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# Personal exposure to nitrogen dioxide ($NO_2$) and the severity of virus-induced asthma in children

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## Summary

**Background** A link between exposure to the air pollutant nitrogen dioxide ($NO_2$) and respiratory disease has been suggested. Viral infections are the major cause of asthma exacerbations. We aimed to assess whether there is a relation between $NO_2$ exposure and the severity of asthma exacerbations caused by proven respiratory viral infections in children.

**Methods** A cohort of 114 asthmatic children aged between 8 and 11 years recorded daily upper and lower respiratory-tract symptoms, peak expiratory flow (PEF), and measured personal $NO_2$ exposures every week for up to 13 months. We took nasal aspirates during reported episodes of upper respiratory-tract illness and tested for infection by common respiratory viruses and atypical bacteria with RT-PCR assays. We used generalised estimating equations to assess the relation between low (<7·5 μg/m³), medium (7·5–14 μg/m³ ), and high (>14 μg/m³) tertiles of $NO_2$ exposure in the week before or after upper respiratory-tract infection and the severity of asthma exacerbation in the week after the start of an infection.

**Findings** One or more viruses were detected in 78% of reported infection episodes, and the medians of $NO_2$ exposure were 5 (IQR 3·6–6·3), 10 (8·7–12·0), and 21 μg/m³ (16·8–42·9) for low, medium, and high tertiles, respectively. There were significant increases in the severity of lower respiratory-tract symptom scores across the three tertiles (0·6 for all viruses [p=0·05] and >2 for respiratory syncytial virus [p=0·01]) and a reduction in PEF of more than 12 L/min for picornavirus (p=0·04) for high compared with low $NO_2$ exposure before the start of the virus-induced exacerbation.

**Interpretation** High exposure to $NO_2$ in the week before the start of a respiratory viral infection, and at levels within current air quality standards, is associated with an increase in the severity of a resulting asthma exacerbation.

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## Introduction

Exposure to nitrogen dioxide ($NO_2$), mainly emitted from gas cooking appliances and motor vehicle exhausts, has been associated with respiratory symptoms in children[1] and adults.[2] Although epidemiological evidence is not consistent, a meta-analysis of 11 studies in children concluded that the excess risk is significant but small.[3] Results from one study suggested that high outdoor $NO_2$ exposure is associated with a raised frequency of lower respiratory-tract symptoms in children with bronchial hyper-responsiveness and a high total IgE concentration.[4] Other workers have noted a dose-response relationship between asthma incidence and $NO_2$ exposure,[5] although the mechanisms remain unknown. Asthma prevalence is increasing in many countries, and exacerbations are the main cause of asthma morbidity and result in very substantial health-care costs.

Respiratory viral infections are the main trigger for acute asthma exacerbations in children.[6] Evidence from studies in animals and humans suggest that $NO_2$ exposure before an infection can impair resistance to respiratory viruses and bacteria through reduction of bacterial clearance[7,8] and local immunity, and by alteration of macrophage function.[9–11] Therefore, $NO_2$ might exert its effects on asthma by increasing the severity of exacerbations induced by respiratory infection. In this prospective study, we aimed to assess whether high personal $NO_2$ exposure increases the severity of asthma exacerbations associated with proven respiratory viral infection in children.

## Methods

### Participants

Between October and December, 1994, we recruited participants from 853 children on asthma registers kept by general practitioners in Southampton, UK. We sent a letter to the parents of each child informing them of the study and inviting their children to participate. Every child was allocated a number, generated by a random number sequence, and their parents were telephoned by a member of the research team in order of the random number sequence about 1 week after the letter was sent. We included children with a history of wheeze or cough (in the absence of infection) in the 12 months before study entry, but excluded those who lived with people who smoked.

The study was approved by the Southampton University Hospitals Ethics Committee. We obtained written and verbal consent from parents and children.

