	Page 12-13
<b>Discussion</b>		
Key results	18	Page 14
Limitations	19	Page 14
Interpretation	20	Page 15
Generalisability	21	Page 16
<b>Other information</b>		
Funding	22	The Lullaby Trust

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

## Is Ambient Air Pollution associated with onset of Sudden Infant Death Syndrome: A case crossover study in the UK

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-018341.R1
Article Type:	Research
Date Submitted by the Author:	20-Dec-2017
Complete List of Authors:	Litchfield, Ian; University of Birmingham, Institute of Applied Health Research Ayres, Jon; University of Birmingham, Institute of Applied Health Research Jaakkola, Jouni; University of Oulu, Center for Environmental and Respiratory Health Research Mohammed, Nuredin; University of Birmingham, Institute of Applied Health Research
<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Occupational and environmental medicine, Paediatrics, Public health, Respiratory medicine
Keywords:	EPIDEMIOLGY, Community child health < PAEDIATRICS, Cot death < PAEDIATRICS, Paediatric thoracic medicine < PAEDIATRICS, PUBLIC HEALTH

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# Is Ambient Air Pollution associated with onset of Sudden Infant Death Syndrome: A case crossover study in the UK

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5 Word count: 3024

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## ABSTRACT

**Objectives:** Air pollution has been associated with increased mortality and morbidity in several studies with indications its effect could be more severe in children. This study examined the relationship between short-term variations in criteria air pollutants and occurrence of sudden infant death syndrome (SIDS).

**Design:** We used a case-crossover study design which is widely applied in air pollution studies and particularly useful for estimating the risk of a rare acute outcome associated with short-term exposure.

**Setting:** The study used data from the West Midlands region in the UK.

**Participants:** We obtained daily time series data on SIDS mortality (ICD-9: 798.0 or ICD-10: R95) for the period 1996-2006 with a total of 211 SIDS events.

**Primary outcome measures:** Daily counts of SIDS events.

**Results:** For an interquartile range increase in previous day pollutant concentration, the percentage increases (95% confidence interval) in SIDS were 16 (6, 27) for PM<sub>10</sub>, 1 (-7, 10) for SO<sub>2</sub>, 5 (-4, 14) for CO, -17 (-27, -6) for O<sub>3</sub>, 16 (2, 31) for NO<sub>2</sub>, and 2 (-3, 8) for NO after controlling for average temperature and national holidays. PM<sub>10</sub> and NO<sub>2</sub> showed relatively consistent association which persisted across different lag structures and after adjusting for co-pollutants.

**Conclusions:** The results indicated ambient air pollutants, particularly PM<sub>10</sub> and NO<sub>2</sub>, were associated with increased SIDS mortality. Thus, future studies are recommended to understand possible mechanistic explanations on the role of air pollution on SIDS incidence and the ways in which we might reduce pollution exposure among infants.

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3 **Clinical trial registration:** Not applicable.  
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7 **Keywords:** Air pollution; Child health; Time-series; Infant mortality.  
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## 11 **Article Summary**

### 12 **Strengths and limitations of this study**

- 13 • Sudden infant death is the leading cause of death in healthy infants between one  
14 month and one year olds and our study is the first based on time series data from the  
15 UK to investigate the relationship between common air pollutants and SIDS.  
16
- 17 • Based on a case-crossover design, we found associations with onset of SIDS and  
18 concentration of PM<sub>10</sub> and NO<sub>2</sub> that lasted days after the initial exposure.  
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- 20 • Though our study is limited in power due to the comparatively small number of daily  
21 SIDS events our chosen design is widely applied in air pollution studies and  
22 particularly useful for estimating the risk of a rare acute outcome associated with  
23 short-term exposure.  
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## 46 **INTRODUCTION**

47 The quality of ambient air is an important factor in the health of adults and children.  
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49 Ambient air quality is the second largest challenge facing public health in the UK.[1] According  
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3 to the World Health Organisation (WHO), over 3.7 million premature deaths per annum may be  
4 attributed to the harmful effects of ambient air. Children it would seem are more vulnerable than  
5 any other group[2] and recent studies have indicated how even low-levels of traffic-related air  
6 pollution can have a negative impact on birth outcomes and perinatal health.[3, 4] A number of  
7 studies have also suggested a link between ambient air quality and the incidence of sudden infant  
8 death syndrome (SIDS).[5-12] and here we examine the effects of the short term variations in air  
9 pollution and the onset of SIDS.  
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21 Sudden infant death is the leading cause of death in healthy infants between one month and  
22 one year old,[13] and the impact on the families is notably traumatic as the death is without  
23 warning or witness.[14] The exact cause continues to tax researchers [15] though is likely the  
24 result of a combination of factors including susceptibility and environmental stressors such as  
25 lower social status of parents,[16] environmental tobacco smoke,[16, 17] the prone position[18]  
26 and the winter season.[5, 18] The impact of tobacco smoke suggests a respiratory trigger may be  
27 involved, however the evidence of an association between SIDS and air pollution warrant further  
28 research as findings from epidemiological studies have been inconsistent.[19, 20] and few have  
29 satisfactorily explored the impact of short-term exposure on SIDs. Our study is the first based on  
30 time series data from the UK to investigate the relationship between common air pollutants and  
31 SIDS. We have collated data from a ten-year period on concentrations of air pollution and onset  
32 of SIDS within the West Midlands one of the largest and most polluted conurbations in the UK  
33 and have conducted a case-crossover study to determine any associations.  
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## METHODS

### Settings

The West Midlands is a metropolitan county in the centre of the UK. It has a population of some 2.8 million. [21] The West Midlands is one of the most heavily urbanized counties in the UK and forms the most populated conurbation in the UK outside London, It is at the heart of the UK motorway network and remains a significant centre of the UK's manufacturing industry.

### Data collection

We combined data on SIDS events with data on total births, air pollution, air temperature and a measure of deprivation.

#### Data on SIDS mortality and total births

We obtained daily time series data on SIDS mortality (ICD-9: 798.0 or ICD-10: R95) for the period 1996-2006 from the Perinatal Institute (PI). All cases were between 0 and 12 months old at onset. This data consisted of the date of death and the first three digits of the postcode to avoid the possibility of identifying individual cases due to the rare nature of SIDS. This allowed us to explore the effects of short-term exposure. We obtained daily births data with West Midlands' postcodes from the Office of National Statistics (ONS) for the period 1996-2006 and was used for descriptive analysis only.

### Air pollution data

The daily time series data on air pollution were compiled from the UK air quality archive managed by Department for the Environment, Food and Rural Affairs (DEFRA). These include a total of ten monitoring stations in the West Midlands measuring PM<sub>10</sub>, SO<sub>2</sub>, NO<sub>2</sub>, NO, NO<sub>x</sub>, CO and O<sub>3</sub> including sites within Birmingham, Coventry, Walsall and Wolverhampton. Before 1996 the reliability of air quality data was inconsistent. Not all monitoring stations had measurements for the range of pollutants over the entire study period and the precise pollutants measured at each monitoring centre are described in Table 1.

*Table 1: Pollutants measured and corresponding time period by monitoring stations*

Name (postcode area)	Pollutants	Time period <sup>a</sup>
Birmingham Centre (B)	PM <sub>10</sub> , SO <sub>2</sub> , NO <sub>2</sub> ,NO, NO <sub>x</sub> , CO, O <sub>3</sub>	01/01/1996-31/12/2006
Birmingham East (B)	PM <sub>10</sub> , SO <sub>2</sub> , NO <sub>2</sub> ,NO, CO, O <sub>3</sub>	01/01/1996-03/08/2004
Birmingham Tyburn (B)	PM <sub>10</sub> , SO <sub>2</sub> , NO <sub>2</sub> ,NO, CO, O <sub>3</sub>	16/08/2004-31/12/2006
Oldbury (B)	PM <sub>10</sub> , SO <sub>2</sub> , NO <sub>2</sub> ,NO, NO <sub>x</sub> , CO, O <sub>3</sub>	27/06/1997-20/09/1998
West Bromwich (B)	PM <sub>10</sub> , SO <sub>2</sub> , NO <sub>2</sub> ,NO, NO <sub>x</sub> , CO, O <sub>3</sub>	04/11/1998-31/12/2006
Coventry Centre (CV)	PM <sub>10</sub> , SO <sub>2</sub> , NO <sub>2</sub> ,NO, NO <sub>x</sub> , CO, O <sub>3</sub>	19/02/1997-31/12/2006
Coventry Memorial (CV)	PM <sub>10</sub> , SO <sub>2</sub> , NO <sub>2</sub> ,NO, NO <sub>x</sub> , CO, O <sub>3</sub>	26/02/2001-31/12/2006
Walsall Alumwell (WS)	NO <sub>2</sub> , NO <sub>x</sub>	01/01/1996-31/12/2006
Walsall Willenhall (WS)	NO <sub>2</sub>	13/05/1997-31/12/2006
Wolverhampton Centre (WV)	PM <sub>10</sub> , SO <sub>2</sub> , NO <sub>2</sub> ,NO, NO <sub>x</sub> , CO, O <sub>3</sub>	19/12/1995-31/12/2006

<sup>a</sup>Period with at least one pollutant being measured and taking into account missing data between start and end dates.

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3 We aimed to examine the association between day-to-day variability in air pollution  
4 exposure and SIDS counts over the entire region rather than contrasting exposure and outcome  
5 between areas within the West Midlands region. Therefore the daily pollution data for West  
6 Midlands were calculated by averaging across all monitoring stations with available  
7 measurements as our models were based on the temporal relationship between air pollution and  
8 SIDS; we did not fit a spatial model.  
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#### 19 Temperature data

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21 Data on daily minimum and maximum temperature were compiled for weather monitoring  
22 stations in the West Midlands from the Meteorological Office British Atmospheric Data Centre  
23 (BADC).[22] We used the average daily temperature which was calculated by taking the average  
24 of the minimum and maximum temperature at each monitoring station for each day to obtain the  
25 daily average temperature for the entire West Midlands.  
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#### 35 Index of multiple deprivation (IMD) score

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37 The IMD score is a composite measure based on seven dimensions of deprivation  
38 including income deprivation, employment deprivation, health deprivation and disability,  
39 education deprivation, crime deprivation, barriers to housing and services deprivation and living  
40 environment deprivation. The data for the 2010 IMD at postcode level were downloaded from  
41 EDINA Digimap ShareGeo facility, an online spatial data repository and was used for  
42 descriptive analysis only.[23]  
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## Statistical analysis

The case-crossover design was used to investigate the association between short-term exposure to air pollution and the occurrence of SIDS events controlling for average daily temperature and national holidays. This design, introduced by Maclure,[20] has been widely applied in air pollution studies and is particularly useful for estimating the risk of a rare acute outcome associated with short-term exposure.[24-27] In case-crossover design each case acts as their own control and like case-control studies[28] the distribution of exposure is compared between ‘cases’ and ‘controls’. That is, exposure at the time just prior to the event (‘case’ or ‘index’ time) is compared with a set of ‘control’ times that represent the expected distribution of exposure for non-event follow-up times. The design helps primarily to control for confounding by subject-specific factors which remain static over time such as ethnicity and gender.

