ORIGINAL ARTICLE

NO_2, as a marker of air pollution, and recurrent wheezing in children: a nested case-control study within the BAMSE birth cohort

G Emenius, G Pershagen, N Berglind, H-J Kwon, M Lewné, S L Nordvall, M Wickman

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See end of article for authors' affiliations

Correspondence to: Dr G Emenius, Department of Environmental Health, Norrbacka 3rd floor, Karolinska Hospital, SE-171 76 Stockholm, Sweden; gunnel.emenius@smd.sll.se

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Aims: To investigate the association between air pollution, including with NO_2, and recurrent wheezing during the first two years of life.
Methods: A birth cohort (BAMSE) comprised 4089 children, for whom information on exposures, symptoms, and diseases was available from parental questionnaires at ages 2 months, and 1 and 2 years. NO_2 was measured during four weeks in and outside the dwellings of children with recurrent wheezing and two age matched controls, in a nested case-control study (540 children).
Results: Conditional logistic regression showed an OR of 1.60 (95% CI 0.78 to 3.26) among children in the highest quartile of outdoor NO_2 exposure in relation to those in the lowest quartile, adjusted for potential confounders. The corresponding OR for indoor NO_2 was 1.51 (95% CI 0.81 to 2.82). An interaction with environmental tobacco smoke (ETS) was indicated with an OR of 3.10 (95% CI 1.32 to 7.30) among children exposed to the highest quartile of indoor NO_2 and ETS. The association between NO_2 and recurrent wheezing appeared stronger in children who did not fulfil the criteria for recurrent wheezing until their second year.
Conclusions: Although the odds of increased recurrent wheezing are not statistically significantly different from one, results suggest that exposure to air pollution including NO_2, particularly in combination with exposure to ETS, increases the risk of recurrent wheezing in children.

Nitrogen dioxide (NO_2) is an irritant gas, produced as a by-product of high temperature combustion. Major outdoor sources include motor vehicles and fossil fuel power plants. Gas burning appliances, including gas stoves, and environmental tobacco smoke constitute important indoor sources.

Epidemiological studies have shown an association between traffic related air pollution, as well as indoor pollutants including NO_2, and respiratory diseases in children.[1–6] For example, the use of gas stoves has been associated with an increased risk of obstructive respiratory disease in children.[7–9] However, the evidence is conflicting, even when based on actual NO_2 measurements.[2 8 10] Some results indicate that girls are more susceptible than boys.[7 11 12] It has also been hypothesised that exposure to NO_2 aggravates asthma symptoms, but that it does not increase the incidence of asthma and other allergic diseases among children.[5 13] Most of the studies have been retrospective, with imprecise and possibly biased exposure assessment as well as with uncertain information on potential confounders.

The BAMSE project (B = children, A = allergy, M = environment, S = Stockholm, E = epidemiology) is a prospective birth cohort study based in certain areas of northern Stockholm, with the aim to study the influence of environmental factors on the development of recurrent wheezing, asthma, and atopic diseases in childhood. This part of the study focuses on the possible association between NO_2 exposure and recurrent wheezing during the first two years of life, and uses a nested case-control design.

MATERIAL AND METHODS

Study subjects

The BAMSE cohort study design is described in detail elsewhere.[14] Briefly, the cohort comprises 4089 children born between 24 February 1994 and 20 November 1996 in certain parts of central and northwestern Stockholm. Both urban and suburban districts were represented, including areas with varying types of traffic exposure, different types of buildings, dwellings with and without gas stoves for cooking, as well as differences in socioeconomy. Access to a community population register ensured that the parents of all children born in the area during the period under study could be approached.