### Procedures

At study entry, we recorded participants' height, forced expiratory volume in 1 s ($FEV_1$) and forced vital capacity (FVC) (Vitalograph, Buckingham, UK), exposure to gas cooking and heating appliances, and social class. We also measured atopic status by skin prick testing to grass, cat, and house dust mite allergens (Miles Inc, Spokane, WA, USA). We showed children the nasal-aspirate sampling technique that would be used during the study.

Participants used a diary card to record the best of three morning and evening prebronchodilator peak expiratory flow (PEF) rates. They also recorded subjective assessments of respiratory symptoms: 0=absent, 1=mild, 2=moderate, and 3=severe. Upper respiratory-tract symptoms were runny nose or sneezing; blocked or stuffy nose; sore throat or hoarse voice; headaches or face aches; aches or pains elsewhere; and feeling chill, fever, or shivers. Lower respiratory-tract symptoms were cough on waking, wheeze on waking, cough during the day, wheeze during the day, shortness of breath during the day, night cough, and wheeze or shortness of breath during the night. Scores were added to give daily upper and lower respiratory-tract scores, respectively.[6] When the upper respiratory-tract score was 4 or greater, parents left a message for study investigators using a 24-h answer phone service. This message triggered a visit within 48 h to obtain a nasal aspirate sample from the child, which would be tested for the presence of a viral infection.

We used Palmes diffusion tubes (GMSS, Didsbury, Manchester, UK) to measure childrens' $NO_2$ exposure.[12,13] Tubes were changed every 7 days, and participants kept a record of duration of exposure with each tube. We asked children to wear the tube on outer clothing during the day, and to place it in their bedroom at night. The family attended a clinic every 4 weeks to hand back and collect diffusion tubes and diary cards. Individual progress was also reviewed at these visits, and the quality of monitoring was assessed by inspection of the used diffusion tubes. Tubes which were not worn (<0·5%) were not sent for analysis.

Greater Manchester Scientific Services (GMSS, Didsbury, Manchester, UK) analysed the diffusion tubes. For quality control, we included laboratory and travelling blanks with each monthly dispatch to the GMSS. We obtained data for outdoor $NO_2$ concentrations from the Atomic Energy Authority (AEA) Technology Environment urban monitoring station located in the centre of Southampton.

We took nasal aspirate samples by suction using a mucus trap (Vygon Laboratories, Ecouen, France). They were mixed with viral transport medium, divided into aliquots, and transported to the laboratory on dry ice and frozen at –70°C.[14] A panel of RT-PCR assays based on previously published and novel primers were developed to screen the aspirates for picornaviruses (mostly rhinoviruses), respiratory syncytial virus, coronaviruses OC43 and 229E, influenza viruses A and B, parainfluenza viruses 1–3, adenovirus, *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* (details of target genes, primer sequences, and cycling parameters are available from the author). We confirmed sensitivity and specificity of each assay by comparison with combinations of cell culture, immunofluorescence, and serology, and by simultaneous analysis of samples from the same children when they did not have symptoms.

An upper respiratory-tract infection was diagnosed when a participant reported a cold and infection was detected by RT-PCR. We determined the start date of infection (day 0) using plots of all recorded upper respiratory-tract symptoms. We then assessed whether $NO_2$ exposure in the week before (days –8 to –2) or after (days 0–6) an upper respiratory-tract infection was related to the severity of the asthma exacerbation in the week immediately after infection. Severity was assessed by the change in mean lower respiratory-tract symptoms or PEF measurements from the week before to the week after the start of infection. $NO_2$ exposure was determined (after logarithmic transformation) from the weighted daily average of the two consecutive 1-week exposure measurements that overlapped the 7-day period. In anticipation of missing $NO_2$ measurements, lower respiratory-tract symptom scores, or PEF measurements during the exposure periods, we decided a priori that at least four of the seven daily personal $NO_2$ exposures, symptom scores, and PEF rates were needed for the event to be included in analyses.

