Exposure to nitrogen dioxide and the occurrence of bronchial obstruction in children below 2 years

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Background The objective of the investigation was to test the hypothesis that exposure to nitrogen dioxide (NO$_2$) has a causal influence on the occurrence of bronchial obstruction in children below 2 years of age.

Methods A nested case-control study with 153 one-to-one matched pairs was conducted within a cohort of 3754 children born in Oslo in 1992/93. Cases were children who developed >2 episodes of bronchial obstruction or one episode lasting >4 weeks. Controls were matched for date of birth. Exposure measurements were performed in the same 14-day period within matched pairs. The NO$_2$ exposure was measured with personal samplers carried close to each child and by stationary samplers outdoors and indoors.

Results Few children (4.6%) were exposed to levels of NO$_2$ >30 µg/m$^3$ (average concentration during a 14-day period). In the 153 matched pairs, the mean level of NO$_2$ was 15.65 µg/m$^3$ (± 0.60, SE) among cases and 15.37 (± 0.54) among controls (paired t = 0.38, P = 0.71).

Conclusions The results suggest that NO$_2$ exposure at levels observed in this study has no detectable effect on the risk of developing bronchial obstruction in children below 2 years of age.

Keywords Asthma, bronchial obstruction, NO$_2$, car traffic, air pollution, case-control study

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It is important to understand the effect of nitrogen dioxide (NO$_2$) on the occurrence of respiratory disease since exposure to NO$_2$ emissions from car traffic is common. It is necessary to distinguish the risk of developing disease from the risk of triggering symptoms in subjects who already have developed disease. Time-series studies that report increased hospital admissions for respiratory disease with increasing levels of air pollution (including NO$_2$ and other pollutants) cannot separate these risks. On the other hand, information about the risk of disease can be drawn from comparative studies of respiratory disease in samples of subjects living in areas with varying degrees of outdoor air pollution. In general, there is no overall tendency that asthma is more prevalent in polluted areas. However, the many confounding factors that can bias these cross-sectional studies makes interpretation difficult. In a case-control study in Stockholm, Pershagen et al. reported a relative risk (RR) of 2.7 of wheezing bronchitis in girls (but not in boys) exposed to levels of NO$_2$ >70 µg/m$^3$ (expressed as 99th percentiles of 1-hour concentrations) as compared to levels <35 µg/m$^3$, using estimates of NO$_2$ exposure at home addresses based on model estimates of NO$_2$ exposure from continuous measurement stations and from data on the proximity to street traffic. Better estimates of the association between NO$_2$ exposure and respiratory disease can be obtained from studies where the exposure is measured directly in the subject’s immediate environment. A case-control study of 3 and 4 year old children with a first-time diagnosis of asthma in Montreal showed an association with the level of NO$_2$ as measured from personal monitoring badges during a 24-hour period. On the other hand, a cohort study of children living in New Mexico, where NO$_2$ levels were measured at regular intervals indoors, did not show any association to respiratory health. Thus, the question of the causal effect of NO$_2$ on development of bronchial obstruction and other respiratory diseases in children is unresolved, particularly for situations where car traffic is the major source of NO$_2$. 

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In Norway, electricity is the predominant source of energy for indoor appliances, including cooking stoves. The major source of NO2 in Oslo is car traffic. The levels of outdoor NO2 have decreased slightly during 1987-1992. The purpose of this study was to test the hypothesis that NO2 exposure from car traffic in Oslo increases the risk of bronchial obstruction in children <2 years.

Methods

Sample

The Oslo Birth Cohort

The Oslo Birth Cohort, which aims to estimate the associations between indoor and outdoor exposures and obstructive airways disease during the first years of life, consists of children born at Ullevål Hospital in 1992 and at Aker Hospital from 10 March 1992 to 9 March 1993. The main inclusion criteria were: permanent address within the city of Oslo, no plans to move from Oslo in the near future, birthweight >2000 g, no serious illness at birth which might impair respiration, no assisted ventilation or oxygen therapy after 6 hours of life, at least one family member able to speak and write Norwegian, at least one biological parent living with the child, and no known drug abuse in the family. A total of 3754 (76%) of the 4973 eligible children entered the study. Questionnaire information on the child's health and environmental exposures were collected at birth, and when the child was 6 months (follow-up rate 95%), 12 months (92%), 18 months (92%) and 24 months (81%).