When the children were 2 months old (median age), their parents answered a questionnaire on housing characteristics, various indoor environmental exposures, and atopic diseases affecting the child's parents. The questions have been used in earlier studies.[15 16] When the children were 1 and 2 years old the parents answered symptom questionnaires. At this time point children with recurrent wheezing according to our definition and two healthy controls, matched by day of birth, were identified from the cohort. The response rate was high: 93% answered all three questionnaires. Our definition of recurrent wheezing stipulated three or more reported episodes of wheezing not associated with common colds after 3 months of age, combined with either symptoms of bronchial hyperreactivity (cough during sleep, play and laughter, etc) or inhaled steroid treatment. Furthermore, to be included in the case-control study, both cases and controls had to reside in the same dwelling as when they were born.

In total, 321 children with recurrent wheezing according to the definition were identified, but only 181 of these, 65 girls and 116 boys, still lived in their first home at the time of recruitment to the case-control study. Controls were matched to cases on day of birth and the control group included 359 children (189 girls and 170 boys). Two hundred and ninety four of the 540 children were recruited at the age of 1 year, including 98 cases and 196 controls. Three controls, selected at 1 year of age fulfilled the criteria of recurrent wheezing at the age of 2, and were also included as cases at that age.

Main messages

- Results suggest that exposure to air pollution, including NO_2, increases the risk of recurrent wheezing in children, particularly in combination with exposure to environmental tobacco smoke.

Residential areas were classified into three different groups, mainly based on geographical location and building type. Areas classified as ''urban'' had narrow streets and mainly old block buildings with enclosed courtyards, ''semi-urban'' had blocks of flats or terraced houses, and ''suburban areas'' had predominantly single family houses (bungalows, detached, semi-detached, etc). According to this classification, 129 children (23.9%) lived in ''urban areas'', 274 (50.7%) in ''semi-urban areas'', and 137 (25.4%) in ''suburban areas''. The distance between the city area and the most distant suburban area is about 25 km.

Environmental measurements

In the first winter season following recruitment in the case-control study, the dwelling of each child was inspected by an environmental health officer and data on building construction, ventilation system, water damage, etc were collected using a standardised form. Furthermore, parents answered questions about renovations of the dwelling and about lifestyle factors, such as smoking, household pets, etc.

During a four week period (mean 28 days, range 26–31), NO_2 was measured indoors, in the main living room at about 1.7–1.8 m above the floor, and outdoors, outside the window of this room, using a passive method (Palmes tube).[17 18] To assess the precision, double measurements were performed at random in some of the 540 dwellings (132 (24.4%) of dwellings for indoor NO_2 and 121 (22.4%) for outdoor NO_2). The intra-class correlation coefficient for both indoor and outdoor NO_2 was 0.99.[19] Furthermore, a comparison was made with NO_2 levels recorded by central urban monitors using the chemiluminescent nitrogen oxide analyser, model AC 31 M (Environnement SA, France) and DOAS (differential optical absorption spectroscopy), model AR500 (OPSIS AB, Sweden).[20 21]

Indoor air exchange rate per hour (ACH) was measured simultaneously in all dwellings during the same period as the NO_2 measurements, using a passive tracer gas technique.[22] The method is described in detail elsewhere.[23 24]

Statistical analysis

Statistical analysis was carried out with STATA software.[25] A conditional logistic multivariate regression model was used to control for potential confounding factors. Crude and adjusted odds ratios (OR) and 95% confidence intervals (CI) were estimated. Cases and controls were matched for day of birth. Analyses were adjusted for gender and heredity (no/yes), maternal age (median, $<26/\geqslant 26$ years), maternal smoking ($\geqslant$1 cigarette/day during pregnancy and/or when answering the questionnaire, at median age 2 months of their child), for any breast feeding (<6 months/$\geqslant 6$ months), and building age (1939 or earlier, 1940–75, 1976 or later). Heredity was defined as doctor diagnosed asthma and/or rhinitis together with allergy to furred pets or to pollen, in one or both parents. When stratifying for gender the matched data sets were dissolved and unconditional logistic regression was used adjusted as above. In a separate regression analysis an interaction term between NO_2 and environmental tobacco smoke (ETS) was calculated. ETS was defined from the dichotomous question ''do you have any smoker in the family'', asked by the inspector when investigating the home. A p value of <0.05 for the interaction coefficient was considered statistically significant, indicating different effects of NO_2 exposure in children exposed and unexposed to ETS. The Spearman rank correlation coefficient was calculated for comparison of measured outdoor and indoor levels of NO_2, and for the correlation between indoor NO_2 levels and ventilation rate, presented as air change rate per hour (ACH).

