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Respiratory effects of sulphur dioxide: a hierarchical multicity analysis in the APHEA 2 study

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Background: Sulphur dioxide (SO_2) was associated with hospital admissions for asthma in children in the original APHEA study, but not with other respiratory admissions.
Aims: To assess the association between daily levels of SO_2 and daily levels of respiratory admissions in a larger and more recent study.
Methods: Time series of daily counts of hospital emergency admissions were constructed for asthma at ages 0–14 years and 15–64 years, COPD and asthma, and all respiratory admissions at ages 65+ years in the cities of Birmingham, London, Milan, Paris, Rome, Stockholm, and in the Netherlands for periods of varying duration between the years 1988 and 1997. A two stage hierarchical modelling approach was used. In the first stage generalised additive Poisson regression models were fitted in each city controlling for weather and season. These results were then combined across cities in a second stage ecological regression that looked at potential effect modifiers.
Results: For an increase of 10 μg/m^3 of SO_2 the daily number of admissions for asthma in children increased 1.3% (95% CI 0.4% to 2.2%). Effect modification among cities by levels of other air pollutants or temperature was not found. The SO_2 effect disappeared after controlling for PM_{10} or CO, but correlation among these pollutants was very high. Other respiratory admissions were not associated with SO_2.
Conclusion: SO_2 is associated with asthma admissions in children, indicating that reduction in current air pollution levels could lead to a decrease in the number of asthma admissions in children in Europe.

Sulphur dioxide (SO_2) causes bronchoconstriction in normal and asthmatic subjects after short term exposures (within five minutes) in chamber studies.[1 2] The response in asthmatics occurs at lower concentrations.[1–3] However, urban atmospheres in Europe rarely attain the levels of SO_2 used in human experiments (200 ppb).[4]

The APHEA study (Air Pollution and Health: a European Approach), the largest epidemiological multicentre study on asthma admissions in Europe, reported significant associations between daily values of SO_2 and the number of daily admissions for asthma in children,[5] but not with asthma or chronic obstructive pulmonary disease (COPD) in adults.[5 6] It is important to note that children have never been challenged in chamber studies and so their experimental response is unknown.

The APHEA 2 study included a larger number of cities with longer and more recent study periods than the original APHEA study. The role of particulate matter on respiratory admissions in the APHEA 2 study has been published, but not the effects of the other pollutants.[7] Our aim was to assess the association between daily levels of SO_2 and daily levels of respiratory admissions. We also planned to investigate the potential effect modification of city specific variables (for example, smoking prevalence).

METHODS

Time series of daily counts of admissions were constructed for four groups of admissions: asthma (International Classification of Diseases, Revision 9: 493) for ages 0–14 years and 15–64 years; COPD and asthma (ICD9 490–496) for ages 65+ years; and all respiratory admissions (ICD9 460–519), also for ages 65+ years.[7] Where possible, emergency admissions resulting in an overnight hospital stay were specified to exclude elective admissions and those resulting only in an emergency room visit. The minimum time period for each series was three years. Eight cities in the APHEA 2 group were able to provide hospital admissions data: Barcelona, Birmingham, London, Milan, the Netherlands (considered as a city because of its relatively small size and relative homogeneity in air pollution levels), Paris, Rome, and Stockholm. Barcelona was excluded because the detection limit for SO_2 was set at an arbitrary cut off of 10 μg/m^3 (a value close to the median). The pollutants were those generally measured in European cities and have been described in detail elsewhere.[7]

The statistical analyses involved fitting a hierarchical model in two steps. First, a Poisson regression coefficient was estimated for each city, controlling for seasonal patterns in the admissions, their dependence on temperature and humidity, and their association with holiday periods and influenza episodes. Because the dependence of respiratory morbidity on weather and season has been shown to be non-linear, generalised additive models were used.[8] Such models allow the use of non-parametric smooth functions to adjust for the effects of weather and season. Non-parametric smooth functions are generalisations of moving averages and provide a flexible fit whose shape is determined by the data. This reduces the risk of confounding by inadequate control for covariates. The use of smooth functions requires a choice of the smoothing parameter related to the number of degrees of freedom used by the covariate. A sensitivity analysis using different convergence criteria for the smoothing parameters resulted in little change in the SO_2 effect estimates. To control for season a smoothing parameter that removed seasonal patterns from the residuals was chosen and, if possible, reduced the residuals to white noise. If this was not possible a smoothing parameter that reduced the correlations in the residuals was selected and incorporated autoregressive terms to control for

Table 1 SO_2 and hospital admissions daily averages (SD) by diagnosis, age group, and city; APHEA 2 study