We applied the time stratified case-crossover approach where the strata are matching days based on the same day of the week, calendar month and year that has previously been used to minimise bias. [29] That is, control days were selected from the same day of the week, within the same calendar month and year as the event day. We applied a conditional Poisson regression model which has been shown to give equivalent estimates as the conditional logistic model but with the advantage of readily allowing for overdispersion and autocorrelation.[30] All our models assume a linear effect for air pollution as reported in previous studies[31 -33] while temperature effects are likely to be non-linear and were modelled using natural splines with 3 degrees of freedom.[34-36]



## Sensitivity analyses

The primary aim was to investigate the risk of SIDS events in relation to air pollution on the previous day in single pollutant models. To examine sensitivities to our *a priori* model specification, additional lag structures were explored including single lags of 0,1,2,...,6 days and also the corresponding average of lags 0-1, 0-2, 0-3,..., 0-6. Moreover, the association between SIDS and air pollution was examined after adjusting for the effect of each of the pollutants PM<sub>10</sub>, SO<sub>2</sub>, NO<sub>2</sub>, NO, CO and O<sub>3</sub> as a second pollutant in turn. The aim of this two-pollutant modelling approach was to account for potential confounding effect of co-pollutants. Further sensitivity analyses were performed by controlling for minimum temperature instead of the average temperature. We excluded NO<sub>x</sub> from the sensitivity analyses as it showed very strong correlation particularly with NO ( $r=0.96$ ).

Results are presented as percentage increases in mortality with 95% confidence intervals (CIs) for an interquartile range (IQR) increase in pollutant concentration. Hypothesis tests were two-sided with a significance level of 0.05. All analyses were performed using the R statistical software; details of the packages used and sample line of code for fitting specific conditional Poisson regression model is given in the supplementary material.[37]

## RESULTS

### Descriptive statistics

Over the study period (1996–2006), there were 211 SIDS events across the four postcode areas (B, CV, WS and WV) included in the analyses which accounted for about approximately

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5% of the days within the study period (Table 2). In the same period and location, a total of 943,937 live (single) births were registered.

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Table 2: Average air pollution ( $\mu\text{gm}^{-3}$ ), temperature ( $^{\circ}\text{C}$ ) and IMD scores for selected West Midlands postcode areas with SIDS and birth counts, 1996-2006

Post town (area)	PM <sub>10</sub>	SO <sub>2</sub>	CO	O <sub>3</sub>	NO <sub>2</sub>	NO	NO <sub>x</sub>	Temp. (Min-Max)	IMD score	SIDS event (%)	Birth count (%)
Birmingham (B)	23.8	6.8	0.4	38.5	33.9	17.5	60	7.2-12.8	36.6	118 (55.9)	753844 (79.9)
Coventry (CV)	18.3	11.3	0.3	32.4	22.5	9.2	36.2	7.7-13.5	23.7	43 (20.4)	91393 (9.7)
Walsall (WS)					41.5		89.4	6.4-14.0	25.2	24 (11.4)	53532 (5.7)
Wolverhampton (WV)	23.8	9.3	0.5	38.9	29.5	18.9	59.5	8.4-12.3	33.4	26 (12.3)	45168 (4.8)
Total										211 (100)	943937 (100)

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The daily average air pollution concentrations and their standard deviations are presented in Table 3 and show that average concentrations tended to be below UK air quality limits as defined by the EU Ambient Air Quality Directive.[38]

Table 3: Descriptive statistics for daily SIDS mortality counts, air pollution ( $\mu\text{g}\text{m}^{-3}$ ), temperature ( $^{\circ}\text{C}$ ) and birth counts for West Midlands, 1996-2006

Variable	Mean	SD	Median	IQR	Min	Max
SIDS count	<1	<1	0	0-0	0	2
Average temperature	10.2	5.4	10.2	6.2-14.5	-4.2	25.0
Max temperature	13.1	6.0	12.9	8.5-17.6	-2.1	29.6
Min temperature	7.4	5.1	7.5	3.6-11.4	-7.5	20.7
PM <sub>10</sub>	23.4	11.6	20.2	15.7-28.2	4.0	128.9
SO <sub>2</sub>	8.5	6.9	7.2	4.4-10.2	0.0	70.8
CO	0.4	0.2	0.4	0.3-0.5	0.1	3.5
O <sub>3</sub>	38.1	18.2	38.0	25.4-50.4	1.3	115.8
NO <sub>2</sub>	33.2	14.3	31.2	22.3-41.8	5.9	113.0
NO	16.9	23.8	9.0	5.4-17.9	0.4	314.9
NO <sub>x</sub>	64.5	49.3	51.1	35.2-76.4	7.9	569.2
Birth count <sup>a</sup>	290	34	296	266 - 314	183	387
IMD score	32.3	12.6	31.7	21.3-40.5	7.2	54.9

<sup>a</sup> Counts are for single births only

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3 Table 4 shows that there was generally a strong correlation between the levels of pollutants  
4 investigated with the exception of the weaker correlation between O<sub>3</sub> and PM<sub>10</sub> (r=-0.26) and  
5 with SO<sub>2</sub> (r=-0.34). What was also notable was the negative correlation between Ozone and the  
6 other pollutants and how in contrast to the other pollutants its positive correlation with  
7 temperature.  
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3 *Table 4: Pairwise Pearson correlations coefficients (r) for pollutants and*  
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5 *temperature*  
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	PM <sub>10</sub>	SO <sub>2</sub>	CO	O <sub>3</sub>	NO <sub>2</sub>	NO	NO <sub>x</sub>
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10	SO <sub>2</sub>	0.53					
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12	CO	0.56	0.59				
13							
14	O <sub>3</sub>	-0.26	-0.34	-0.56			
15							
16	NO <sub>2</sub>	0.66	0.56	0.76	-0.62		
17							
18	NO	0.54	0.48	0.87	-0.58	0.73	
19							
20	NO <sub>x</sub>	0.59	0.56	0.90	-0.62	0.86	0.96
21							
22	Temperature	-0.08	-0.24	-0.39	0.40	-0.40	-0.38
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3 Comparing the four postcode areas, Birmingham had the highest SIDS mortality (about  
4 56%) and births rates (about 80%). Air pollution concentrations were more or less similar for  
5 Birmingham and Wolverhampton except slightly lower levels of NO<sub>2</sub> and higher levels of SO<sub>2</sub>  
6 observed for the latter. Coventry had the lowest pollution level with respect to all pollutants  
7 except SO<sub>2</sub>. Walsall had measurements for NO<sub>2</sub> and NO<sub>x</sub> only which were very large compared  
8 to the other postcode areas (Table 2). Similarly, Birmingham and Wolverhampton had higher  
9 average deprivation scores compared to Coventry and Walsall (Table 2). Also, SIDS counts and  
10 pollution levels tended to be larger in highly deprived areas and near motorways and A-road  
11 networks which may be a reflection of population density (Figure 1; see Supplementary File:  
12 Figure S1). There was also indication of seasonal pattern for SIDS occurrence; the highest  
13 proportions of SIDS were observed in January and February (about 10%) and among the  
14 relatively colder months and in July (about 14%) among the warmer months (data not shown).  
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### 33 **Case-crossover analysis**

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35 Figure 2 shows the estimated odds ratio (OR) (95% CI) for the association of SIDS events  
36 with each of the pollutants considered based on the conditional Poisson model. For an  
37 interquartile range increase in previous day pollutant concentration, the percentage increase  
38 (95% confidence interval) for the risk of SIDS death was 16 (6, 27);  $p = 0.002$  for PM<sub>10</sub>, 1 (-7,  
39 10);  $p = 0.83$  for SO<sub>2</sub>, 5 (-4, 14);  $p = 0.33$  for CO, -17 (-27, -6) ;  $p = 0.004$  for O<sub>3</sub>, 16 (2, 31);  $p =$   
40 0.02 for NO<sub>2</sub>, 2 (-3, 8);  $p = 0.47$  for NO and 8 (-1, 18);  $p = 0.07$  for NO<sub>x</sub> after controlling for  
41 average temperature and national holidays. Therefore, considering pollutant levels at lag 1,  
42 significant association with increased risk of SIDS was indicated only for PM<sub>10</sub> and NO<sub>2</sub> while a  
43 protective effect was apparent for O<sub>3</sub>.  
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## Sensitivity analyses

Lag structures: Analyses exploring relationships between SIDS and air pollution for other lag structures (lags 0, 2, 3, ..., 6 and corresponding average of lags 0-1, 0-2, 0-3, ..., 0-6) indicated associations were somewhat sensitive to the choice of lag (Figure 3). In the single lag models, there was an impression of stronger delayed effects for CO, NO<sub>2</sub>, O<sub>3</sub>, PM<sub>10</sub> and SO<sub>2</sub> compared to relatively recent lags (lag 0 and lag 1). The effect of NO appeared to remain comparatively flat across lags. Relatively more consistent association across lags was observed for NO<sub>2</sub> and PM<sub>10</sub> and to some extent for CO. Likewise, in average lag models, ORs tended to increase with averaging over more lags with exception of NO where such an effect was not observed. Results were also similar (at least qualitatively) after adjusting for minimum temperature instead of the average temperature (see Supplementary File: Figure S2).

Multi-pollutant models: Further investigation using two-pollutant models also showed associations were sensitive to control of other pollutants. In general, adjusting for co-pollutants appeared to attenuate ORs towards the null except for NO<sub>2</sub> and PM<sub>10</sub> where effects remained to persist (Figure 4). Interestingly, after controlling for PM<sub>10</sub>, the protective effect of O<sub>3</sub> and the adverse effect of NO<sub>2</sub> observed in the single pollutant models were not apparent for most of the lag choices. Similarly, none of the other pollutants showed marked association with SIDS after controlling for PM<sub>10</sub> effects. The estimates from the multi-pollutant model should, however, be interpreted with caution as most of the pollutants were correlated.

## COMMENTS

### Summary of findings

In this study we hypothesised a delayed effect (lag 1) of air pollution on SIDS incidence and investigated additional lags in sensitivity analyses and in single and multi-pollutant models. Though confidence intervals were wide, we found evidence suggesting association of SIDS mortality with PM<sub>10</sub> and NO<sub>2</sub> exposure. Compared to other pollutants, their effects persisted after controlling for co-pollutants and across the various lag structures investigated. The exception was controlling for O<sub>3</sub> did attenuate the risk estimates observed for both PM<sub>10</sub> and NO<sub>2</sub>. There were no consistent associations observed with exposure to the remaining pollutants investigated (CO, SO<sub>2</sub>, NO, NO<sub>x</sub>). An exception was the protective effect observed in relation to O<sub>3</sub> exposure.