Measurements were originally performed for all children in the case-control study. Due to technical failure, some results of NO_2 measurements were lost (7.2% (40/540) of the indoor NO_2 measurements and 7.7% (42/540) of the outdoor NO_2 measurements). In order to reduce the loss of efficiency we used a multiple imputation method, in which we first generated five copies of the original data set; each of those with missing values were replaced by values randomly generated by the imputation model.[26] After performing identical conditional logistic regressions on each of five data sets, the results were combined to produce overall estimates and standard errors. Multiple imputation was performed using NORM.[27]

To compensate for the fact that NO_2 was measured at each site only once (albeit over a four week period), and thus was influenced by weather conditions during that time period, an adjustment factor was calculated to estimate the average outdoor wintertime exposure. Using daily measurements from three central urban background monitors, the adjustment factor was calculated as the difference between the average NO_2 level of each measurement period, and the average NO_2 level for the entire period. The adjustment factor was then subtracted from each measured value, resulting in a value adjusted for time period.

RESULTS

Table 1 presents the variables used in the regression model, including gender, allergic heredity, maternal age and smoking, duration of breast feeding, and building age. The association between building related exposure such as building age and construction will be further explored in a separate paper.

The mean NO_2 level for all outdoor measurements was 21.8 $\mu g/m^3$ (SD 8.5). Levels were highest in urban areas and decreased in areas less exposed to traffic; this was true both for outdoor and indoor levels (table 2). Mean urban background NO_2 during the four winter seasons, measured with three monitors at roof level, was 26.0 $\mu g/m^3$ (SD 9.9), whereas corresponding mean outdoor NO_2 levels for home measurements within the same area, measured at different levels from the ground, was 31.5 $\mu g/m^3$ (SD 6.0). Gas stoves were mainly present in buildings erected before 1940, which predominated in the urban area. Within this area, mean levels of NO_2 in homes where gas stoves were used was 22.6 $\mu g/m^3$, compared with 16.4 $\mu g/m^3$ in homes without gas. In homes where gas was not used and where no family member smoked, a correlation was seen between measured indoor and outdoor levels of NO_2 ($r = 0.69$, $p < 0.001$). For dwellings equipped with a gas stove there was no such correlation ($r = 0.13$, $p = 0.43$, smokers included; and $r = 0.06$, $p = 0.75$, when smokers were excluded). A weak positive correlation was also found for air change rate (ACH) and indoor NO_2 levels in dwellings without a gas stove or smoking family members ($r = 0.34$, $p < 0.001$), whereas no correlation could be shown for dwellings with gas stoves ($r = -0.04$, $p = 0.77$).

For the whole group of children, no clear association was seen between exposure to NO_2 and recurrent wheezing during the first two years. However, there was a tendency towards an increased risk for the highest quartile of exposure, both for indoor and outdoor measurements (OR

Table 1 OR and 95% confidence intervals for recurrent wheezing in children up to 2 years of age, related to variables used for adjustment in the analysis of the BAMSE case-control study

Exposure	Cases	Controls	OR_{crude}	95% CI	OR_{adj}*	95% CI
Gender (boy vgirl)	116	170	2.03	1.38 to 2.98	2.13	1.40 to 3.25
Heredity (yes v no)	72	109	1.47	1.01 to 2.13	1.52	1.01 to 2.28
Maternal age (<26/>26)	28	42	1.37	0.80 to 2.31	1.13	0.63 to 2.02
Maternal smoking (yes v no)	41	53	1.69	1.02 to 2.74	1.53	0.88 to 2.66
Breast feeding(>6 v <6 month)	137	295	0.64	0.40 to 1.05	0.70	0.41 to 1.19
Building age†						
1940–75	83	153	1.61	1.00 to 2.56	1.69	1.01 to 2.89
1975 onwards	63	104	1.81	1.09 to 2.99	1.86	1.05 to 3.27

*Adjusted for remaining variables in the table.
†Reference category; buildings erected before 1940.