City (years)	SO_2 (μg/m³)	Asthma <15 y	Asthma 14–64 y	COPD + asthma (>64 y)	All respiratory (>64 y)
Birmingham (1992–94)	24.3 (12.7)	8.1 (4.4)	4.9 (2.5)	6.7 (3.3)	19.4 (7.4)
London (1992–94)	23.6 (23.7)	20.3 (10.3)	14.1 (5.8)	22.9 (7.6)	58.4 (19.5)
Milan (1990–97)	32.5 (37.5)	0.7 (1.0)	0.5 (0.7)	2.9 (2.2)	9.2 (4.7)
Netherlands (1988–95)	8.5 (7.7)	5.9 (3.5)	5.2 (2.7)	27.0 (11.3)	53.6 (21.8)
Paris (1992–96)	17.7 (12.5)	5.8 (3.8)	7.7 (3.7)	5.4 (3.2)	23.4 (9.4)
Rome (1995–97)	9.8 (9.9)	1.8 (1.7)	2.0 (1.6)	9.2 (4.0)	19.4 (7.1)
Stockholm (1988–96)	6.8 (6.2)	1.3 (1.3)	1.3 (1.2)	5.0 (2.5)	10.3 (4.5)

Table 2 Percentage increase (95% CI) in respiratory emergency room admissions (RERA) per each increase in 10 μg/m³ of sulphur dioxide, according to the regression model

		Regression model	
RERA	Age	Fixed effects	Random effects
Asthma	0–14	1.3 (0.4 to 2.2)	1.3 (0.4 to 2.2)
Asthma	15–64	0.0 (–0.9 to 1.0)	0.0 (–0.9 to 1.0)
COPD + asthma	>64	0.6 (0.0 to 1.2)	0.4 (–0.6 to 1.2)
All respiratory	>64	0.5 (0.1 to 0.9)	0.4 (–0.4 to 1.2)

the remaining short term serial correlation in the residuals.[9] Temperature and humidity on the day of admission were included in all models and the smoothing parameter that minimised Akaike's Information Criterion, a likelihood based measure of goodness of fit, was chosen. This criterion was used to determine if, in addition, there were delayed effects of weather variables (up to three days before the admission) by testing whether such variables improved the model fit. Further details of this approach to model selection have been published previously.[10]

In every city, the air pollution indicator (that is, SO_2) was introduced as a linear term of arithmetic averages of the same day (as admission) and the previous day measures. Finally, two pollutant models were fitted to assess the changes in the SO_2 estimates after the inclusion of the other pollutants in the regression model.

In the second stage the results were combined using a meta-regression approach. This consists of an ecological regression where the estimated effect of SO_2 in each city was regressed on possible explanatory factors that vary across the cities. These included climatic variables, population differences, and levels of other air pollutants. If no factors explained any differences across the cities the regression with only an intercept term gave the inverse variance weighted average. An iterative maximum likelihood based approach was used to estimate a random variance component in these regressions. It reflects any unexplained variance in the results by city that do not appear to be due to chance; the significance of the random variance component was tested using a χ^2 test for heterogeneity.[7]

RESULTS

There was a wide range in the SO_2 daily averages among the seven participating areas, from 6.8 μg/m³ in Stockholm to 32.5 μg/m³ in Milan (table 1). There was also considerable variability in potential effect modifiers such as levels of co-pollutants, mean wintertime temperature, and standardised mortality rates as shown elsewhere.[10] Daily admissions for respiratory illness also varied substantially between the seven cities.

Among the four groups of respiratory admissions studied, only daily admissions for asthma in children were associated with daily values of SO_2 (table 2). The associations with asthma in children were homogeneous among the seven centres ($p = 0.7$); thus the fixed and the random effects models gave very similar results (at 2 significant figures). We did not find evidence for effect modification with climatic variables or pollutant levels in the second stage analysis.

The association of SO_2 with childhood asthma admissions was sensitive to inclusion of a second pollutant in the models (percentage increase due to SO_2: −3.7% and −0.7% after controlling for particulate matter (PM_{10}) and carbon monoxide (CO) respectively; $p > 0.1$). However, the correlation between SO_2 and both pollutants was very strong in all areas (the median correlation coefficient among the seven cities was 0.64 for PM_{10} and 0.53 for CO). Control for other pollutants in models for the other respiratory admissions did not change the lack of association found in the single pollutant models.

DISCUSSION

We found daily variations in SO_2 were related to daily number of asthma admissions in children, but not with other respiratory diseases in other age groups. These findings agree with the results of the original APHEA study.[5] The analysis for SO_2 in the original APHEA study only included the cities of Helsinki, London, and Paris.[5] The present study shows a very similar magnitude of the association with asthma in children after studying seven cities. Previous studies carried out during the 1960s with higher urban levels reported an increase in respiratory infections in relation to SO_2 in children[11] and in children with asthma,[12] but SO_2 has not been shown to be related to asthma admissions in adults, even at high values of exposure.[13]

The pattern of association (with childhood asthma but not other respiratory admissions) may be related to exposure factors. Asthmatic reactions can occur in response to a short term exposure, whereas exacerbations of other respiratory conditions, for example pneumonia, are more likely to be in response to a longer term insult. The nature of SO_2 exposure

makes it more likely that high pollution days result in peak exposure to a subpopulation of children who play outside during the day than in a substantial multi-hour or day exposure of relevance for the other outcomes. This is because SO_2 is a highly reactive gas whose concentration is very seasonal, peaking in the winter.[14] Because of this reactivity, indoor concentrations of SO_2 are usually much lower than outdoor concentrations. Since people spend most of their time indoors in western society, particularly in the winter, exposures indoors remain low, even when levels are raised outdoors. Hence it may be less likely that the elderly will receive exposures high enough to exacerbate infection, and more likely that children may receive short term exposures high enough to trigger asthma attacks.

