Effect of outdoor and indoor nitrogen dioxide on respiratory symptoms in schoolchildren

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Background Nitrogen dioxide (NO_2), an oxidant gas that contaminates both outdoor and indoor air, is considered to be a potential risk factor for asthma. We investigated concurrently the effects of outdoor and indoor NO_2 on the prevalence and incidence of respiratory symptoms among children.

Methods A cohort study was carried out over 3 years on 842 schoolchildren living in seven different communities in Japan. Indoor NO_2 concentrations over 24 hours were measured in both winter and summer in the homes of the subjects, and a 3-year average of the outdoor NO_2 concentration was determined for each community. Respiratory symptoms were evaluated every year from responses to questionnaires.

Results The prevalence of bronchitis, wheeze, and asthma significantly increased with increases of indoor NO_2 concentrations among girls, but not among boys. In neither boys nor girls were there significant differences in the prevalence of respiratory symptoms among urban, suburban, and rural districts. The incidence of asthma increased among children living in areas with high concentrations of outdoor NO_2. Multiple logistic regression analysis showed that a 10 parts per billion (ppb) increase of outdoor NO_2 concentration was associated with an increased incidence of wheeze and asthma (odds ratios [OR] = 1.76, 95% CI : 1.04–3.23 and OR = 2.10, 95% CI : 1.10–4.75, respectively), but that no such associations were found with indoor NO_2 concentration (OR = 0.73, 95% CI : 0.45–1.14 and OR = 0.87, 95% CI : 0.51–1.43, respectively).

Conclusions These findings suggest that outdoor NO_2 air pollution may be particularly important for the development of wheeze and asthma among children. Indoor NO_2 concentrations were associated with the prevalence of respiratory symptoms only among girls. Girls may be more susceptible to indoor air pollution than boys.

Keywords Nitrogen dioxide, air pollution, indoor environment, wheeze, asthma, cohort study

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Recently, the prevalence of asthma has been increasing in many countries.[1,2] Several hypotheses have been advanced to explain this increase.[3] Nitrogen dioxide (NO_2), an oxidant gas produced by the combustion of fossil fuels, is considered to be a potential risk factor for asthma.[4] At high concentrations encountered in the home environment, NO_2 is known to increase the bronchial responsiveness of patients with asthma.[5] Automobile exhaust is the main source of NO_2 in outdoor air in urban areas.[4] Some studies have shown high prevalence rates of wheeze[6–8] or asthma[7] among children living in areas with high NO_2 concentrations. However, the available epidemiological evidence is limited and the effect of NO_2 concentrations in ambient air is not conclusive.[9,10]

The domestic use of combustion appliances also produces high indoor concentrations of NO_2.[11,12] In homes with unvented cooking or heating appliances, indoor concentrations of NO_2 may exceed outdoor levels.[13] Therefore, in evaluating the effects of ambient air pollution on human health, several studies have assessed the indoor or personal exposure levels of NO_2.[14,15] Because of methodological problems, however, these studies have not sufficiently evaluated the effects of indoor air pollution.[13]

To evaluate the effects of environmental factors on respiratory health, we conducted a series of epidemiological surveys in schoolchildren.[12,16] Indoor NO_2 concentrations in the homes of these children have been detailed previously.[12] The objective of this study was to investigate the association of the prevalence and incidence of respiratory symptoms in children with outdoor air pollution and indoor NO_2 concentrations in their homes.

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Methods

Subjects

The study subjects were 1029 fourth grade pupils (aged 9–10 years) who, on October 1992, were attending nine elementary schools from seven different communities of Chiba Prefecture, Japan. Of these schools, six in four communities (Chiba, Funabashi, Ichikawa, and Kashiwa) are located in urban areas, and their school districts are intersected by major trunk roads that are national highways or motorways. The subjects in Chiba and Funabashi were from two schools, respectively, in adjacent districts in each community. One of the remaining three schools is located in a suburban community (Eirakudai), and the other two schools are in rural communities (Ichihara and Tateyama). In each of these cases, there were no major roads or factories within the school district.

The 3-year average concentrations of NO_2 in 1991–1993, measured at ambient air monitoring stations in the vicinities of these schools, were 25.3–31.3 parts per billion (ppb) for the urban communities, 19.3 ppb for the suburban community, and 7.0–10.7 ppb for the rural communities.