### Strengths and limitations

Previous studies have tended to focus on relatively longer-term exposure to air pollutants.[39-41] Our study is one of the first to use case-crossover methodology to explore the impact of air pollution on SIDS based on data from UK. Using an approach that is suitable for estimating the risk of a rare acute outcome such as SIDS events, we were able to investigate various lags and multi-pollutant models indicating delayed effects of pollutants that persisted after controlling for co-pollutants. However, measurement error for air pollution exposure a potential limitation in this study as we did not use personal measurements. Other epidemiological studies using data from ambient monitoring stations have shown a good level of correlation between daily personal exposure and daily ambient air pollution measurements,[36, 37] though

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3 there is the potential for measurement error that can attenuate regression coefficient estimates.  
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5 That is, such misclassification will likely lead to an under estimation of the effects. We were also  
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7 unable to control for influenza and humidity as we did not have access to reliable data for these  
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9 variables.  
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### 11 12 13 14 15 **Detailed discussion**

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17 Certain groups of the population are more vulnerable to ambient air pollution than others  
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19 and children figure predominantly amongst them due to the fragility of their immune system and  
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21 the ratio of their lung capacity to their size. [42] Particulate matter has been recognised as the  
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23 most significant contributor to air quality related morbidity and mortality [43] and a number of  
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25 studies have reported a link between infant mortality and PM<sub>10</sub> at similar concentrations of  
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27 pollutant below air quality guidelines as are described in this study.[44-46, 11] However  
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29 previous evidence of a direct association with SIDS is inconclusive and few studies describe a  
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31 significant association of PM<sub>10</sub> with increased risk. [6, 47]  
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36 The potential association with NO<sub>2</sub> we found reflected the findings of a multi-city study  
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38 from Canada that found an increased risk for SIDS with a lag of two-days.[8] The issue of lag is  
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40 interesting we found the strongest association with SIDS with PM<sub>10</sub> and NO<sub>2</sub> occurred over  
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42 several lags in line with previous studies that have found evidence of a lag between exposure to  
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44 criteria pollutants and mortality. For PM<sub>10</sub>, a single days exposure has been shown to have an  
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46 effect for up to 5 days [48, 49] and numbers of respiratory deaths appear to be more affected by  
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48 air pollution levels on previous days, than cardiovascular deaths that are impacted by same-day  
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50 pollution.[50] For example myocardial infarction represents an acute response to a trigger.[51]  
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3 This is biologically plausible when considering how a wider and more lagged response can  
4 be expected for deaths from respiratory responses to pollution (eg, COPD) via the proposed  
5 mechanisms, such as pulmonary or systemic inflammation and modulated immunity.[52]

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8 With regards the apparent protective properties of O<sub>3</sub> that we describe here it's worth noting that  
9 these have been seen previously.[40] One possible reason for the negative association of O<sub>3</sub> and  
10 SIDS might be its negative correlation with other pollutants, in particular that with fine  
11 particulate matter pollution.[53] O<sub>3</sub> also showed a positive correlation with temperature while all  
12 other pollutants were negatively correlated.  
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24 Concern around the effects of air pollution continue to mount particularly within developing  
25 economies [54] where it contributes to 3.3 million premature deaths worldwide per year a figure  
26 estimated to double by 2050 if the issue remains unattended.[55] However it appears that  
27 recently fossil fuel emissions have begun to increase again due to the developing world's  
28 reliance on them to power their expanding economies.[56] In the developed West, policy  
29 initiatives are beginning to recognise the mounting issue posed by the adverse effects on health  
30 posed by ambient air pollution. However shifting political priorities in the United States has seen  
31 a commitment to revitalise the coal industry [57] and an increase in the production of shale oil  
32 [58] However mitigating these risks is not a straightforward proposition and government policies  
33 appear slow to react, for example in the UK pledges to cease sales of diesel and petrol cars do  
34 not come into effect until 2040.[59]  
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49 In the absence of coherent policy to address the issue a number of proposals have been put  
50 forward to mitigate the effects of high levels of ambient exposure. Knowing that children and  
51 young adults may be highly susceptible to some of the subclinical changes caused by air  
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3 pollution [60,61] and as indoor concentrations are lower than ambient levels advice has been to  
4 remain indoors to reduce exposure and acute health risks on high air pollution days.[62] There  
5 are also systems available for cleaning indoor air though these may be deemed expensive for the  
6 economically deprived.[63] There has also been a case made for chemo-preventive interventions,  
7 such as antioxidant or antithrombotic agents, but without data on health outcomes, no  
8 recommendations can be made in their use for primary prevention. [64]  
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## 19 **Conclusions**

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21 Understanding the effects of air pollution on child health is more relevant than ever. Our work  
22 here has highlighted a potential association of Sudden Infant Death with PM<sub>10</sub> and NO<sub>2</sub> and the  
23 association with particulate matter and infant mortality in particular is widely recognised.  
24 However, until policy reflects the growing evidence and responds to mounting public concern, it  
25 would appear to be the responsibility of individuals to take independent action to mitigate the  
26 effects of air pollution and protect the health of their young ones.  
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## ACKNOWLEDGMENTS

**Funding:** This work was supported by The Lullaby Trust, grant number 260.

**Competing interests:** All authors declare: grants from The Lullaby Trust; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years and no other relationships or activities that could appear to have influenced the submitted work.

**Author contributions statement:** IJL contributed to the conceptualisation of the study, initial draft manuscript and supervised the research project at all stages. NIM contributed to the research design, performed the data management, analysis and interpretation, and with IJL drafted the initial manuscript; JGA contributed to the conceptualisation of the study, data interpretation and critically reviewed the manuscript; JJKJ contributed to the conceptualisation of the study, data interpretation and critically reviewed the manuscript; All authors approved the final manuscript as submitted.

**Transparency:** As lead author, I can confirm that the manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects have been omitted and there are no discrepancies from the planned study.

**Ethics committee approval:** Ethical approval was given by the University of Birmingham, Life and Health Sciences Ethical Review Committee.

**Data sharing:** No additional data available.

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## 44 **FIGURE LEGENDS**

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49 **Fig. 1** Air pollution monitoring sites with road networks (motorways and A-roads) and SIDS events in the  
50 study area. We used ArcGIS Desktop 10.2 (<http://www.esri.com/software/arcgis>) to create the map  
51 combining shapefiles for postcode areas and motorways and overlaying air pollution and SIDS data.  
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3 **Fig. 2** Estimated risk of SIDS for an IQR increase in lag 1 pollutant concentration before and after  
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5 controlling for confounding by average temperature and national holidays  
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9 **Fig. 3** Risk of SIDS associated with an IQR increase in pollution for selected lags and average of lags;  
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11 models adjusted for average temperature and national holidays  
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15 **Fig. 4** Risk of SIDS associated with an IQR increase in air pollution after controlling for co-pollutants,  
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17 average temperature and national holidays(panel titles indicate: main and co-pollutant respectively)  
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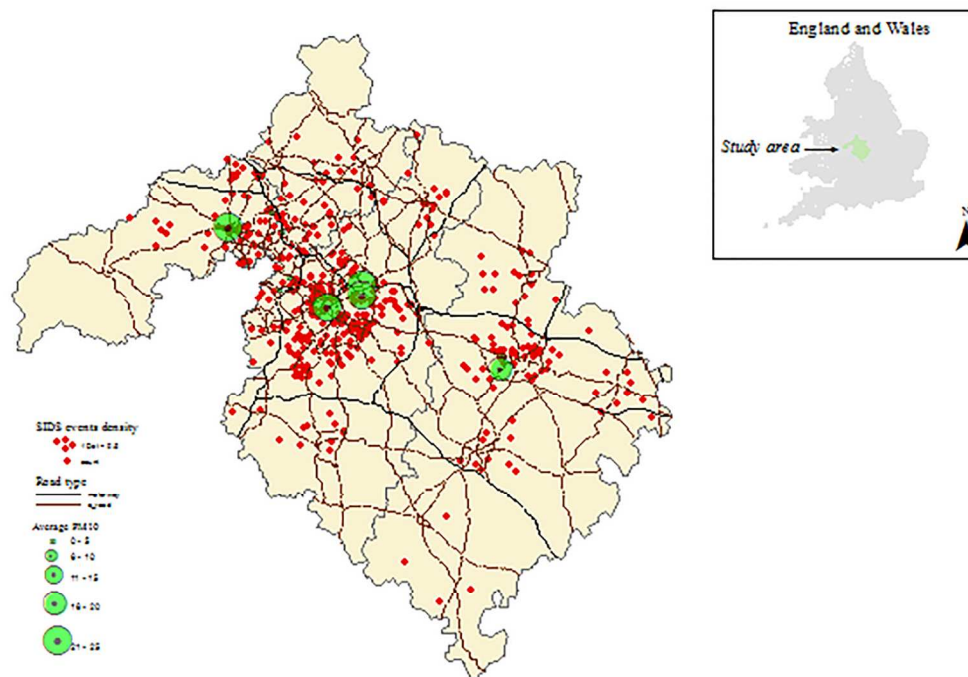


Fig. 1 Air pollution monitoring sites with road networks (motorways and A-roads) and SIDS events in the study area. We used ArcGIS Desktop 10.2 (<http://www.esri.com/software/arcgis>) to create the map combining shapefiles for postcode areas and motorways and overlaying air pollution and SIDS data.