SO_2 is a gas produced by fuel combustion. Currently, the major source of combustion pollution in most cities is traffic. Hence, SO_2 might be a surrogate of the traffic pollution mixture. The high correlations between SO_2 , PM_{10}, and CO did not allow the effects of these pollutants to be separated in the multi-pollutant regression models. However, two recent studies in eastern European countries suggested that SO_2 by itself might be related to respiratory diseases in children.[15 16] In the Czech Republic and Poland, among 6959 children from 130 different sites, the winter concentrations of SO_2 were associated with asthma prevalence diagnosed by a doctor.[15] In three areas of eastern Germany, decreases in levels of SO_2 were associated with a decrease of respiratory symptoms among 7632 children.[16]

We did not find evidence of effect modification by levels of other air pollutants or temperature. While our study had limited power to detect such associations, with only seven cities examined, we note that previous analyses of hospital admissions in the eight APHEA 2 cities did find indications of effect modification for PM_{10} on the same outcomes.[7]

We conclude that daily values of SO_2 were associated with increases in the number of daily emergency admissions for asthma in children in European cities. However, our study cannot differentiate as to whether these associations were due to SO_2 itself or to other pollutants emitted from the fuel combustion processes. Nevertheless, this study suggests that a reduction in current outdoor SO_2 levels could lead to a decrease in the number of admissions for asthma among children in Europe. We failed to find evidence for an association between SO_2 and other respiratory conditions in adults.

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REFERENCES

1 **Sheppard D**, Wong WS, Uehara CF, *et al*. Lower threshold and greater bronchomotor reponsiveness of asthmatic subjects to sulfur dioxide. *Am Rev Respir Dis* 1980;**122**:873–8.
2 **Stacy RW**, Seal E, House DE, *et al*. A survey of effects of gaseous and aerosol pollutants on pulmonary function of normal males. *Arch Environ Health* 1983;**38**:104–5.
3 **Sheppard D**, Saisho A, Nadel JA, *et al*. Exercise increases sulfur dioxide induced bronchoconstriction in asthmatic subjects. *Am Rev Respir Dis* 1981;**123**:486–91.
4 **Linn Ws**, Avol EL, Peng RC, *et al*. Replicated dose-response study of sulfur dioxide effects in normal, atopic and asthmatic volunteers. *Am Rev Respir Dis* 1987;**136**:1127–34.
5 **Sunyer J**, Spix C, Quénel P, *et al*. Urban air pollution and emergency room admissions for asthma in four European cities: the APHEA Project. *Thorax* 1997;**52**:760–5.
6 **Anderson HR**, Spix C, Medina S, *et al*. Air pollution and daily admissions for chronic obstructive pulmonary disease in 6 European cities: results from the APHEA project. *Eur Respir J* 1997;**10**:1064–71.
7 **Atkinson R**, Anderson HR, Sunyer J, *et al*. Acute effects of particulate air pollution on respiratory admissions: results from APHEA 2 project. Air pollution and health: a European approach. *Am J Respir Crit Care Med* 2001;**164**:1860–6.
8 **Hastie T**, Tibshirani R. *Generalized additive models*. London: Chapman and Hall, 1990.
9 **Brumback BA**, Ryan LM, Schwartz J, *et al*. Transitional regression models with application to environmental time series. *JASA* 2000;**95**:16–28.
10 **Katsouyanni K**, Touloumi G, Samoli E, *et al*. Confounding and effect modification in the short-term effects of ambient particles on total mortality:results from 29 european cities within the APHEA project. *Epidemiology* 2001;**12**:521–31.
11 **Girsh L**, Shubin E, Dick CH. A study on the epidemiology of asthma in children of Philadelphia. *J Allergy* 1967;**39**:347–57.
12 **Douglas JWB**, Waller RE. Air pollution and respiratory infections in children. *Br J Prev Soc Med* 1966;**20**:1–8.
13 **Donoghue AM**, Thomas M. Point source sulfur dioxide peaks and hospital presentation for asthma. *Occup Environ Med* 1999;**56**:232–6.
14 **Sunyer J**, Antó JM, Murillo C, *et al*. Effects of urban air pollution on emergency room admissions for chronic obstructive pulmonary disease. *Am J Epidemiol* 1991;**134**:277–86.
15 **Pikhart H**, Bobak M, Gorynski P, *et al*. Outdoor sulphur dioxide and respiratory symptoms in Czech and Polish children: a small area study (SAVIAH). *Int Arch Occup Environ Health* 2001;**74**:574–8.
16 **Heinrich J**, Hoelscher B, Frye C, *et al*. Improved air quality in reunified Germany and decreases in respiratory symptoms. *Epidemiology* 2002;**13**:394–401.