1.51, 95% CI 0.81 to 2.82; and OR 1.60, 95% CI 0.78 to 3.26, respectively; table 3). Analyses performed with the imputed data set did not change odds ratios essentially, compared with results based on the measured data sets, but the confidence intervals became narrower (data not presented). Nor did analyses using data based on calculated annual average mean exposure change the OR markedly.

Stratification for age when children were included in the case-control study indicated a dose-response trend, particularly for children who fulfilled the criterion of recurrent wheezing at 2 years of age (table 4). Again, the findings were consistent after adjustment for annual average NO_2 levels. No consistent indications of gender related effects were found (not in table).

Conditional logistic regression analysis using continuous outdoor NO_2 levels resulted in an odds ratio of 1.20 (95% CI 0.90 to 1.60) for an increase of 10 $\mu g/m^3$ of NO_2. Corresponding analysis of the association between indoor NO_2 levels and recurrent wheezing gave an odds ratio of 1.06 (95% CI 0.74 to 1.52) for an increase of 10 $\mu g/m^3$ of NO_2. For children taken ill after the age of 1, outdoor OR was 1.73 (95% CI 1.05 to 2.82) and indoor OR 0.92 (95% CI 0.54 to 1.60), respectively, for an increase of 10 $\mu g/m^3$ of NO_2.

An interaction between indoor NO_2 exposure and ETS, defined as ''any smoking family member'' was found in relation to recurrent wheezing ($p = 0.04$). When dividing NO_2 exposure on the 4th quartile, OR for exposure to both NO_2 and ETS was 3.10 (95% CI 1.32 to 7.30), compared with children unexposed to ETS and in the lower quartile of NO_2. OR for children exposed to higher NO_2 levels only was 1.09 (95% CI 0.62 to 1.91) and OR for exposure to ETS only was 0.96 (95% CI 0.51 to 1.83) (tables 5 and 6). The corresponding interaction for outdoor NO_2 levels did not reach statistical significance ($p = 0.15$), but the OR for exposure to both outdoor NO_2 and ETS was 3.60 (95% CI 1.37 to 9.45), compared with children in the lowest exposure category for both agents. No marked differences in risk estimates were obtained when no adjustment was made for mothers smoking during pregnancy.

Gas was used for cooking only. When the children were newborn 49 dwellings were equipped with a gas stove, but at the time of investigation gas was used in 46 of 540 homes (8.52%). Only four of the homes with a gas stove were equipped with separate stove ventilation connected to a mechanical exhaust ventilation system, and another 22 kitchens had carbon filter ventilators. The adjusted OR for recurrent wheezing associated with the use of a gas stove was 1.72 (95% CI 0.77 to 3.87), without any differences in gender. No difference appeared when analysing presence of a gas stove in the home when the children were newborn, compared with use of a gas stove at the time of the investigation of the home.

DISCUSSION

This study focuses on the association between exposure to air pollution, including NO_2, and recurrent wheezing in children up to 2 years of age. Effects of outdoor and indoor exposure were evaluated and a relation between exposure to NO_2 and recurrent wheezing is suggested. When the material was stratified for age, the association between wheezing and NO_2 exposure appeared stronger among children who did not fulfil the criteria until the age of 2. This might be explained by reduced misclassification of disease in the older children, or it may be that prolonged exposure time is required for ambient air pollution to induce recurrent wheezing at those exposure levels. It should be noted that NO_2 is used as an indicator of air pollution exposure and other components may be of importance, such as airborne particulate matter

Table 2 NO_2 levels in and characteristics of the homes of children in the BAMSE case-control study