Questionnaire

A survey of respiratory symptoms was conducted on all the subjects in October of each year from 1992 (fourth grade) to 1994 (sixth grade). In the first survey, a standard respiratory symptom questionnaire, the modified Japanese version of ATS-DLD-78-C,[17] was sent, through the schools, to the parents of all subjects. The questionnaire covered respiratory symptoms and medical history of the children, feeding method in infancy, history of allergic diseases of the parents, and smoking habits of household members, as well as certain characteristics of the house, such as the type of heating. In the second and third surveys, we used a simple questionnaire on only respiratory symptoms and on any changes in the residential environment for the past year. These questionnaires were filled out by either parent. All incomplete questionnaires, accompanied by a request for completion, were returned to the subjects.

According to the responses to the questionnaires, bronchitis was defined as any chest illness ever diagnosed as bronchitis by a physician. Wheeze was a positive response to the question 'Has your child had wheezing or whistling in the chest during the last 12 months?' Asthma was defined as 'two or more episodes of wheezing accompanied by dyspnoea that had ever been given the diagnosis of asthma by a physician' and 'the occurrence of asthmatic attacks or the need for any medication for asthma during the past 2 years'. For children who had no previous history of wheeze or asthma in the first survey, the incidence of wheezing or asthmatic symptoms in the second or third surveys was evaluated. The definitions of wheeze and asthma were consistent across the three surveys. Children who had been diagnosed as having eczema, atopy, allergic rhinitis, or pollinosis by a physician, or who had received hyposensitization therapy, were considered to have a history of allergic diseases.

Measurements of indoor nitrogen dioxide concentration

Measurements of indoor NO_2 concentrations were carried out in each subject's home on two occasions, in winter (January or February 1993) and in summer (June or July 1993). The 24-hour average concentration of indoor NO_2 (ppb) was measured in the living room using badge-type samplers (Toyo Roshi, Tokyo, Japan). Details of the measurement procedure have been given elsewhere.[12]

For homes in which the measurement time was >22 hours and <26 hours in both seasons, the annual average of the indoor NO_2 concentration was calculated as the geometrical mean of the two seasonal NO_2 concentrations, according to the method described by Neas *et al*.[14]

Data analysis

The prevalence of respiratory symptoms in each survey was first compared in relation to sex, district, indoor NO_2 concentration, parental smoking habits, and type of heating appliance. Annual averages of indoor NO_2 concentrations were categorized in four groups: 0–19, 20–29, 30–39 and ⩾40 ppb. The relationship between the prevalence of respiratory symptoms and indoor NO_2 concentrations was estimated by Armitage's method.[18]

The effects of outdoor and indoor NO_2 concentrations, parental smoking habits, and the use of an unvented heater in winter on the prevalence of respiratory symptoms were assessed using multiple logistic regression models, separately by sex. The models also included a history of allergic diseases, respiratory diseases under 2 years old, feeding method in infancy, and parental history of allergic diseases. The 3-year average of NO_2 concentrations in 1991–1993, measured at the monitoring station near each school, was used as the outdoor NO_2 concentration. We counted outdoor and indoor NO_2 concentrations as continuous variables, and the other factors as having variables consisting of two categories.

The correlation between the incidence rate of wheeze or asthma and ambient concentration of NO_2 in each community was estimated. A logistic regression model was used to evaluate the effects of various factors on the incidence of wheeze or asthma. Because wheezing symptoms arose during the study period among only 13 boys and 9 girls, and asthmatic symptoms arose among only 13 boys and 5 girls, the models combined both sexes and included sex in addition to the above factors as independent variables. All analyses were conducted using SAS software (Version 6, SAS Institute, Inc., Cary, NC).

Results

Completed respiratory symptom questionnaires were obtained from 1018 of the target population (98.9%) in the first survey. The NO_2 samplers were collected from 1022 homes (99.3%) in winter and 1006 homes (97.8%) in summer. For the 905 homes in which available measurements were conducted in both winter and summer, annual averages of indoor NO_2 concentrations were calculated. Responses to the questionnaire were not available for 63 children in the second or third surveys, primarily because of changed residence. Thus, the final sample for analysis comprised 842 children (434 boys and 408 girls). There were no differences between the characteristics of the children in whose homes indoor NO_2 measurements were conducted and children from whom only questionnaires were obtained. The percentage of children who were not followed up in the second and third surveys was slightly higher in the urban districts than in the suburban and rural districts, although the difference was not significant (Table 1).