Cases and controls

Cases were children who developed ≥2 episodes of bronchial obstruction during the first 2 years of life or who experienced one episode lasting >4 weeks. Participating families were instructed to contact the project paediatrician when their child had symptoms suggestive of obstructive airways disease. Also, outpatient clinics were instructed to refer children to the project paediatrician. The parents were provided with cards to be filled in by physicians whenever the child was examined for any respiratory symptoms. Additionally, questionnaires with positive responses to questions on respiratory symptoms were extracted and parents contacted for verification. At least one of the episodes of bronchial obstruction had to be diagnosed by physicians by direct observation, and the guidelines for physicians emphasized that at least three out of five symptoms or signs (wheezing, chest recession, rhonchi during auscultation, forced expiration, and rapid breathing) should be observed. The final diagnosis of bronchial obstruction was made by a consensus decision of three senior paediatricians based on data from the paediatric clinical examination and from family physician, hospital, and outpatient records.

The child born next in time to the index case was selected as the control in that pair, provided there was no history suggestive of obstructive disease. For the whole cohort, 304 cases were identified. Among these, 256 were still living in Oslo (and had not changed address within the past 3 months) at the time of diagnosis, and were candidates for home visits. In three pairs, parents were not willing to have home visits and two other pairs were not visited for other reasons. Such visits were not made in the summer months (June, July and August). For economic reasons, NO2 measurements were terminated after measurements had been performed for 186 pairs. For one or both members of 33 pairs a successful measurement of NO2 was not obtained for the personal sampler, mainly due to loss of the sampler or water exposure to the sampler. Thus, the analyses of NO2 measurements are restricted to 153 matched pairs.

Variables

NO2 measurements

When a case was diagnosed and a control child selected, both were contacted to plan parallel visits. The measurements were always performed in the same time period for the matched pairs. Average NO2 concentrations were determined using passive samplers (Palms diffusion tubes). With triethanolamine as adsorbing medium (Passam, Männdorf, Switzerland). Samplers were placed on the child for 2 weeks. In order to prevent samplers from contact with water or from manipulation by the child, the samplers were alternatively attached to equipment in close proximity of the child. In addition, passive samplers were placed on walls in the kitchen, the bedroom of the child and in the main living room about 1.7–1.8 m above ground level. For children who attended day care, a passive sampler was located on an indoor wall at the day-care site. After exposure of the sampler had been terminated, the total amount of absorbed NO2 was extracted and determined colorimetrically at 540 nm after addition of colour reagent. The NO2 concentrations in μg/m3 were calculated according to Fick's equation. The limit of detection is 2 μg/m3 for an exposure time of 2 weeks. The overall precision was determined from triplicate analyses of side-by-side replicate samples (n = 11). The coefficient of variation was 5% at 47 μg NO2/m3. In the statistical analyses, NO2 concentrations were treated as a continuous and as a categorical variable (quintiles of the combined distribution of cases and controls).

Car traffic

One question, taken from the birth questionnaire, was used to determine the exposure of the child to car traffic: 'What is the distance from your house to the nearest main road?' (>100 m: 50–100 m: 10–49 m: <10 m).

Maternal educational level

From the questionnaire, maternal education was categorized as low (<12 years), medium (12–15 years) and high (>15 years).

Smoking habits

The child was considered to be exposed to environmental tobacco smoke if the mother responded in the birth questionnaire that she or other people in the household smoked.

Birthweight

Birthweight in g as recorded in the hospital flies was used. The variable was used as a continuous variable.

Asthma in parents

This variable is based on the responses in the birth questionnaire to the question of whether any of the parents has or has ever had asthma.

Length of breastfeeding

This variable is based on information on the endpoint of breastfeeding as reported in the 6-month and 12-month questionnaires. For the present purpose the variable is dichotomized as <6 months and >6 months of breastfeeding.
NITROGEN DIOXIDE EXPOSURE AND BRONCHIAL OBSTRUCTION

Statistical methods
The NO$_2$ levels were compared between cases and controls using paired $t$-tests and the determinants of NO$_2$ level were studied with correlation and analysis of variance, employing the PC-version of SPSS. Conditional logistic regression, employing Egret, was used to estimate odds ratios (OR) for bronchial obstruction according to levels of the independent variables.