### Statistical analysis

We used previously reported data for $NO_2$ exposures in Southampton schoolchildren to calculate sample size.[15] We expected up to 70% of upper respiratory-tract episodes with a confirmed infection to be followed by symptoms in the lower respiratory tract, or reductions in PEF measurements, and that the mean number of reported upper respiratory episodes per child would be between 2 and 4. A risk ratio of 1·2 for increments of 30 μg/m³ indoor $NO_2$ exposure (equivalent to the presence of a gas cooker in the home) was derived from a meta-analysis of 11 studies.[3] From our pilot study we expected a 30 μg/m³ equivalent difference in the personal $NO_2$ exposure between the lowest and highest tertiles. We did simulations to assess the effect of the absence of independence of episodes within a child, and this seemed to have a minimal effect on estimates of the standard errors of the coefficient for $NO_2$ exposure. Even with extremely high correlation between episodes within children, the standard error only increased by 14%. If three to four episodes were reported per child, we anticipated 70% to 80% power, respectively, based on standard methods for the analysis of proportions, with the assumption of a risk ratio of 1·2 for children distributed between the highest and lowest tertiles. Furthermore, we anticipated the power of the analysis would be further improved by use of actual personal $NO_2$ values in a regression model rather than crude categorical differences in exposure such as the presence or absence of a gas cooker. We estimated that with a sample size of 100–120 children, we would have sufficient power to test our main objectives.

To allow for repeated observations within children, we used generalised estimating equations[16] with random effects regression models (XTREG procedure) in STATA (version 5.0). We used regression models to test whether age, sex, social class, atopy, and use at baseline of inhaled $\beta_2$ agonists, inhaled corticosteroids, or oral corticosteroids were confounding factors.

### Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

## Results

Of the 853 children on asthma registers, we did not have contact telephone numbers for 59. Of these, 27 contacted the research team in response to the letter, and five expressed an interest in the study. The remaining 22 did

| | $NO_2$ exposure tertile (median [n, range]) | | |
|---|---|---|---|
| | Low | Medium | High |
| Before infection (μg/m³)* | 5·0 (61, 0·7–7·3) | 9·8 (77, 7·6–13·4) | 20·9 (71, 14·1–75) |
| After infection (μg/m³)† | 5·1 (65, 1–7·4) | 10·2 (75, 7·6–13·5) | 20·7 (69, 14·1–93) |
| Rest of study period (μg/m³) | 5·1 (1058, 0·7–7·4) | 10·1 (1086, 7·5–13·9) | 21·2 (968, 14·1–214) |

*Days –8 to –2 from infection. †Days 0 to 6 from infection.

Table 1: **Median $NO_2$ exposures before and after infection by exposure tertile**

not wish to participate, or stated that their child no longer had symptoms of asthma. Other reasons for declining participation included an unwillingness to take part in an arduous study, emigration, domestic difficulties, and the possibility that the project could interfere with school work. After a 2-week training period, 116 children entered the study.