152x105mm (300 x 300 DPI)



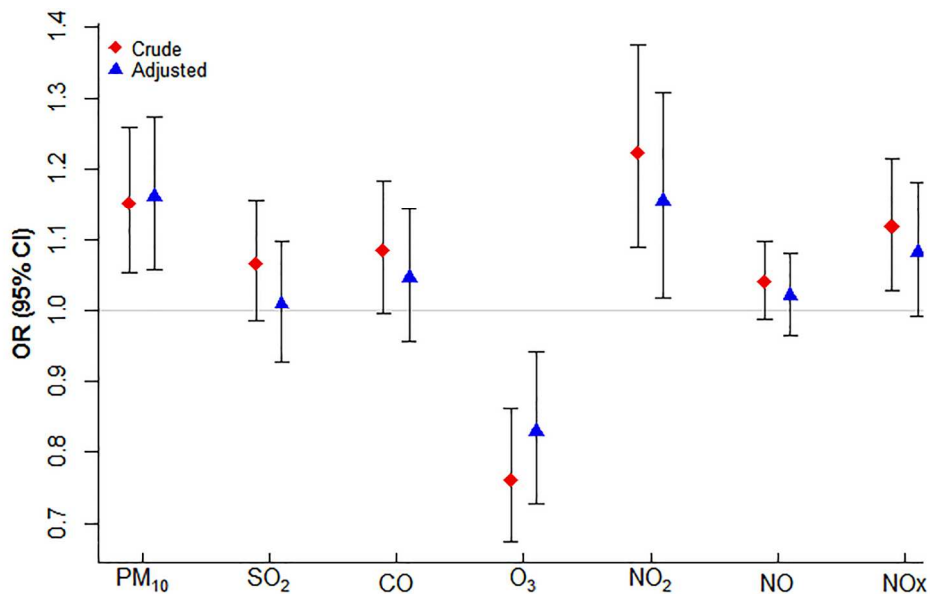


Fig. 2 Estimated risk of SIDS for an IQR increase in lag 1 pollutant concentration before and after controlling for confounding by average temperature and national holidays

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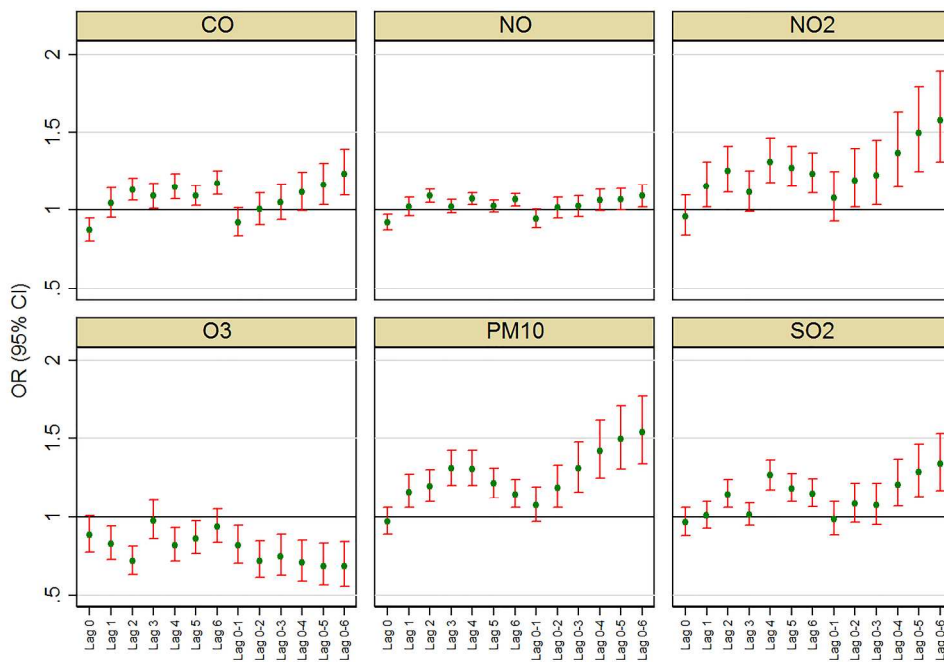


Fig. 3 Risk of SIDS associated with an IQR increase in pollution for selected lags and average of lags; models adjusted for average temperature and national holidays

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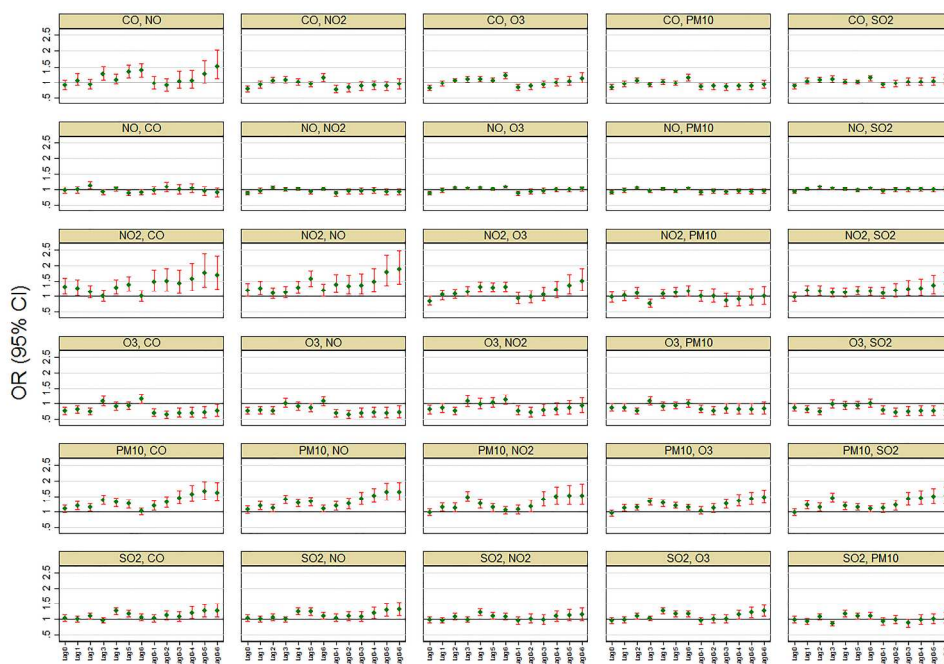
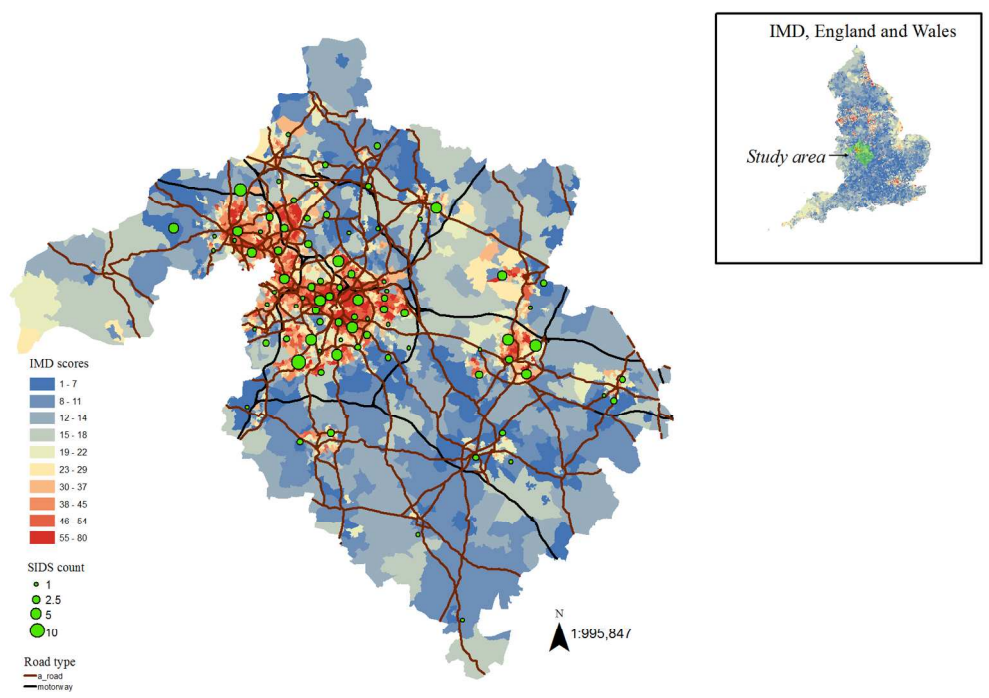


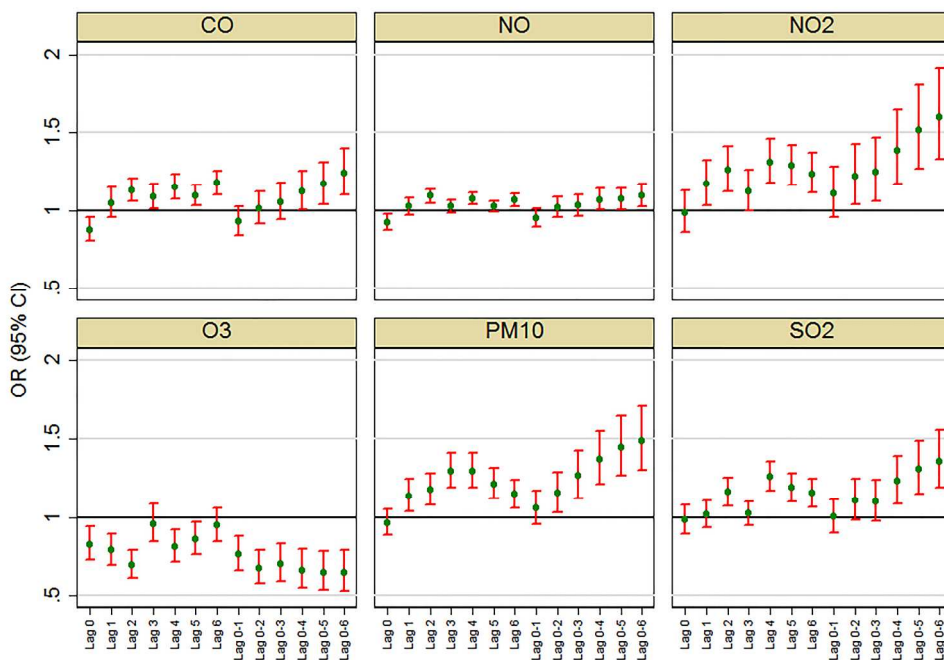
Fig. 4 Risk of SIDS associated with an IQR increase in air pollution after controlling for co-pollutants, average temperature and national holidays(panel titles indicate: main and co-pollutant respectively)

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STROBE (STrengthening the Reporting of OBServational studies in Epidemiology) Checklist for authors of CORR

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	Item No	Recommendation	Please insert check where included or N/A where not applicable
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	√
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	√
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 8
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	Page 8/9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, treatment, follow-up, and data collection	Tbc
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 6
		<i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	
		<i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of treated and untreated	Page 9
		<i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage	(page 11 –descriptive statistics)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on other treatments and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	(Table 2) n/a
Variables	7	Clearly define all outcomes, treatments, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Table 2 and 3
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 6 and Page 8
Bias	9	Describe any efforts to address potential sources of bias	Page 9
Study size	10	Explain how the study size was arrived at	Page 6 – Data on SIDS mortality
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 9
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	Page 8/9 n/a n/a Page 8/9

# BMJ Open

## Is Ambient Air Pollution associated with onset of Sudden Infant Death Syndrome: A case crossover study in the UK

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-018341.R2
Article Type:	Research
Date Submitted by the Author:	02-Feb-2018
Complete List of Authors:	Litchfield, Ian; University of Birmingham, Institute of Applied Health Research Ayes, Jon; University of Birmingham, Institute of Applied Health Research Jaakkola, Jouni; University of Oulu, Center for Environmental and Respiratory Health Research Mohammed, Nuredin; University of Birmingham, Institute of Applied Health Research
<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Occupational and environmental medicine, Paediatrics, Public health, Respiratory medicine
Keywords:	EPIDEMIOLGY, Community child health < PAEDIATRICS, Cot death < PAEDIATRICS, Paediatric thoracic medicine < PAEDIATRICS, PUBLIC HEALTH

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# Is Ambient Air Pollution associated with onset of Sudden Infant Death Syndrome: A case crossover study in the UK

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4  
5 Word count: 3024

6 Number of figures: 4

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8 Number of tables: 4  
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## ABSTRACT

**Objectives:** Air pollution has been associated with increased mortality and morbidity in several studies with indications its effect could be more severe in children. This study examined the relationship between short-term variations in criteria air pollutants and occurrence of sudden infant death syndrome (SIDS).