Results
NO$_2$ from personal samplers
The NO$_2$ concentrations, obtained from personal monitoring of the 306 children in 153 matched case-control pairs, ranged from <2 to 59.3 µg/m$^3$ (mean 15.5, SD 7.0, and median 14.2 µg/m$^3$). Figure 1 shows the distribution of NO$_2$ concentrations for cases and controls. The mean NO$_2$ concentrations were 15.65 µg/m$^3$ (SE 0.60) for cases and 15.37 µg/m$^3$ (SE 0.54) for controls (paired $t = 0.38$, $P = 0.71$). There was no association with case-control status (OR = 1.007, 95% CI: 0.973–1.042), when the NO$_2$ concentration was used as a continuous measure in conditional logistic regression. Conditional logistic regression, employing the PC-version of SPSS, was used to estimate odds ratios (OR) for bronchial obstruction as shown in Table 2. The mean (± SE) concentration measured on the outside wall was higher (gender * NO$_2$) as independent variables and bronchial obstruction as the dependent, no significant interaction was found (OR = 1.068, 95% CI: 0.990–1.152).

Distance from main road
Distance from main road had no significant association with bronchial obstruction as shown in Table 2. The mean (± SE) NO$_2$ concentration measured on the outside wall was higher for homes <10 m from a main road (30.0 µg/m$^3$ ± 1.8) than for homes 10–49 m (24.8 µg/m$^3$ ± 1.2), 50–100 m (25.6 µg/m$^3$ ± 1.2), or >100 m away (23.3 µg/m$^3$ ± 1.0), $F = 4.74$, 3 d.f., $P < 0.01$. For the personal sampler NO$_2$ concentrations ($F = 0.79$, 3 d.f., $P = 0.50$) and for the NO$_2$ measured in the main living room ($F = 0.91$, 3 d.f., $P = 0.44$), no significant association to distance from road was observed.

NO$_2$ from stationary samplers
Table 3 shows the distributions of NO$_2$ according to place of measurement for cases and controls pooled. The outdoor measure was significantly higher than the indoor measures, which showed little variability in mean values. The correlations between indoor measurements (kitchen, sleeping room and living room) are above 0.85, while the correlation between the personal sampler concentration and the indoor concentrations range from 0.52 to 0.77 (Table 4). The correlations between the outdoor measurement and the indoor measures range from 0.51 to 0.61. There was no association between the concentrations of NO$_2$ outside (OR = 0.995, 95% CI: 0.971–1.019, using 149 matched case-control pairs) or concentration of NO$_2$ in the main living room (OR = 1.014, 95% CI: 0.975–1.054, using 144 matched case-control pairs) and bronchial obstruction.

Table 1 Mean birthweight and distribution of gender, parental history of asthma, exposure to tobacco smoke, length of breastfeeding, and length of maternal education for children exposed to concentrations of NO$_2$ below and above the median value of 14.2 µg/m$^3$

<table>
<thead>
<tr>
<th>Gender</th>
<th>Below median NO$_2$</th>
<th>Above median NO$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SE)</td>
<td>Mean (SE)</td>
</tr>
<tr>
<td>Boy</td>
<td>3533 (41)</td>
<td>3636 (41)</td>
</tr>
<tr>
<td>Girl</td>
<td>86 (56)</td>
<td>83 (54)</td>
</tr>
</tbody>
</table>

Table 2 Mean birthweight and distribution of gender, parental history of asthma, exposure to tobacco smoke, length of breastfeeding, and length of maternal education for children exposed to concentrations of NO$_2$ below and above the median value of 14.2 µg/m$^3$

<table>
<thead>
<tr>
<th>Gender</th>
<th>Below median NO$_2$</th>
<th>Above median NO$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SE)</td>
<td>Mean (SE)</td>
</tr>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Boy</td>
<td>86 (56)</td>
<td>83 (54)</td>
</tr>
<tr>
<td>Girl</td>
<td>67 (44)</td>
<td>70 (46)</td>
</tr>
</tbody>
</table>

Table 3 shows the distributions of NO$_2$ according to place of measurement for cases and controls pooled. The outdoor measure was significantly higher than the indoor measures, which showed little variability in mean values. The correlations between indoor measurements (kitchen, sleeping room and living room) are above 0.85, while the correlation between the personal sampler concentration and the indoor concentrations range from 0.52 to 0.77 (Table 4). The correlations between the outdoor measurement and the indoor measures range from 0.51 to 0.61. There was no association between the concentrations of NO$_2$ outside (OR = 0.995, 95% CI: 0.971–1.019, using 149 matched case-control pairs) or concentration of NO$_2$ in the main living room (OR = 1.014, 95% CI: 0.975–1.054, using 144 matched case-control pairs) and bronchial obstruction.

Figure 1 Frequency (percentage of cases and controls) distribution of 14-day average concentration of NO$_2$ (µg/m$^3$) as measured from personal samplers, for cases and controls.