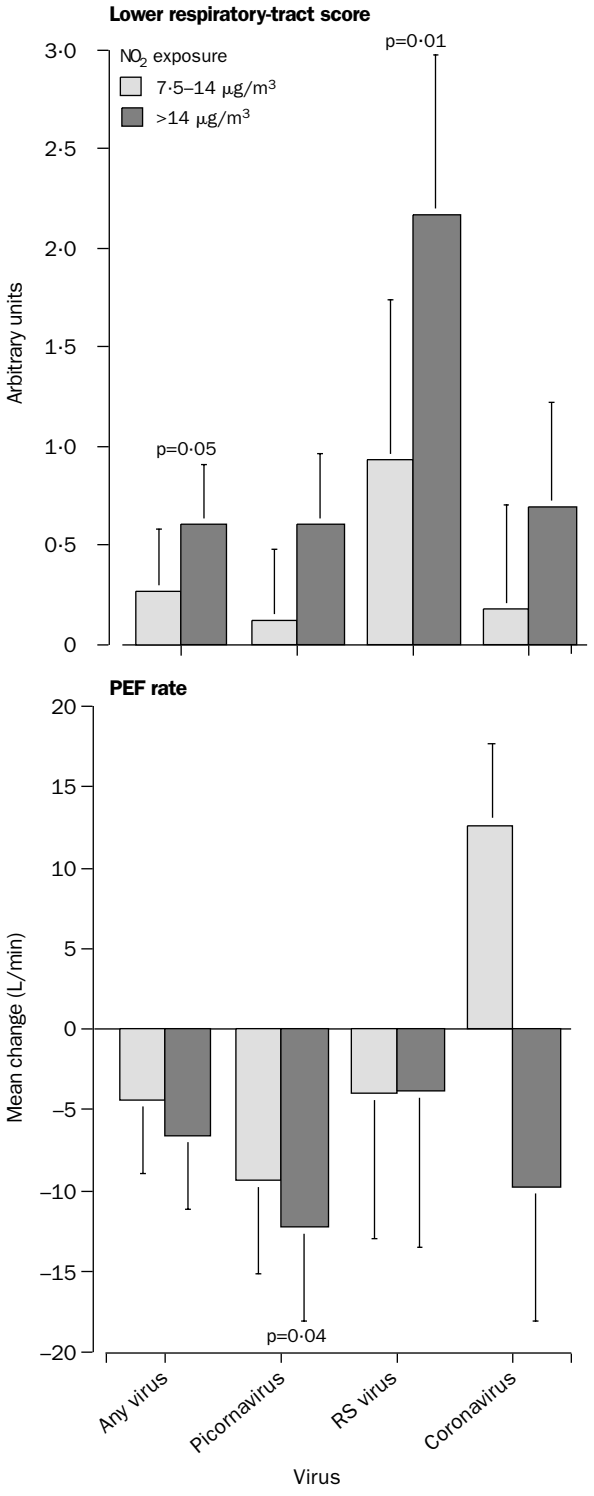


Figure 1: **Mean change in respiratory-tract symptom scores and PEF rates after viral infection for children in medium and high $NO_2$ exposure tertiles compared with children in the low exposure tertile**
RS=respiratory syncytial. Bars show SE.

The study cohort included 63 boys and 51 girls (mean age 10·2 years, range 7·9–11·6 yrs). 72 children (63%) were atopic. Two children withdrew within 4 weeks of commencement because of poor compliance in recording the diary cards and wearing the $NO_2$ diffusion tubes, provision of nasal aspirate samples, and reluctance to take further part in the study. Mean follow-up was 37 weeks (range 3–49, excluding the summer recess between July and August, 1995). The mean $FEV_1$ at entry was 1·73 L (range 1·03–2·49) with a mean percent of predicted $FEV_1$ of 78% (49–105). 103 children (87%) used inhaled $\beta_2$ agonists and 78 (67%) used regular inhaled corticosteroids. For cooking fuel, 35 children lived in households with gas only, 34 with gas and electricity, and 45 with electricity only.

We collected a total of 29 405 child-days of $NO_2$ monitoring and diary data. 2·8% of respiratory symptom scores, 7% of PEF measurements, and 13·2% of $NO_2$ measurements were missing. Missing $NO_2$ measurements were mostly because of lost or damaged tubes.

99 children reported 280 upper respiratory-tract symptom episodes (colds) (mean=2·5, range 0–7 episodes per child). We detected infection in 219 episodes (78%). More than 70% of the episode samples were collected either on the same day or within 3 days of the start date of infection. The most frequently detected organisms were picornavirus (131 [46%]), respiratory syncytial virus (52 [18%]), *M pneumoniae* (43 [14%]), and coronavirus (33 [12%]).

We tested for all upper respiratory-tract infections in combination and by individual virus type (apart from *C pneumoniae*, influenza, parainfluenza, and adenoviruses because of insufficient numbers). The distribution of the individual $NO_2$ exposures before upper respiratory-tract infections was divided into low (<7·5 μg/m³), medium (7·5–14 μg/m³), and high (>14 μg/m³) tertiles and the changes in lower respiratory-tract score or PEF rates over these groups were assessed. The number of infections with sufficient exposure and diary card data that we used in the analyses by low, medium, and high tertiles of exposure were 62, 60, and 60, respectively, for all viruses combined; 42, 33, and 34 for picornavirus; 13, 16, and 12 for respiratory syncytial virus; and 8, 8, and 11 for coronavirus.