**Design:** We used a case-crossover study design which is widely applied in air pollution studies and particularly useful for estimating the risk of a rare acute outcome associated with short-term exposure.

**Setting:** The study used data from the West Midlands region in the UK.

**Participants:** We obtained daily time series data on SIDS mortality (ICD-9: 798.0 or ICD-10: R95) for the period 1996-2006 with a total of 211 SIDS events.

**Primary outcome measures:** Daily counts of SIDS events.

**Results:** For an interquartile range increase in previous day pollutant concentration, the percentage increases (95% confidence interval) in SIDS were 16 (6, 27) for PM<sub>10</sub>, 1 (-7, 10) for SO<sub>2</sub>, 5 (-4, 14) for CO, -17 (-27, -6) for O<sub>3</sub>, 16 (2, 31) for NO<sub>2</sub>, and 2 (-3, 8) for NO after controlling for average temperature and national holidays. PM<sub>10</sub> and NO<sub>2</sub> showed relatively consistent association which persisted across different lag structures and after adjusting for co-pollutants.

**Conclusions:** The results indicated ambient air pollutants, particularly PM<sub>10</sub> and NO<sub>2</sub>, may show an association with increased SIDS mortality. Thus, future studies are recommended to understand possible mechanistic explanations on the role of air pollution on SIDS incidence and the ways in which we might reduce pollution exposure among infants.

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3 **Clinical trial registration:** Not applicable.  
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7 **Keywords:** Air pollution; Child health; Time-series; Infant mortality.  
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## 11 **Article Summary**

### 12 **Strengths and limitations of this study**

- 13 • Sudden infant death is the leading cause of death in healthy infants between one  
14 month and one year olds and our study is the first based on time series data from the  
15 UK to investigate the relationship between common air pollutants and SIDS.  
16
- 17 • Though our study is limited in power due to the comparatively small number of daily  
18 SIDS events our chosen design is widely applied in air pollution studies and  
19 particularly useful for estimating the risk of a rare acute outcome associated with  
20 short-term exposure.  
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## 50 **INTRODUCTION**

51 The quality of ambient air is an important factor in the health of adults and children.  
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53 Ambient air quality is the second largest challenge facing public health in the UK.[1] According  
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3 to the World Health Organisation (WHO), over 3.7 million premature deaths per annum may be  
4 attributed to the harmful effects of ambient air. Children it would seem are more vulnerable than  
5 any other group[2] and recent studies have indicated how even low-levels of traffic-related air  
6 pollution can have a negative impact on birth outcomes and perinatal health.[3, 4] A number of  
7 studies have also suggested a link between ambient air quality and the incidence of sudden infant  
8 death syndrome (SIDS).[5-12] Here we examine the effects of the short term variations in air  
9 pollution and the onset of SIDS.  
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21 Sudden infant death is the leading cause of death in healthy infants between one month and  
22 one year old,[13] and the impact on the families is notably traumatic as the death is without  
23 warning or witness.[14] The exact cause continues to tax researchers [15] though is likely the  
24 result of a combination of factors including susceptibility and environmental stressors such as  
25 lower social status of parents,[16] environmental tobacco smoke,[16, 17] the prone position[18]  
26 and the winter season.[5, 18] The impact of tobacco smoke suggests a respiratory trigger may be  
27 involved, however the evidence of an association between SIDS and air pollution warrant further  
28 research as findings from epidemiological studies have been inconsistent.[19, 20] and few have  
29 satisfactorily explored the impact of short-term exposure on SIDS. Our study is the first based on  
30 time series data from the UK to investigate the relationship between common air pollutants and  
31 SIDS. We have collated data from a ten-year period on concentrations of air pollution and onset  
32 of SIDS within the West Midlands one of the largest and most polluted conurbations in the UK  
33 and have conducted a case-crossover study to determine any associations.  
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## METHODS

### Settings

The West Midlands is a metropolitan county in the centre of the UK. It has a population of some 2.8 million. [21] The West Midlands is one of the most heavily urbanized counties in the UK and forms the most populated conurbation in the UK outside London, It is at the heart of the UK motorway network and remains a significant centre of the UK's manufacturing industry.

### Data collection

We combined data on SIDS events with data on total births, air pollution, air temperature and a measure of deprivation.

#### Data on SIDS mortality and total births

We obtained daily time series data on SIDS mortality (ICD-9: 798.0 or ICD-10: R95) for the period 1996-2006 from the Perinatal Institute (PI). All cases were between 0 and 12 months old at onset. This data consisted of the date of death and the first three digits of the postcode to avoid the possibility of identifying individual cases due to the rare nature of SIDS. This allowed us to explore the effects of short-term exposure. We obtained daily births data with West Midlands' postcodes from the Office of National Statistics (ONS) for the period 1996-2006 and was used for descriptive analysis only.

## Air pollution data

The daily time series data on air pollution were compiled from the UK air quality archive managed by Department for the Environment, Food and Rural Affairs (DEFRA). These include a total of ten monitoring stations in the West Midlands measuring PM<sub>10</sub>, SO<sub>2</sub>, NO<sub>2</sub>, NO, NO<sub>x</sub>, CO and O<sub>3</sub> including sites within Birmingham, Coventry, Walsall and Wolverhampton. Before 1996 the reliability of air quality data was inconsistent. Not all monitoring stations had measurements for the range of pollutants over the entire study period and the precise pollutants measured at each monitoring centre are described in Table 1.

*Table 1: Pollutants measured and corresponding time period by monitoring stations*

Name (postcode area)	Pollutants	Time period <sup>a</sup>
Birmingham Centre (B)	PM <sub>10</sub> , SO <sub>2</sub> , NO <sub>2</sub> ,NO, NO <sub>x</sub> , CO, O <sub>3</sub>	01/01/1996-31/12/2006
Birmingham East (B)	PM <sub>10</sub> , SO <sub>2</sub> , NO <sub>2</sub> ,NO, CO, O <sub>3</sub>	01/01/1996-03/08/2004
Birmingham Tyburn (B)	PM <sub>10</sub> , SO <sub>2</sub> , NO <sub>2</sub> ,NO, CO, O <sub>3</sub>	16/08/2004-31/12/2006
Oldbury (B)	PM <sub>10</sub> , SO <sub>2</sub> , NO <sub>2</sub> ,NO, NO <sub>x</sub> , CO, O <sub>3</sub>	27/06/1997-20/09/1998
West Bromwich (B)	PM <sub>10</sub> , SO <sub>2</sub> , NO <sub>2</sub> ,NO, NO <sub>x</sub> , CO, O <sub>3</sub>	04/11/1998-31/12/2006
Coventry Centre (CV)	PM <sub>10</sub> , SO <sub>2</sub> , NO <sub>2</sub> ,NO, NO <sub>x</sub> , CO, O <sub>3</sub>	19/02/1997-31/12/2006
Coventry Memorial (CV)	PM <sub>10</sub> , SO <sub>2</sub> , NO <sub>2</sub> ,NO, NO <sub>x</sub> , CO, O <sub>3</sub>	26/02/2001-31/12/2006
Walsall Alumwell (WS)	NO <sub>2</sub> , NO <sub>x</sub>	01/01/1996-31/12/2006
Walsall Willenhall (WS)	NO <sub>2</sub>	13/05/1997-31/12/2006
Wolverhampton Centre (WV)	PM <sub>10</sub> , SO <sub>2</sub> , NO <sub>2</sub> ,NO, NO <sub>x</sub> , CO, O <sub>3</sub>	19/12/1995-31/12/2006

<sup>a</sup>Period with at least one pollutant being measured and taking into account missing data between start and end dates.

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3 We aimed to examine the association between day-to-day variability in air pollution  
4 exposure and SIDS counts over the entire region rather than contrasting exposure and outcome  
5 between areas within the West Midlands region. Therefore the daily pollution data for West  
6 Midlands were calculated by averaging across all monitoring stations with available  
7 measurements as our models were based on the temporal relationship between air pollution and  
8 SIDS; we did not fit a spatial model.  
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#### 19 Temperature data

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21 Data on daily minimum and maximum temperature were compiled for weather monitoring  
22 stations in the West Midlands from the Meteorological Office British Atmospheric Data Centre  
23 (BADC).[22] We used the average daily temperature which was calculated by taking the average  
24 of the minimum and maximum temperature at each monitoring station for each day to obtain the  
25 daily average temperature for the entire West Midlands.  
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#### 35 Index of multiple deprivation (IMD) score

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37 The IMD score is a composite measure based on seven dimensions of deprivation  
38 including income deprivation, employment deprivation, health deprivation and disability,  
39 education deprivation, crime deprivation, barriers to housing and services deprivation and living  
40 environment deprivation. The data for the 2010 IMD at postcode level were downloaded from  
41 EDINA Digimap ShareGeo facility, an online spatial data repository and was used for  
42 descriptive analysis only.[23]  
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## Statistical analysis

The case-crossover design was used to investigate the association between short-term exposure to air pollution and the occurrence of SIDS events controlling for average daily temperature and national holidays. This design, introduced by Maclure,[20] has been widely applied in air pollution studies and is particularly useful for estimating the risk of a rare acute outcome associated with short-term exposure.[24-27] In case-crossover design each case acts as their own control and like case-control studies[28] the distribution of exposure is compared between ‘cases’ and ‘controls’. That is, exposure at the time just prior to the event (‘case’ or ‘index’ time) is compared with a set of ‘control’ times that represent the expected distribution of exposure for non-event follow-up times. The design helps primarily to control for confounding by subject-specific factors which remain static over time such as ethnicity and gender.