Table 1 Initial characteristics of the study subjects followed for 2 years, subjects not followed, and those without indoor nitrogen dioxide (NO_2) measurements

	Indoor NO_2 measurements			
Characteristics	Follow-up (n = 842) (%)	No follow-up (n = 63) (%)	**Questionnaire only (n = 113) (%)**	***P*-value[a]**
Sex				
Male	51.5	58.7	50.4	0.518
Female	48.5	41.3	49.6	
Bronchial asthma	5.8	6.3	8.0	0.667
History of allergic diseases	50.4	49.2	54.9	0.645
Respiratory diseases under 2 years of age	9.0	7.9	5.3	0.408
Breastfeeding in infancy	32.8	42.9	32.7	0.259
Parental history of allergic diseases	43.7	44.4	41.6	0.903
Districts				
Urban	60.0	69.8	69.9	0.154
Suburban	13.5	9.5	8.0	
Rural	26.5	20.6	22.1	
Indoor NO_2 concentration				
0–19 ppb[b]	29.8	31.7		0.840[c]
20–29 ppb	29.8	33.3		
30–39 ppb	23.4	19.0		
⩾40 ppb	17.0	15.9		
Parental smoking habits				
Neither smokes	33.7	33.3	37.2	0.264
Father only smokes	54.9	49.2	47.8	
Mother only smokes	3.7	1.6	4.4	
Both smoke	7.7	15.9	10.6	
Use of unvented heater in winter	67.9	69.8	61.1	0.311

[a] Comparison among the three groups.

[b] Parts per billion.

[c] Comparison between the subjects followed for 2 years and the subjects not followed.

The indoor NO_2 concentrations according to community and type of heating appliances are shown in Table 2. Overall, 270 homes used vented heaters and 572 homes used unvented heaters in winter. In all communities, the indoor NO_2 concentrations in winter were very much higher in homes with unvented heaters than in homes with vented heaters. Indoor NO_2 concentrations were lower in summer than in winter, independent of the type of heater used. The annual average of indoor NO_2 concentrations was higher in homes with unvented heaters (mean: 32.4 ppb, range: 4.7–73.7 ppb) than in homes with vented heaters (18.4 ppb, 3.5–49.2 ppb) (Figure 1).

Table 3 shows the prevalence of allergic diseases and respiratory symptoms by district, indoor NO_2 concentration, parental smoking habits, and type of heating appliance used in winter. A history of allergic diseases was not related to any of these variables. Among boys, the prevalence rates of wheeze and asthma were highest in urban districts, except for asthma in the first survey. However, these differences among the districts were not significant. There was no consistent association between respiratory symptoms and indoor NO_2 concentration among boys throughout the three surveys.

Among girls, the prevalence rates of wheeze and asthma were highest in the urban districts, except for asthma in the third survey, although these differences were not significant. Over the 3-year period of survey, the prevalence of respiratory symptoms was highest among girls living in homes with an annual average indoor NO_2 concentration ⩾40 ppb. There were significant trends of increasing respiratory symptoms among girls in association with increasing indoor NO_2 concentrations, except for asthma on the third survey. The prevalence of respiratory symptoms did not significantly differ in relation to parental smoking habits and the type of heating appliance among either boys or girls.

The association of respiratory symptoms with outdoor and indoor NO_2 concentrations was analysed using logistic regression models. The adjusted odds ratios (OR) were expressed as the effect of a 10-ppb increase in outdoor or indoor NO_2 concentration in the child's home (Table 4). No significant relationship of history of allergic diseases with these environmental factors was present among either boys or girls. Among boys, neither wheeze nor asthma was associated with outdoor or indoor NO_2 concentration. The factors that significantly impacted on wheeze and asthma among boys were history of allergic diseases (OR = 4.39 and 4.86, respectively) in the first survey and history of allergic diseases (OR = 2.61 and 2.98, respectively) and respiratory disease under 2 years old (OR = 2.80 and 2.94, respectively) in the second survey.