The frequency of *M pneumoniae* was higher than anticipated, which might have occurred because the study period coincided with a cyclical *M pneumoniae* epidemic year. As 30 of 43 (70%) *M pneumoniae* infections were identified in association with another virus (mostly picornavirus), we did not test for *M pneumoniae* as an individual agent. However, they were included for all infections combined.

WHO recommends a 1 h guideline of 200 μg/m³, and an annual average of 40 μg/m³ as a safe threshold to protect public health.[17] The tertiles of $NO_2$ exposure used in this study are much lower than levels mentioned by WHO, although 23 (20%) children recorded at least one personal $NO_2$ exposure of more than 100 μg/m³, 32 (>1%) of the total personal measurements were greater than 100 μg/m³, and 599 (14%) were less than 5 μg/m³. Median personal $NO_2$ exposure was higher in children from families using gas for cooking (12·0 μg/m³ [range 4·8–58·2]) compared with families using only electricity (8·5 μg/m³ [4·2–15·6]), p<0·0001 (Wilcoxon rank-sum test). Median $NO_2$ exposures in the week before infection, the week after infection, and for the rest of the study period (excluding the week before and the week after infections) are reported by tertile in the table. Medians of the low, medium, and high tertiles of personal $NO_2$ exposure for children in homes where gas was used for