Dwelling location	Building age	Number of dwellings (cases)*	Number of single family houses	Number with natural draft†	Mean ACH‡	Number with gas stoves	Mean NO_2 indoor§, $\mu g/m^3$ [range]	Mean NO_2 outdoor§, $\mu g/m^3$ [range]
Urban	1939 or earlier	111 (30)	0	83 (22)	0.60	42 (12)	18.3	31.5
	1940–75	7 (4)	0	1 (1)	0.68	0	[8.0–45.1]	[17.9–46.7]
	1976 or later	11 (4)	0	1 (0)	0.75	0		
Semi-urban	1939 or earlier	14 (2)	2 (0)	7 (2)	0.57	2 (1)	12.2	21.6
	1940–75	172 (60)	1 (0)	29 (8)	0.68	1 (0)	[4.4–25.1]	[8.7–36.4]
	1976 or later	88 (33)	4 (2)	0	0.77	0		
Suburban	1939 or earlier	12 (3)	11 (2)	12 (3)	0.71	1	8.1	13.7
	1940–75	57 (19)	57 (19)	47 (16)	0.43	0	[2.3–21.1]	[6.0–29.0]
	1976 or later	68 (26)	59 (21)	3 (1)	0.55	0		

*Number of cases given in parenthesis throughout table.
†Natural draft ventilation—that is, ventilation without support by fans.
‡Air change rate per hour.
§Mean NO_2 levels are presented for the entire areas; range of concentrations in individual measurements given in brackets.

Table 3 Odds ratios and 95% confidence intervals for recurrent wheezing in children up to the age of 2, in the BAMSE case-control study, in relation to measured and calculated annual outdoor and indoor NO_2 exposure

			Concentration of NO_2 ($\mu g/m^3$)						
			<25th centile	25–50th centile		51–75th centile		>75th centile	
	Controls	Cases	OR	OR*	95% CI	OR*	95% CI	OR*	95% CI
Indoor exposure†									
Based on measurements:									
In quartiles	330	170	1	0.96	0.52 to 1.77	1.08	0.57 to 2.03	1.51	0.81 to 2.82
Exposed to >75th centile *v* lower			1					1.48	0.91 to 2.42
Outdoor exposure‡									
Based on measurements:									
In quartiles	332	168	1	0.76	0.42 to 1.36	0.80	0.43 to 1.47	1.60	0.78 to 3.26
Exposed to >75th centile *v* lower			1					1.92	1.05 to 3.53
Based on calculated annual average exposure:									
In quartiles	332	171	1	0.73	0.41 to 1.31	0.71	0.38 to 1.34	1.74	0.87 to 3.49
Exposed to >75th centile *v* lower			1					1.92	1.05 to 3.53

*Adjusted for gender, heredity, maternal age and smoking, any breast feeding, and building age.
†Indoor NO_2 exposure, range within different quartiles: <8.4 $\mu g/m^3$; 8.4–11.6 $\mu g/m^3$; 11.7–15.6 $\mu g/m^3$; and >15.6 $\mu g/m^3$, respectively.
‡Outdoor NO_2 exposure, range within different quartiles: <14.8 $\mu g/m^3$; 14.8–21.3 $\mu g/m^3$; 21.4–28.4 $\mu g/m^3$; and >28.4 $\mu g/m^3$, respectively.

and ozone. However, it is also worth noting that the NO_2 levels measured in our study lie well below the current European guidelines for annual exposure (40 $\mu g/m^3$).[28]

In contrast, a Norwegian study on bronchial obstruction in children, as well as a study of childhood asthma in four regions of Scandinavia (PEACE project), by Forsberg *et al* did not show any consistent pattern in the relation between air pollution, including NO_2, and asthma.[4 29] However, a newly presented international collaborative study on the impact of traffic related air pollution and asthma (TRAPCA), in turn, indicates an association between traffic related air pollution and cough. In contrast to our results, the associations between symptoms and NO_2 exposure were found to be weaker for the second year of life.[30] The reasons for the apparent inconsistency between different study results remain unclear.