We applied the time stratified case-crossover approach which has previously been used to minimise bias. [29] That is, control days were selected from the same day of the week, within the same calendar month and year as the event day. We applied a conditional Poisson regression model which has been shown to give equivalent estimates as the conditional logistic model but with the advantage of readily allowing for overdispersion and autocorrelation.[30] All our models assume a linear effect for air pollution as reported in previous studies[31 -33] while temperature effects are likely to be non-linear and were modelled using natural splines with 3 degrees of freedom.[34-36]

## Sensitivity analyses

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3 The primary aim was to investigate the risk of SIDS events in relation to air pollution on  
4 the previous day in single pollutant models. To examine sensitivities to our *a priori* model  
5 specification, additional lag structures were explored including single lags of 0,1,2,...,6 days and  
6 also the corresponding average of lags 0-1, 0-2, 0-3,..., 0-6. Moreover, the association between  
7 SIDS and air pollution was examined after adjusting for the effect of each of the pollutants PM<sub>10</sub>,  
8 SO<sub>2</sub>, NO<sub>2</sub>, NO, CO and O<sub>3</sub> as a second pollutant in turn. The aim of this two-pollutant modelling  
9 approach was to account for potential confounding effect of co-pollutants. Further sensitivity  
10 analyses were performed by controlling for minimum temperature instead of the average  
11 temperature. We excluded NO<sub>x</sub> from the sensitivity analyses as it showed very strong correlation  
12 particularly with NO (r=0.96).  
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28 Results are presented as percentage increases in mortality with 95% confidence intervals  
29 (CIs) for an interquartile range (IQR) increase in pollutant concentration. Hypothesis tests were  
30 two-sided with a significance level of 0.05. All analyses were performed using the R statistical  
31 software; details of the packages used and sample line of code for fitting specific conditional  
32 Poisson regression model is given in the supplementary material (See Supplementary  
33 File:S1).[37]  
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## 45 RESULTS

### 46 Descriptive statistics

47 Over the study period (1996–2006), there were 211 SIDS events across the four postcode  
48 areas (B, CV, WS and WV) included in the analyses which accounted for about approximately  
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5% of the days within the study period (Table 2). In the same period and location, a total of 943,937 live (single) births were registered.

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Table 2: Average air pollution ( $\mu\text{gm}^{-3}$ ), temperature ( $^{\circ}\text{C}$ ) and IMD scores for selected West Midlands postcode areas with SIDS and birth counts, 1996-2006

Post town (area)	PM <sub>10</sub>	SO <sub>2</sub>	CO	O <sub>3</sub>	NO <sub>2</sub>	NO	NO <sub>x</sub>	Temp. (Min-Max)	IMD score	SIDS event (%)	Birth count (%)
Birmingham (B)	23.8	6.8	0.4	38.5	33.9	17.5	60	7.2-12.8	36.6	118 (55.9)	753844 (79.9)
Coventry (CV)	18.3	11.3	0.3	32.4	22.5	9.2	36.2	7.7-13.5	23.7	43 (20.4)	91393 (9.7)
Walsall (WS)					41.5		89.4	6.4-14.0	25.2	24 (11.4)	53532 (5.7)
Wolverhampton (WV)	23.8	9.3	0.5	38.9	29.5	18.9	59.5	8.4-12.3	33.4	26 (12.3)	45168 (4.8)
Total										211 (100)	943937 (100)

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The daily average air pollution concentrations and their standard deviations are presented in Table 3 and show that average concentrations tended to be below UK air quality limits as defined by the EU Ambient Air Quality Directive.[38]

Table 3: Descriptive statistics for daily SIDS mortality counts, air pollution ( $\mu\text{g}\text{m}^{-3}$ ), temperature ( $^{\circ}\text{C}$ ) and birth counts for West Midlands, 1996-2006

Variable	Mean	SD	Median	IQR	Min	Max
SIDS count	<1	<1	0	0-0	0	2
Average temperature	10.2	5.4	10.2	6.2-14.5	-4.2	25.0
Max temperature	13.1	6.0	12.9	8.5-17.6	-2.1	29.6
Min temperature	7.4	5.1	7.5	3.6-11.4	-7.5	20.7
PM <sub>10</sub>	23.4	11.6	20.2	15.7-28.2	4.0	128.9
SO <sub>2</sub>	8.5	6.9	7.2	4.4-10.2	0.0	70.8
CO	0.4	0.2	0.4	0.3-0.5	0.1	3.5
O <sub>3</sub>	38.1	18.2	38.0	25.4-50.4	1.3	115.8
NO <sub>2</sub>	33.2	14.3	31.2	22.3-41.8	5.9	113.0
NO	16.9	23.8	9.0	5.4-17.9	0.4	314.9
NO <sub>x</sub>	64.5	49.3	51.1	35.2-76.4	7.9	569.2
Birth count <sup>a</sup>	290	34	296	266 - 314	183	387
IMD score	32.3	12.6	31.7	21.3-40.5	7.2	54.9

<sup>a</sup> Counts are for single births only

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3 Table 4 shows that there was generally a strong correlation between the levels of pollutants  
4 investigated with the exception of the weaker correlation between O<sub>3</sub> and PM<sub>10</sub> (r=-0.26) and  
5 with SO<sub>2</sub> (r=-0.34). What was also notable was the negative correlation between Ozone and the  
6 other pollutants and how in contrast to the other pollutants its positive correlation with  
7 temperature.  
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3 *Table 4: Pairwise Pearson correlations coefficients (r) for pollutants and*  
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5 *temperature*  
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	PM <sub>10</sub>	SO <sub>2</sub>	CO	O <sub>3</sub>	NO <sub>2</sub>	NO	NO <sub>x</sub>
8							
9							
10	SO <sub>2</sub>	0.53					
11							
12	CO	0.56	0.59				
13							
14	O <sub>3</sub>	-0.26	-0.34	-0.56			
15							
16	NO <sub>2</sub>	0.66	0.56	0.76	-0.62		
17							
18	NO	0.54	0.48	0.87	-0.58	0.73	
19							
20	NO <sub>x</sub>	0.59	0.56	0.90	-0.62	0.86	0.96
21							
22	Temperature	-0.08	-0.24	-0.39	0.40	-0.40	-0.38
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3 Comparing the four postcode areas, Birmingham had the highest SIDS mortality (about  
4 56%) and births rates (about 80%). Air pollution concentrations were more or less similar for  
5 Birmingham and Wolverhampton except slightly lower levels of NO<sub>2</sub> and higher levels of SO<sub>2</sub>  
6 observed for the latter. Coventry had the lowest pollution level with respect to all pollutants  
7 except SO<sub>2</sub>. Walsall had measurements for NO<sub>2</sub> and NO<sub>x</sub> only which were very large compared  
8 to the other postcode areas (Table 2). Similarly, Birmingham and Wolverhampton had higher  
9 average deprivation scores compared to Coventry and Walsall (Table 2). Also, SIDS counts and  
10 pollution levels tended to be larger in highly deprived areas and near motorways and A-road  
11 networks which may be a reflection of population density (Figure 1; see Supplementary File:  
12 Figure S2). There was also indication of seasonal pattern for SIDS occurrence; the highest  
13 proportions of SIDS were observed in January and February (about 10%) and among the  
14 relatively colder months and in July (about 14%) among the warmer months (data not shown).  
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### 33 **Case-crossover analysis**

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35 Figure 2 shows the estimated odds ratio (OR) (95% CI) for the association of SIDS events  
36 with each of the pollutants considered based on the conditional Poisson model. For an  
37 interquartile range increase in previous day pollutant concentration, the percentage increase  
38 (95% confidence interval) for the risk of SIDS death was 16 (6, 27);  $p = 0.002$  for PM<sub>10</sub>, 1 (-7,  
39 10);  $p = 0.83$  for SO<sub>2</sub>, 5 (-4, 14);  $p = 0.33$  for CO, -17 (-27, -6) ;  $p = 0.004$  for O<sub>3</sub>, 16 (2, 31);  $p =$   
40 0.02 for NO<sub>2</sub>, 2 (-3, 8);  $p = 0.47$  for NO and 8 (-1, 18);  $p = 0.07$  for NO<sub>x</sub> after controlling for  
41 average temperature and national holidays. Therefore, considering pollutant levels at lag 1,  
42 significant association with increased risk of SIDS was indicated only for PM<sub>10</sub> and NO<sub>2</sub> while a  
43 protective effect was apparent for O<sub>3</sub>.  
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## Sensitivity analyses

Lag structures: Analyses exploring relationships between SIDS and air pollution for other lag structures (lags 0, 2, 3, ..., 6 and corresponding average of lags 0-1, 0-2, 0-3, ..., 0-6) indicated associations were somewhat sensitive to the choice of lag (Figure 3). In the single lag models, there was an impression of stronger delayed effects for CO, NO<sub>2</sub>, O<sub>3</sub>, PM<sub>10</sub> and SO<sub>2</sub> compared to relatively recent lags (lag 0 and lag 1). The effect of NO appeared to remain comparatively flat across lags. Relatively more consistent association across lags was observed for NO<sub>2</sub> and PM<sub>10</sub> and to some extent for CO. Likewise, in average lag models, ORs tended to increase with averaging over more lags with exception of NO where such an effect was not observed. Results were also similar (at least qualitatively) after adjusting for minimum temperature instead of the average temperature (see Supplementary File: Figure S3).

Multi-pollutant models: Further investigation using two-pollutant models also showed associations were sensitive to control of other pollutants. In general, adjusting for co-pollutants appeared to attenuate ORs towards the null except for NO<sub>2</sub> and PM<sub>10</sub> where effects remained to persist (Figure 4). Interestingly, after controlling for PM<sub>10</sub>, the protective effect of O<sub>3</sub> and the adverse effect of NO<sub>2</sub> observed in the single pollutant models were not apparent for most of the lag choices. Similarly, none of the other pollutants showed marked association with SIDS after controlling for PM<sub>10</sub> effects. The estimates from the multi-pollutant model should, however, be interpreted with caution as most of the pollutants were correlated.

## COMMENTS

### Summary of findings

In this study we hypothesised a delayed effect (lag 1) of air pollution on SIDS incidence and investigated additional lags in sensitivity analyses and in single and multi-pollutant models. Though confidence intervals were wide, we found evidence suggesting association of SIDS mortality with PM<sub>10</sub> and NO<sub>2</sub> exposure. Compared to other pollutants, their effects persisted after controlling for co-pollutants and across the various lag structures investigated. The exception was controlling for O<sub>3</sub> did attenuate the risk estimates observed for both PM<sub>10</sub> and NO<sub>2</sub>. There were no consistent associations observed with exposure to the remaining pollutants investigated (CO, SO<sub>2</sub>, NO, NO<sub>x</sub>). An exception was the protective effect observed in relation to O<sub>3</sub> exposure.