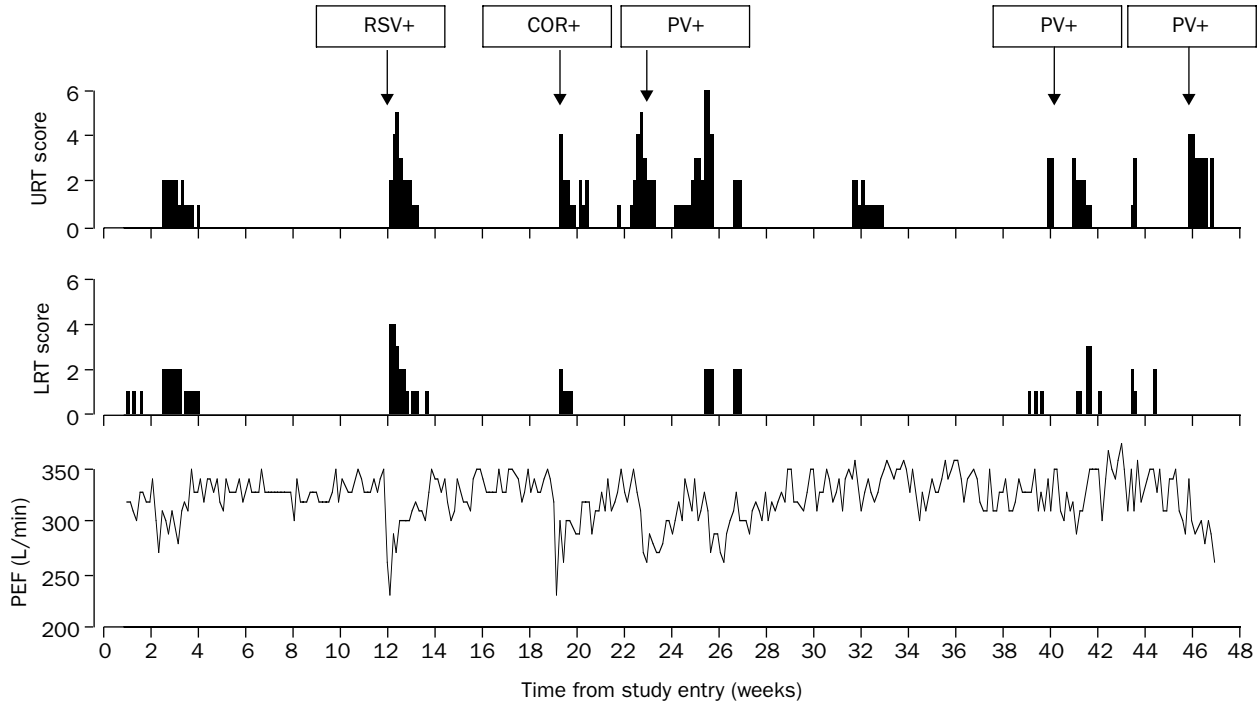


Figure 2: **Upper and lower respiratory-tract symptoms and PEF rate in relation to virus detection**
URT=upper respiratory tract. LRT=lower respiratory tract. PEF=peak expiratory flow. RSV=respiratory syncytial virus. PV=picornavirus. COR=coronavirus. Temporal relation between infection and symptom variables in one child are shown. Symptom scores are based on an arbitrary scale, and only symptoms recorded for 2 or more consecutive days are shown.

cooking were 5·3, 10·2, and 22·9 μg/m³, respectively, and 5·1, 9·9, and 18·9 μg/m³, respectively for those in households where electricity was used for cooking. Of the total number of personal $NO_2$ measurements across the tertiles, the proportion from children from gas-cooking homes were 51%, 62%, and 78%, for the low, medium, and high tertiles of exposure, respectively. Personal $NO_2$ exposures varied widely from week to week and from child to child. Analysis of variance showed that variation in exposure within participants accounted for much more of the scatter (74%) than did the variance between children (26%).

Median lower respiratory-tract scores in the week before infection for all children was 1·1 (range 0–8) and 2·1 (range 0–18) in the week after infection. Median PEF rates in the weeks before and after infection were 302 L/min (110–460) and 286 L/min (50–440), respectively.

The severity of lower respiratory-tract symptoms was increased and PEF measurements dropped with rising personal $NO_2$ exposure in the week before infection when analysed for all respiratory-tract infections in combination, and for the two most common cold viruses (picornavirus and respiratory syncytial virus) (figure 1). The exposure-response relationship with lower respiratory-tract scores was significant for all virus types together and for respiratory syncytial virus alone, with increases in symptom scores of 0·6 (95% CI 0·01–1·18) and 2·1 (0·52–3·81), respectively with an exposure of more than 14 μg/m³ compared with one of less than 7·5 μg/m³ (figure 1). Trends across the three $NO_2$ tertiles were significant in both cases (all viruses, p=0·05; respiratory syncytial virus, p=0·01). An exposure-response relationship with the severity of reduction in PEF was significant for picornavirus with a reduction of 12 L/min (95% CI –23·6 to –0·80) associated with exposure greater than 14 μg/m³ compared with exposure less than 7·5 μg/m³ (p for trend across tertiles=0·04; figure 1). There was no significant change in lower respiratory-tract symptoms or PEF measurements with high personal $NO_2$ exposure in the week after infection.

Figure 2 shows one child's respiratory symptoms and reductions in PEF in relation to infections detected by RT-PCR.

## Discussion

Our results show an association between increased personal exposure to the air pollutant $NO_2$ and the severity of virus-induced asthma exacerbations in children. High personal $NO_2$ exposure in the week before an upper respiratory infection was associated with either increased severity of lower respiratory-tract symptoms or reductions in PEF for all virus types together, and for two of the common respiratory viruses (picornavirus and respiratory syncytial virus) individually.

The detailed nature of our study design reduced potential bias from misclassification of either pollutant exposure or health outcome; we did a combination of longitudinal assessments of personal $NO_2$ exposure, daily diary card monitoring of upper and lower respiratory-tract symptom scores, and PEF rates and confirmation of the presence of virus or atypical bacterial infection by sensitive RT-PCR. Continuous personal $NO_2$ monitoring was needed to capture exposures accurately immediately before and after the start of an infection. Less frequent monitoring would have been inadequate because of the significant week to week variability in $NO_2$ exposures in children of this age, as reported in our pilot study.[12] Although the measurement of personal $NO_2$ exposure improved the quality of data compared with static indoor $NO_2$ monitoring in the home, we estimated 7-day exposures before an infection by the weighted average of exposure in the two adjacent weeks. This approach would be expected to mask any relation between exposure and asthma exacerbations if exposure was misclassified. Furthermore, the use of a panel of RT-PCR assays identified many more infections than would have been possible with less sensitive conventional diagnostic methods.[15]