The suggested increase in risk of recurrent wheezing was mainly confined to the children most strongly exposed to NO_2 and who in addition had at least one smoking family member. A significant interaction could be shown for children exposed to the upper quartile of indoor NO_2 levels in combination with any smoking family member. A similar interaction was also seen between outdoor levels of NO_2. We are not aware of any other studies that provide information on the interaction between NO_2 and ETS on recurrent wheeze or asthma. Our results also suggest that a rather low degree of exposure to air pollution, including NO_2, may be harmful in combination with other environmental factors.

Nitrogen dioxide was measured during a four week period, approximately the same period for the sets of matched cases and their respective controls. The limited measuring period could result in substantial misclassification of long term exposure. However, analysis of the estimated annual average exposure levels confirmed the results obtained with the measured data. We measured NO_2 at fixed sites, in and outside the dwellings, respectively. Because of this, imprecise assessment of child exposure could have occurred due to the position of the child's room in relation to the street and the living room, where NO_2 had been measured. Further, some studies indicate that exposure estimated by personal sampling is better correlated to indoor NO_2 levels than to outdoor levels.[31 32] It may thus be expected that exposure estimates

Table 4 Odds ratios and 95% confidence intervals for recurrent wheezing in children in the BAMSE case-control study, classified as having recurrent wheezing at 1 year and 2 years of age, respectively, in relation to measured and calculated annual outdoor and indoor NO_2 exposure

	Concentration of NO_2 ($\mu g/m^3$)								
			<25th centile	25–50th centile		51–75th centile		>75th centile	
	Controls	Cases	OR	OR*	95%CI	OR*	95%CI	OR*	95%CI
Indoor exposure†									
Measured data:									
Age 1 year	176	90	1	0.97	0.42 to 2.24	1.17	0.46 to 2.99	1.42	0.59 to 3.43
Age 2 year	154	88	1	0.79	0.29 to 2.08	0.97	0.38 to 2.48	1.31	0.49 to 3.47
Outdoor exposure‡									
Measured data:									
Age 1 year	174	89	1	0.88	0.38 to 2.03	0.35	0.14 to 0.93	1.48	0.53 to 4.14
Age 2 year	156	79	1	0.93	0.36 to 2.44	1.85	0.72 to 4.76	2.81	0.93 to 8.46
Calculated annual average exposure:									
Age 1 year	174	89	1	1.08	0.49 to 2.39	0.38	0.14 to 1.02	1.88	0.65 to 5.43
Age 2 year	156	79	1	0.79	0.29 to 2.17	1.50	0.54 to 4.14	2.27	0.82 to 6.30

*Adjusted for gender, heredity, maternal age and smoking, any breast feeding, and building age.
†Indoor NO_2 exposure, range within different quartiles: <8.4 $\mu g/m^3$; 8.4–11.6 $\mu g/m^3$; 11.7–15.6 $\mu g/m^3$; and >15.6 $\mu g/m^3$, respectively.
‡Outdoor NO_2 exposure, range within different quartiles: <14.8 $\mu g/m^3$; 14.8–21.3 $\mu g/m^3$; 21.4–28.4 $\mu g/m^3$; and >28.4 $\mu g/m^3$, respectively.

Table 5 Odds ratios and 95% confidence intervals for recurrent wheezing in children exposed both to the upper quartile of NO_2 levels and environmental tobacco smoke, compared with double unexposed children; exposure to indoor NO_2

	Below 4th quartile				Above 4th quartile				Exposure to ETS—independent of NO_2			
Exposure to ETS	**Cases**	**Controls**	**OR***	**95% CI**	**Cases**	**Controls**	**OR***	**95% CI**	**Cases**	**Controls**	**OR***	**95% CI**
Not exposed	90	188	1		28	63	1.09	0.62 to 1.91	118	251	1	
Exposed	33	63	0.96	0.51 to 1.83	19	15	3.10	1.32 to 7.30	52	78	1.31	0.75 to 2.30
Exposure to NO_2—independent of ETS	123	251	1		47	78	1.47	0.91 to 2.37				

*Adjusted for gender, heredity, maternal age and smoking during pregnancy, breast feeding, and building age.