### Strengths and limitations

Previous studies have tended to focus on relatively longer-term exposure to air pollutants.[37,39,40] Our study is one of the first to use case-crossover methodology to explore the impact of air pollution on SIDS based on data from UK. Using an approach that is suitable for estimating the risk of a rare acute outcome such as SIDS events, we were able to investigate various lags and multi-pollutant models indicating delayed effects of pollutants that persisted after controlling for co-pollutants. However, measurement error for air pollution exposure a potential limitation in this study as we did not use personal measurements. Other epidemiological studies using data from ambient monitoring stations have shown a good level of correlation between daily personal exposure and daily ambient air pollution measurements,[36, 37] though

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3 there is the potential for measurement error that can attenuate regression coefficient estimates.  
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5 That is, such misclassification will likely lead to an under estimation of the effects. We were also  
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7 unable to control for influenza and humidity as we did not have access to reliable data for these  
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9 variables.  
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### 14 **Detailed discussion**

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17 Certain groups of the population are more vulnerable to ambient air pollution than others  
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19 and children figure predominantly amongst them due to the fragility of their immune system and  
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21 the ratio of their lung capacity to their size. [41] Particulate matter has been recognised as the  
22  
23 most significant contributor to air quality related morbidity and mortality [42] and a number of  
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25 studies have reported a link between infant mortality and PM<sub>10</sub> at similar concentrations of  
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27 pollutant below air quality guidelines as are described in this study.[11,43,44] However previous  
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29 evidence of a direct association with SIDS is inconclusive and few studies describe a significant  
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31 association of PM<sub>10</sub> with increased risk. [6, 45]  
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36 The potential association with NO<sub>2</sub> we discovered reflected the findings of a multi-city  
37  
38 study from Canada that found an increased risk for SIDS with a lag of two-days.[8] More  
39  
40 broadly our findings are in line with previous studies that have found evidence of a lag between  
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42 exposure to criteria pollutants and mortality. For PM<sub>10</sub>, a single days exposure has been shown to  
43  
44 have an effect for up to 5 days [46, 47] and numbers of respiratory deaths appear to be more  
45  
46 affected by air pollution levels on previous days, than cardiovascular deaths that are impacted by  
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48 same-day pollution.[48] For example myocardial infarction represents an acute response to a  
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50 trigger.[49]  
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3 This is biologically plausible when considering how a wider and more lagged response can  
4 be expected for deaths from respiratory responses to pollution (eg, COPD) via the proposed  
5 mechanisms, such as pulmonary or systemic inflammation and modulated immunity.[50]

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8 With regards the apparent protective properties of O<sub>3</sub> that we describe here it's worth noting that  
9 these have been seen previously.[39] One possible reason for the negative association of O<sub>3</sub> and  
10 SIDS might be its negative correlation with other pollutants, in particular that with fine  
11 particulate matter pollution.[51] O<sub>3</sub> also showed a positive correlation with temperature while all  
12 other pollutants were negatively correlated.  
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24 Concern around the effects of air pollution continue to mount particularly within developing  
25 economies [52] where it contributes to 3.3 million premature deaths worldwide per year a figure  
26 estimated to double by 2050 if the issue remains unattended.[53] However it appears that  
27 recently fossil fuel emissions have begun to increase again due to the developing world's  
28 reliance on them to power their expanding economies.[54] In the developed West, policy  
29 initiatives are beginning to recognise the mounting issue posed by the adverse effects on health  
30 posed by ambient air pollution. However shifting political priorities in the United States has seen  
31 a commitment to revitalise the coal industry [55] and an increase in the production of shale oil  
32 [56] However mitigating these risks is not a straightforward proposition and government policies  
33 appear slow to react, for example in the UK pledges to cease sales of diesel and petrol cars do  
34 not come into effect until 2040.[57]  
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49 In the absence of coherent policy to address the issue a number of proposals have been put  
50 forward to mitigate the effects of high levels of ambient exposure. Knowing that children and  
51 young adults may be highly susceptible to some of the subclinical changes caused by air  
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3 pollution [58,59] and as indoor concentrations are lower than ambient levels advice has been to  
4 remain indoors to reduce exposure and acute health risks on high air pollution days.[60] There  
5 are also systems available for cleaning indoor air though these may be deemed expensive for the  
6 economically deprived.[61] There has also been a case made for chemo-preventive interventions,  
7 such as antioxidant or antithrombotic agents, but without data on health outcomes, no  
8 recommendations can be made in their use for primary prevention. [62]  
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## 19 **Conclusions**

20  
21 Understanding the effects of air pollution on child health is more relevant than ever. Our work  
22 here has highlighted a potential association of Sudden Infant Death with PM<sub>10</sub> and NO<sub>2</sub> and the  
23 association with particulate matter and infant mortality in particular is widely recognised.  
24 However, until policy reflects the growing evidence and responds to mounting public concern, it  
25 would appear to be the responsibility of individuals to take independent action to mitigate the  
26 effects of air pollution and protect the health of their young ones.  
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## ACKNOWLEDGMENTS

**Funding:** This work was supported by The Lullaby Trust, grant number 260.

**Competing interests:** All authors declare: grants from The Lullaby Trust; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years and no other relationships or activities that could appear to have influenced the submitted work.

**Author contributions statement:** IJL contributed to the conceptualisation of the study, initial draft manuscript and supervised the research project at all stages. NIM contributed to the research design, performed the data management, analysis and interpretation, and with IJL drafted the initial manuscript; JGA contributed to the conceptualisation of the study, data interpretation and critically reviewed the manuscript; JJKJ contributed to the conceptualisation of the study, data interpretation and critically reviewed the manuscript; All authors approved the final manuscript as submitted.

**Transparency:** As lead author, I can confirm that the manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects have been omitted and there are no discrepancies from the planned study.

**Ethics committee approval:** Ethical approval was given by the University of Birmingham, Life and Health Sciences Ethical Review Committee.

**Data sharing:** No additional data available.

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## 26 **FIGURE LEGENDS**

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30 **Fig. 1** Air pollution monitoring sites with road networks (motorways and A-roads) and SIDS events in the  
31 study area. We used ArcGIS Desktop 10.2 (<http://www.esri.com/software/arcgis>) to create the map  
32 combining shapefiles for postcode areas and motorways and overlaying air pollution and SIDS data.  
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39 **Fig. 2** Estimated risk of SIDS for an IQR increase in lag 1 pollutant concentration before and after  
40 controlling for confounding by average temperature and national holidays  
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45 **Fig. 3** Risk of SIDS associated with an IQR increase in pollution for selected lags and average of lags;  
46 models adjusted for average temperature and national holidays  
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51 **Fig. 4** Risk of SIDS associated with an IQR increase in air pollution after controlling for co-pollutants,  
52 average temperature and national holidays(panel titles indicate: main and co-pollutant respectively)  
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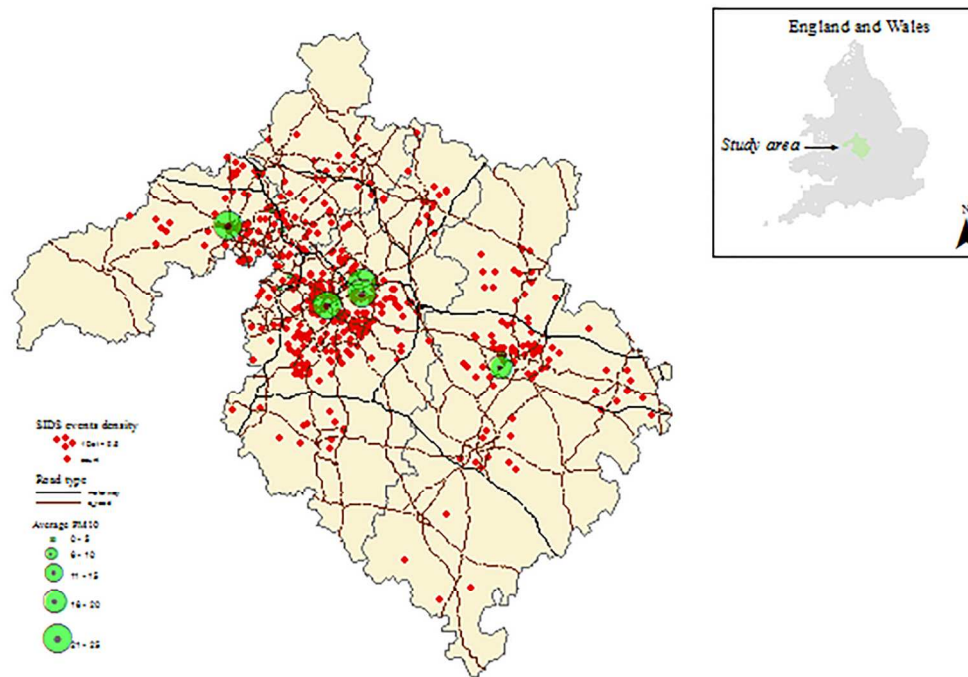


Fig. 1 Air pollution monitoring sites with road networks (motorways and A-roads) and SIDS events in the study area. We used ArcGIS Desktop 10.2 (<http://www.esri.com/software/arcgis>) to create the map combining shapefiles for postcode areas and motorways and overlaying air pollution and SIDS data.

152x105mm (300 x 300 DPI)

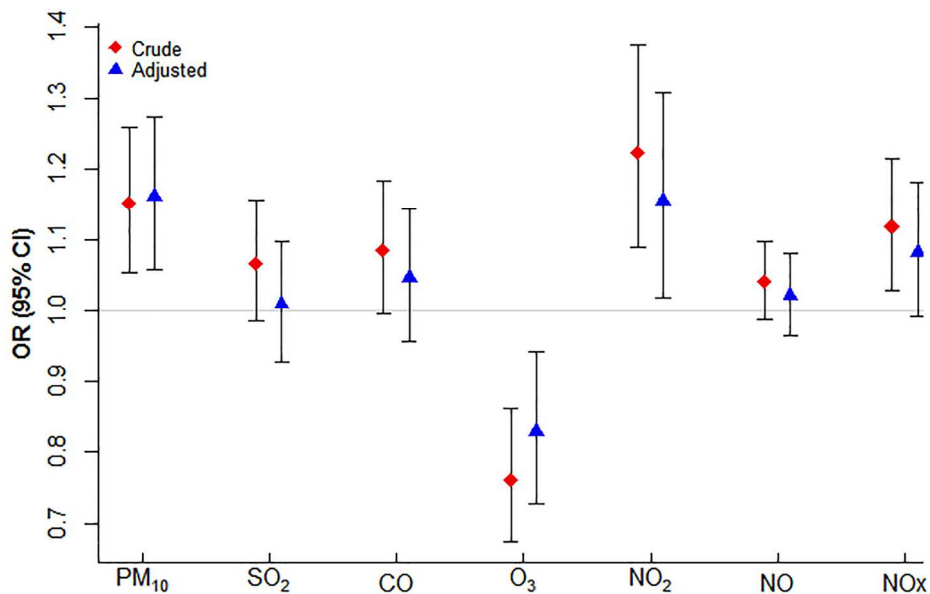


Fig. 2 Estimated risk of SIDS for an IQR increase in lag 1 pollutant concentration before and after controlling for confounding by average temperature and national holidays