For respiratory symptoms among girls, the adjusted OR of indoor NO_2 concentrations were above one in all three surveys and the ratios were significantly different from one in the first

Table 2 Indoor nitrogen dioxide (NO_2) concentrations by community and type of heating appliance used in winter

Community	Type of heating appliance	N	Mean indoor NO_2 concentrations (ppb)			Outdoor NO_2 concentrations (ppb)[a]
			Annual	Winter	Summer[b]	
Chiba	Vented	27	20.4	25.8	18.1	25.3
	Unvented	38	35.7	70.0		
Funabashi	Vented	61	21.0	27.2	17.6	29.0
	Unvented	95	35.7	76.1		
Ichikawa	Vented	50	18.6	25.5	15.6	31.3
	Unvented	113	33.2	74.4		
Kashiwa	Vented	50	18.5	22.6	17.1	25.7
	Unvented	71	33.9	73.4		
Eirakudai	Vented	25	16.1	20.9	14.6	19.3
	Unvented	89	34.7	84.9		
Ichihara	Vented	15	15.2	24.0	10.4	10.7
	Unvented	84	26.8	75.1		
Tateyama	Vented	42	15.3	19.8	12.5	7.0
	Unvented	82	27.7	68.2		
Total	Vented	270	18.4	24.0	15.2	–
	Unvented	572	32.4	75.1		

[a] 3-year average concentration of NO_2 in 1991–1993, measured at an ambient air monitoring station adjacent to each school.
[b] Mean of NO_2 concentrations at all subjects' homes in each community, independent of the type of heating appliance used in winter.

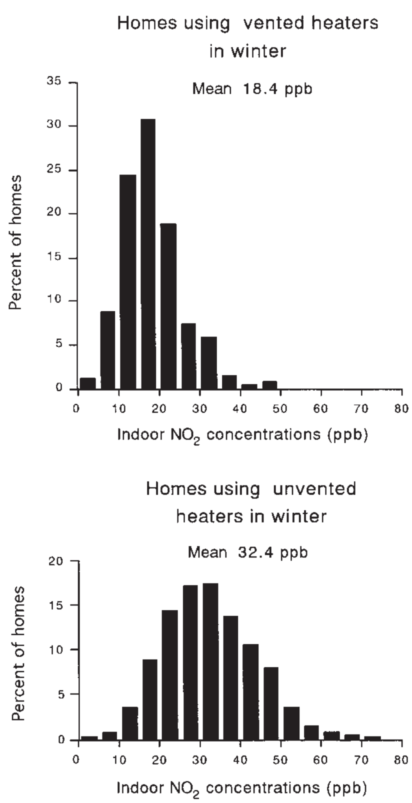

Figure 1 Annual average of indoor nitrogen dioxide (NO_2) concentration by type of heater used in winter

and second surveys. The adjusted OR of outdoor NO_2 concentrations were above one in the first and second surveys, although none of the values were significant. The prevalence of wheeze among girls was also significantly related to a history of allergic diseases in all three surveys (OR = 4.36, 8.50 and 4.96). In the first and second surveys, the effects of breastfeeding in infancy (OR = 2.32 and 2.64) and respiratory disease under 2 years of age (OR = 6.35 and 3.65) were additionally significant. The prevalence of asthma among girls was significantly related to a history of allergic diseases in all the three surveys (OR = 5.28, 7.11, and 10.86), and breastfeeding in infancy in the first and second surveys (OR = 3.14 and 3.75).

The incidence of wheeze and asthma in the second or third surveys was evaluated among children who had no symptoms in the first survey. The incidence rates of wheeze and asthma for each community were 0–6.5% and 0–3.6%, respectively. Asthmatic symptoms tended to develop significantly with increasing outdoor NO_2 concentrations ($r^2 = 0.783$, $P = 0.008$, Figure 2). The logistic regression models examined the effects of various factors on incidence (Table 5). The adjusted OR of the incidence of wheeze and asthma were 1.76 and 2.13, respectively, per 10-ppb increase in outdoor NO_2 concentration; values that were significantly different from one. A history of allergic diseases was also related to a significant increase in the incidence of wheeze and asthma. Breastfeeding in infancy was related to a significant decrease in the incidence of wheeze. The effects of sex, indoor NO_2, parental smoking habits, and use of unvented heaters were not significant.

Discussion

Air pollutants, such as NO_2, have been considered as one of the environmental factors that affects the prevalence of wheezing bronchitis or asthma.[6,7] Exposure to an ambient level of NO_2 has been shown to enhance asthmatic reaction to an inhaled allergen.[19] However, most of the previous epidemiological studies are cross-sectional, and few prospective cohort studies have estimated the incidence of wheeze or asthma. Neas *et al.*[14] conducted a cohort study for 3 years and examined the effect of NO_2

Table 3 Prevalence of respiratory symptoms in relation to district, indoor nitrogen dixoide (NO_2) concentration, parental smoking habits, and type of heating appliance