Table 6 Odds ratios and 95% confidence intervals for recurrent wheezing in children exposed both to the upper quartile of NO_2 levels and environmental tobacco smoke, compared with double unexposed children; exposure to outdoor NO_2

	Below 4th quartile				Above 4th quartile				Exposure to ETS—independent of NO_2			
Exposure to ETS	**Cases**	**Controls**	**OR***	**95% CI**	**Cases**	**Controls**	**OR***	**95% CI**	**Cases**	**Controls**	**OR***	**95% CI**
Not exposed	87	184	1		30	67	1.58	0.84 to 2.96	117	251	1	
Exposed	38	63	1.08	0.58 to 2.02	13	15	3.60	1.37 to 9.45	51	78	1.31	0.74 to 2.30
Exposure to NO_2—independent of ETS	125	247	1		43	82	1.86	1.0 to 3.34				

*Adjusted for gender, heredity, maternal age and smoking during pregnancy, breast feeding, and building age.

based on outdoor measurements will contribute to a dilution of any relation between NO_2 exposure and recurrent wheezing, especially for children living in homes equipped with a gas stove.[33 34]

Children exposed to combustion products from gas appliances have in some surveys shown an increased risk of respiratory symptoms.[7–9] However, we found no clear association between the use of gas stoves and recurrent wheezing. Our risk estimate for use of gas stoves was of the same order of magnitude as for those exposed to increased levels of outdoor and indoor NO_2, but the number of gas stoves was low. Therefore, the present results on gas stoves and recurrent wheezing should be interpreted carefully. Nor did we find any clear and consistent differences related to gender, although others have shown such findings.[7 10 35]

One notable finding in our study was the confounding effect of the age of the children's homes on the risk estimates of NO_2 exposure. When we included the age of the building in the regression model, an increased risk of NO_2 exposure was suggested, which was not obvious without this adjustment. Most children exposed to increased levels of NO_2 lived in old brick built apartment blocks, erected before 1940. Children less exposed to NO_2 lived more often in buildings erected after 1940 with other design and construction, including single family houses. The impact of building age has also been discussed by Krämer *et al*, who found an increased OR for the association between NO_2 and some atopic diseases, when building age was included in the analysis.[36] The findings indicate that health effects associated with building age, or more likely building related factors, should be taken into consideration when evaluating the association between NO_2 exposure and health.[37] This may be important, especially in areas with rather low NO_2 levels, and in regions with a temperate climate and high demand on energy saving measures with a consequent effect on the indoor environment.

Studies reporting data on air change rate when measuring indoor NO_2 exposure seem to be lacking. In our study, data on ventilation were available. The lack of association between ACH and indoor NO_2 levels in dwellings with a gas stove may have several explanations. We did not register the use of the gas stove in terms of ''time in use'', or evaluate the effects of the condition of the stove. For homes without a gas stove, the positive correlation between ACH and measured indoor NO_2 levels is probably explained by outdoor levels of NO_2; the better the ventilation, the more outdoor combustion products come into the dwelling. This will have an impact, especially in more polluted areas. Similar results have been reported by Spengler *et al*, who measured increased levels of NO_2 inside homes without gas appliances but with a kitchen fan, compared with similar homes without a kitchen fan.[33]

Conclusion

In the present study, outdoor sources constitute major determinants of indoor NO_2 levels in dwellings without a gas stove. Although chance cannot be discounted, an increase in recurrent wheezing is suggested for those children in the study most highly exposed to NO_2, even though the levels were lower than the current European recommended annual level of 40 $\mu g/m^3$. The combination of exposure to ambient air pollution and ETS appears important for development of recurrent wheezing in children.

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Authors' affiliations

G Emenius, N Berglind, M Lewné, M Wickman, Department of Environmental Health, Stockholm County Council, Sweden
G Pershagen, H-J Kwon, Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden
S L Nordvall, Department of Women's and Children's Health, Uppsala University, Sweden

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