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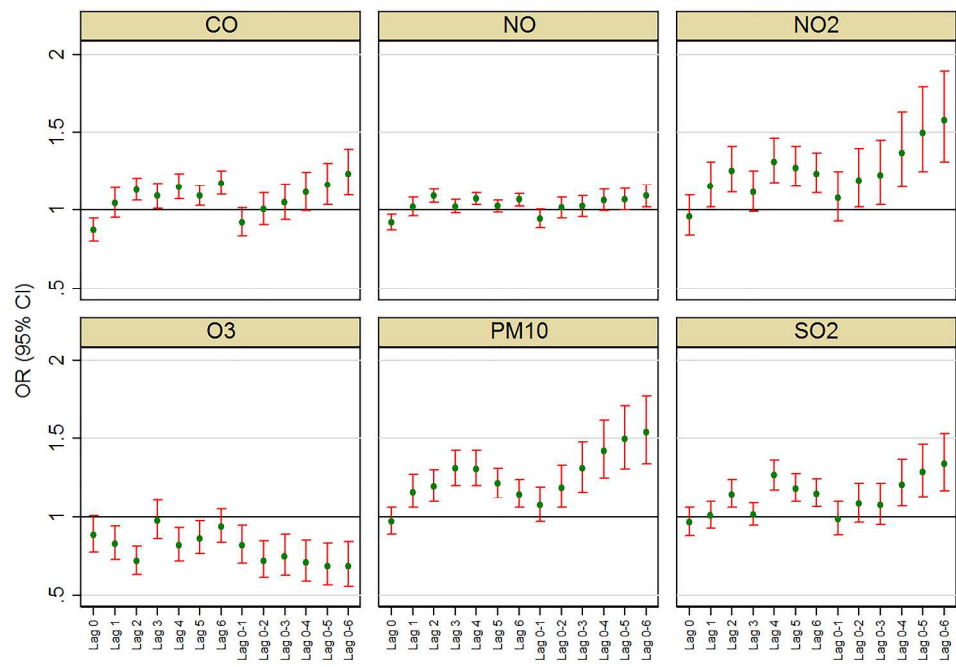


Fig. 3 Risk of SIDS associated with an IQR increase in pollution for selected lags and average of lags; models adjusted for average temperature and national holidays

475x346mm (300 x 300 DPI)

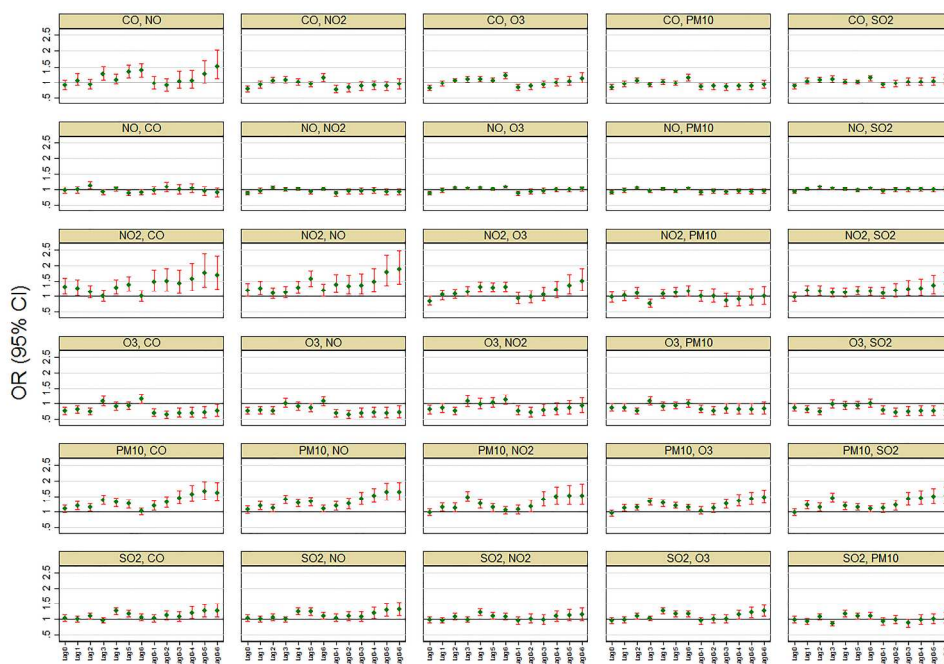


Fig. 4 Risk of SIDS associated with an IQR increase in air pollution after controlling for co-pollutants, average temperature and national holidays(panel titles indicate: main and co-pollutant respectively)

475x346mm (300 x 300 DPI)

### Conditional Poisson Regression (CPR)

Here we applied the time stratified case-crossover approach where the strata are matching days based on the same day of the week, calendar month and year that has previously been used to minimise bias [Janes et al. 2005]. That is, control days were selected from the same day of the week, within the same calendar month and year as the event day. We applied a conditional Poisson regression model which has been shown to give equivalent estimates as the conditional logistic model but with the advantage of readily allowing for overdispersion.

Thus, to fit the CPR model we first create the strata for yearXmonthXday-of-week from the original time series data and then fit the regression using the 'gmn' package adjusting for temperature spline and holiday effects, conditional on strata as detailed in Armstrong et al. [2014]. An example line of R code to fit the CPR model using the R package 'gmn' is given below: `CPR_model <- gmn(sids_freq ~ Lag(pollution, k) + ns(temperature,3) + holiday, data=data, family=quasipoisson, eliminate=factor(stratum))`

where

Lag(pollution, k): pollution exposure at lag k

ns(temperature,3): temperature splines

sids\_freq: SIDS count

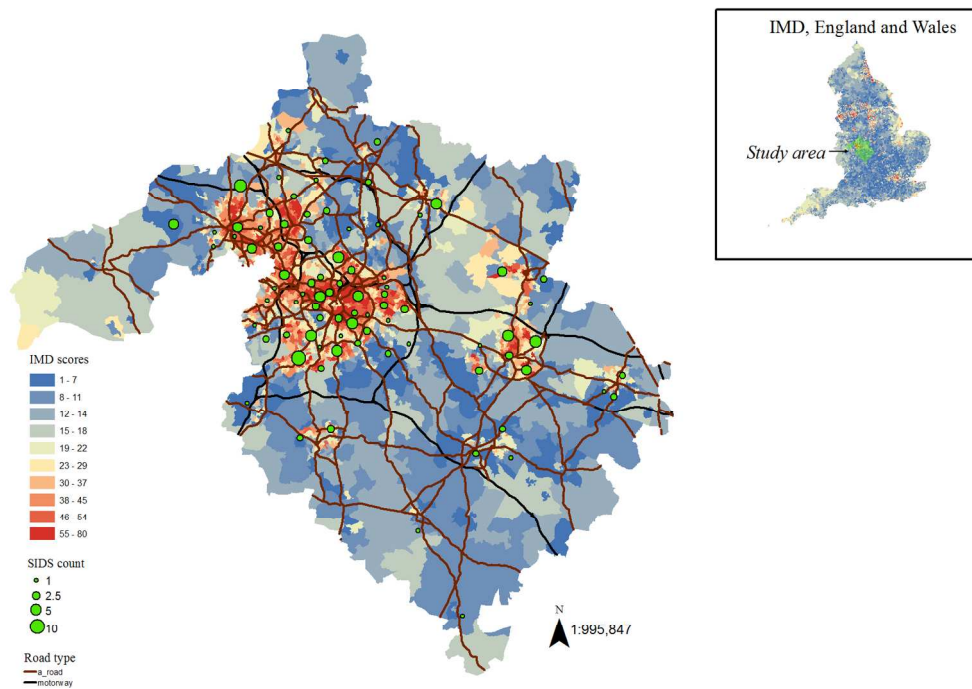
stratum: stratum indicator (for yearXmonthXday-of-week)

### References

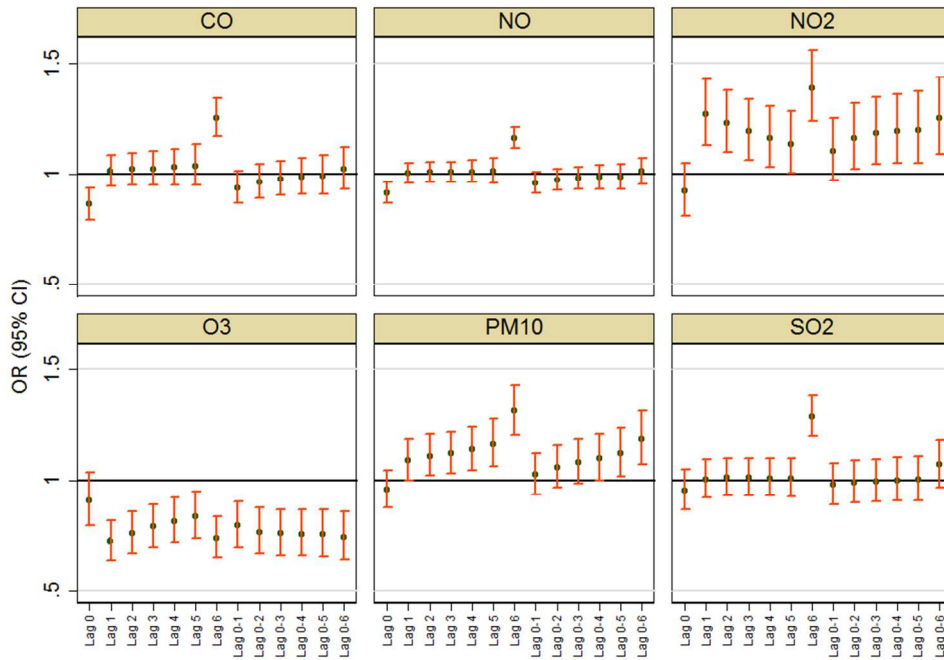
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Armstrong BG, Gasparini A, Tobias A. Conditional Poisson models: a flexible alternative to conditional logistic case cross-over analysis. *BMC Med Res Methodol* 2014;14:122.

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Preprint only

STROBE Statement—Checklist of items that should be included in reports of *case-control studies*

	Item No	Recommendation	Response
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Case-crossover study included in title – Title page
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Completed – including toning down the conclusion as per the associate editor's instruction page 2
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 3
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 3
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	Page 4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 4
Participants	6	(a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	The study is a case-crossover study where effectively individuals act as their own controls Page 4
		(b) For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 4-6
Bias	9	Describe any efforts to address potential sources of bias	Pages 4-6
Study size	10	Explain how the study size was arrived at	Page 4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Page 4-6

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(b) Describe any methods used to examine subgroups and interactions	Page 6
(c) Explain how missing data were addressed	Page 4
(d) If applicable, explain how matching of cases and controls was addressed	N/A (Case-crossover study)
(e) Describe any sensitivity analyses	Page 7

**Results**

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 8
		(b) Give reasons for non-participation at each stage	Page 8
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 8
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	Page 9-10
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 9-10
		(b) Report category boundaries when continuous variables were categorized	N/A
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 11-12
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	Page 13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 14
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 15
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 22

\*Give information separately for cases and controls.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.