We have previously assessed how indoor and outdoor sources contributed to the temporal variation of personal $NO_2$ exposure in children. In a study of 46 children aged 9–11 years, personal $NO_2$ exposure was assessed in parallel with measurements in the child's home, classroom, and school outdoors for three week-long periods. Although personal exposures correlated weakly with concentrations of $NO_2$ recorded in the home, the relation was far from precise. Factors associated with increased personal exposure included the use of gas appliances, cohabitation with smokers, and travel to school by means other than a car. However, together these variables explained less than 30% of the temporal variation in personal exposures.[12] We have also investigated the relation between fluctuations in personal $NO_2$ exposure in this group of Southampton schoolchildren and changes in outdoor $NO_2$ concentrations measured at a fixed site in the centre of Southampton for 32 weeks. Of the 114 children monitored in the study, all but two lived within 20 km of the outdoor monitoring station, and 50 were resident in the city (near major roads). We confirmed that there was great variation from week to week in personal $NO_2$ exposure in children and that little, if any, of this variation was the result of fluctuations in the concentrations of $NO_2$ in outdoor air, even when the analyses were restricted to children residing in the city and those from homes that did not use gas for cooking.[18] Despite any limitation in recording mean personal $NO_2$ exposure per week, the findings from both studies emphasised the need for personal monitoring of $NO_2$ exposure instead of outdoor and indoor measurements to reduce misclassification of true exposure, which could reduce the power of the study and mask any important health effect.

Cigarette smoke emits various oxides of nitrogen, which could explain the low personal $NO_2$ exposures recorded in this study since children who lived with smokers were excluded. However, results of several studies suggest that exposure to domestic cigarette smoke has no significant effects on measured personal $NO_2$ exposure.[12,14,19] We selected children from non-smoking households because of the potential confounding effects of exposure to components of environmental tobacco smoke other than $NO_2$,[20] either by their direct toxic effects, or indirectly by raising concentrations of other indoor pollutants such as particulates[21] and volatile organic compounds. To avoid over-reporting of symptoms and colds by children from homes with a major $NO_2$ source, we did not inform families of the specific aims of our study when they were recruited. Likewise, families were not told the results of exposure monitoring until after data and sample collections were complete.

Although social class is an established risk factor for respiratory infection and symptoms in this age group,[22] adjustment for this variable had no effect on the results of our analyses. To avoid recall bias, diary cards were used to assess respiratory symptoms prospectively and we visited children at home to validate reports of upper respiratory-tract symptoms. Monthly visits were used to provide motivation and encouragement for the children to record diary cards and wear the $NO_2$ diffusion tubes. Although we could not assess compliance at school, to ensure consistency of monitoring we wrote to relevant class teachers to inform them of a child's participation in the study.

There are several potential mechanisms by which $NO_2$ exacerbates asthma in the presence of viral infections.[23] These include direct effects on the upper and lower airways by ciliary dyskinesis,[24] epithelial damage,[25] increases in pro-inflammatory mediators and cytokines,[26] rises in IgE concentration,[27] and interaction with allergens,[28] or indirectly through impairment of bronchial immunity.[11] Results of two in-vitro studies lend support to our observations by showing that $NO_2$ exposure before infection might increase the susceptibility of respiratory epithelial cells to injury from respiratory syncytial virus[29] and concurrent exposure could exacerbate rhinovirus-induced inflammation.[30] The effects could also be mediated by an increase in intercellular adhesion molecule-1 (ICAM-1, the major group rhinovirus receptor) in the presence of air pollution, which could heighten the risk of rhinovirus infection.[31]