Parents' smoking

<table>
<thead>
<tr>
<th>Parental smoking</th>
<th>Below median NO$_2$</th>
<th>Above median NO$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>22 (14)</td>
<td>21 (14)</td>
</tr>
<tr>
<td>No</td>
<td>131 (86)</td>
<td>132 (86)</td>
</tr>
</tbody>
</table>

Exposure to tobacco smoke

<table>
<thead>
<tr>
<th>Exposure to tobacco smoke</th>
<th>Below median NO$_2$</th>
<th>Above median NO$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>49 (32)</td>
<td>66 (43)</td>
</tr>
<tr>
<td>No</td>
<td>104 (68)</td>
<td>86 (57)</td>
</tr>
</tbody>
</table>

Length of breastfeeding

<table>
<thead>
<tr>
<th>Length of breastfeeding</th>
<th>Below median NO$_2$</th>
<th>Above median NO$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 months</td>
<td>52 (34)</td>
<td>61 (42)</td>
</tr>
<tr>
<td>&gt;6 months</td>
<td>99 (66)</td>
<td>85 (58)</td>
</tr>
</tbody>
</table>

Length of maternal education

<table>
<thead>
<tr>
<th>Length of maternal education</th>
<th>Below median NO$_2$</th>
<th>Above median NO$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12 years</td>
<td>53 (35)</td>
<td>64 (42)</td>
</tr>
<tr>
<td>12–15 years</td>
<td>16 (11)</td>
<td>22 (15)</td>
</tr>
<tr>
<td>&gt;15 years</td>
<td>84 (55)</td>
<td>66 (43)</td>
</tr>
</tbody>
</table>
the opportunity of performing long-term exposure measurements which can detect occasions of high exposure. It is possible that our measurements have not captured children with rare, high exposures. The inconsistency between our findings and the findings in Stockholm should be seen in this light.

For the questions regarding proximity to car traffic, the exposure was determined by questionnaires in advance of any knowledge of the episodes of bronchial obstruction. This exposure is imprecise, since the parental opinion of what constitutes a main road will differ. However, the question may not be invalid since the highest NO$_2$ concentrations, measured outdoors, were found for families living <10 m from a main road.

The level of exposure (the mean NO$_2$ concentration for a 14-day sampling period was 15.5 pg/m$^3$) was relatively low, compared to international guidelines for NO$_2$ exposure. Recently, it has been suggested that the 1-hour guideline should be 200 pg/m$^3$, and the annual guideline should be 40 pg/m$^3$. A recent study of four Nordic cities (Kuopio in Finland, Malmö and Umeå in Sweden and Oslo, Norway) showed that Oslo had the highest levels of NO$_2$. The mean 24-hour outdoor NO$_2$ concentration in winter was 49 pg/m$^3$ in urban parts of Oslo while it was 20 pg/m$^3$ in suburban parts. In that study, which focused on school-children, no association between asthma attacks and urban residency or between asthma attacks and NO$_2$ level was found. In a study of schoolchildren living close
to motorways in The Netherlands, the school room NO\textsubscript{2} concentrations ranged from 9 to 33 \textmu g/m\textsuperscript{3}, and no clear associations between NO\textsubscript{2} levels and lung function was found.\textsuperscript{13} On the other hand, the study found associations between truck traffic, particulate matter (PM\textsubscript{10}) and lung function,\textsuperscript{15} suggesting that particles from diesel exhaust may be of greater relevance for lung disease than exhaust from ordinary car traffic.\textsuperscript{16}

Studies on school-children are not directly comparable to our study, since we used recurrent or long-lasting bronchial obstruction in children under 2 years as our dependent variable. In a follow-up study of children during the first 6 years of life, it was concluded that: 'the majority of infants with wheezing have transient conditions associated with diminished airways and do not have increased risks of asthma or allergies later in life'.\textsuperscript{17}

To our knowledge, there are no comparable cohort studies of newborn children where NO\textsubscript{2} exposure from car traffic is the main exposure. However, a cohort study of 823 infants in New Mexico, with gas cooking stoves as the principal source of NO\textsubscript{2} exposure for small children, found no association between NO\textsubscript{2} levels and wheezing in young children during the first 18 months of life.\textsuperscript{5} In line with this result, a Swiss study with 6-week monitoring of indoor and outdoor NO\textsubscript{2} in houses with children below 4 years, did not find evidence for an effect of NO\textsubscript{2} on the incidence of breathing difficulties.\textsuperscript{18}

In conclusion, exposure to NO\textsubscript{2} as measured in this matched case-control study does not appear to increase the risk of bronchial obstructions in children below 2 years of age.

Acknowledgements

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