Separate analyses have allowed us to show possible biological differences between virus types. It is noteworthy that the trends indicating an association between $NO_2$ exposure and severity of asthma exacerbation were consistent in direction for all viruses, for picornavirus and for respiratory syncytial virus, but not coronavirus (figure 1). Both respiratory syncytial viruses and picornaviruses are known to infect the lower respiratory tract,[32] but there is no evidence to show that this is the case for coronaviruses. The absence of an association with coronavirus could be because the numbers of such infections were small or because they might not interact with $NO_2$ in the way that respiratory syncytial virus or picornavirus do. Or perhaps, they are unable to infect the lower respiratory tract, a suggestion that is supported by previous findings that coronaviruses are much less likely than other virus types to cause a drop in PEF or an increase in lower respiratory-tract symptoms in asthmatic children aged 9–11 years.[6]

Increases in symptom scores were measured on an arbitrary scale, and the size of the increases in virus-induced lower respiratory-tract symptoms was just over half a point for all viruses together. The increase was more than 2 points (the equivalent of transition from none to moderate, or mild to severe symptoms) for respiratory syncytial virus alone. However, although the absolute increase in severity of LRT scores and reductions in PEF were modest, they should be interpreted within the context of several factors. First, the increase in the median lower respiratory-tract symptom scores between the week before and after infection was 1 (arbitrary units), and likewise, the reduction in PEF between the same was 16 L/min. Therefore, the increased severity of these symptom scores represents increases of 60–200%, and reductions in PEF of 75% compared with changes in median scores between the weeks before and after infection for all children. Second, the major site of $NO_2$-induced lung injury is the transitional zone (the area between the terminal bronchioles and alveoli),[33] so conventional pulmonary function tests (such as PEF) that are sensitive to changes in large airway function might be an insensitive method of detecting the responses in small peripheral airways. Third, as most children in this study used $\beta_2$ agonists (87%), symptom severity and decrements in peak expiratory flow might have been diminished and led to the effects of $NO_2$ exposure and virus infections being underestimated if measured during an exacerbation. Although reductions in peak expiratory flow and increases in lower respiratory-tract symptoms were small, because of the ubiquitous nature of $NO_2$ exposure the proportion of children exposed would lead to a large number with attributable morbidity if applied to the general population of asthmatic children.

Other studies to assess the health effects of $NO_2$ have related peak $NO_2$ concentrations during cooking hours to personal $NO_2$ exposures per week. Investigators suggest

that personal $NO_2$ concentrations during cooking hours exceed weekly average personal $NO_2$ exposures by an order of three to five.[34] This calculation would translate a weekly average of 21 $\mu g/m^3$ personal $NO_2$ exposure (as we noted for the highest tertile of exposure) into several hours of exposure to $NO_2$ concentrations in the 60–100 $\mu g/m^3$ range. Likewise, 20% of children who had personal $NO_2$ exposures of more than 100 $\mu g/m^3$ are likely to have had peak concentrations of 300–500 $\mu g/m^3$ at least once. Such concentrations are higher than would be expected from other sources of $NO_2$, and would exceed thresholds judged safe by WHO air quality standards.[17]

That $NO_2$ was not the causative agent but a marker of other unmeasured gas-related indoor pollutants, such as particulates, is possible.[35] Although gas cookers could generate ultrafine particulates, we believe that the effect of particulates from other indoor sources is unlikely because children who lived with smokers (cigarette smoke is a major source of particulates in indoor air) were specifically excluded from the study.

We have shown that higher personal $NO_2$ exposure might increase the severity of virus-induced asthma exacerbations and these findings have potential implications for public health. Severe exacerbations have the largest effect on the health costs associated with asthma, especially those that result in visits to primary-care providers and admissions. In asthmatic children with colds, high $NO_2$ pollution results in more severe exacerbations. These observations (and therefore health costs) could be reduced through control of $NO_2$ pollution.

*Contributors*

A J Chauhan, H M Inskip, C H Linaker, S L Johnston, and S T Holgate designed the study, and did data collection, analysis, and interpretation. S Smith and J Schreiber modified the study design, recruited families, and collected the data.

*Conflict of interest statement*

None declared.

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