Factors	N	History of allergic diseases[a]	Bronchitis ever[a]	Wheeze 4th grade (1992)	Wheeze 5th grade (1993)	Wheeze 6th grade (1994)	Asthma 4th grade (1992)	Asthma 5th grade (1993)	Asthma 6th grade (1994)
Males									
Districts									
Urban	280	52.9	20.0	11.1	9.3	6.8	6.8	7.9	4.6
Suburban	57	61.4	24.6	7.0	5.3	5.3	7.0	5.3	3.5
Rural	97	50.5	13.4	8.2	7.2	4.1	5.2	5.2	4.1
P-value		0.402	0.194	0.533	0.549	0.616	0.839	0.578	0.921
Indoor NO_2 concentration									
0–19 ppb[b]	128	50.8	18.8	11.7	9.4	7.0	8.6	7.0	6.3
20–29 ppb	125	53.6	22.4	8.8	9.6	4.8	5.6	8.0	4.0
30–39 ppb	105	58.1	16.2	12.4	7.6	7.6	8.6	6.7	3.8
⩾40 ppb	76	51.3	18.4	5.3	5.3	3.9	1.3	5.3	2.6
P-value[c]		0.653	0.674	0.308	0.276	0.610	0.129	0.607	0.216
Parental smoking habits									
Neither smokes	150	55.3	22.0	8.7	8.0	4.7	6.0	6.7	4.0
Father only smokes	228	50.9	18.4	11.0	8.3	7.5	7.5	7.9	5.3
Mother only smokes	14	64.3	21.4	14.3	14.3	7.1	7.1	7.1	0.0
Both smoke	42	57.1	11.9	7.1	7.1	2.4	2.4	2.4	2.4
P-value		0.634	0.505	0.752	0.861	0.505	0.660	0.638	0.678
Type of heating appliance									
Vented	134	53.7	23.1	14.2	11.9	9.0	9.7	9.7	6.7
Unvented	300	53.3	17.3	8.0	6.7	4.7	5.0	5.7	3.3
P-value		0.939	0.186	0.056	0.066	0.123	0.066	0.126	0.112
Females									
Districts									
Urban	225	45.3	19.1	9.8	7.1	5.8	6.2	6.2	2.7
Suburban	57	52.6	15.8	7.0	5.3	3.5	3.5	3.5	3.5
Rural	126	47.6	13.5	4.8	4.0	4.0	4.0	3.2	2.4
P-value		0.608	0.392	0.238	0.476	0.656	0.548	0.390	0.909
Indoor NO_2 concentration									
0–19 ppb[b]	123	48.8	13.8	3.3	2.4	1.6	1.6	2.4	0.8
20–29 ppb	126	46.0	11.1	7.1	5.6	6.3	5.6	4.8	4.0
30–39 ppb	92	44.6	19.6	8.7	5.4	5.4	4.3	4.3	2.2
⩾40 ppb	67	49.3	29.9	16.4	13.4	9.0	11.9	10.4	4.5
P-value[c]		0.889	0.003	0.002	0.006	0.040	0.007	0.031	0.223
Parental smoking habits									
Neither smokes	134	47.0	17.2	9.7	7.5	7.5	6.0	6.7	3.7
Father only smokes	234	47.9	17.1	7.3	6.0	4.7	5.1	4.7	2.6
Mother only smokes	17	41.2	23.5	11.8	0.0	0.0	5.9	0.0	0.0
Both smoke	23	43.5	8.7	0.0	0.0	0.0	0.0	0.0	0.0
P-value		0.937	0.649	0.381	0.375	0.291	0.693	0.387	0.643
Type of heating appliance									
Vented	136	47.8	14.0	6.6	3.7	2.2	2.9	3.7	2.2
Unvented	272	46.7	18.4	8.5	7.0	6.6	6.3	5.5	2.9
P-value		0.833	0.262	0.515	0.181	0.057	0.234	0.477	0.758

[a] The first survey (1992) only.

[b] Parts per billion.

[c] *P*-value for the trend by Armitage's method.

Table 4 Odds ratios (OR) and 95% CI for effect of nitrogen dioxide (NO_2) exposure and indoor environmental factors on the prevalence of respiratory symptoms

					Wheeze						**Asthma**					
	History of allergic diseases[a]		**Bronchitis ever**[a]		4th grade (1992)		5th grade (1993)		6th grade (1994)		4th grade (1992)		5th grade (1993)		6th grade (1994)	
Factors	OR[b]	95% CI	OR[c]	95% CI	OR[c]	95% CI	OR[c]	95% CI	OR[c]	95% CI	OR[c]	95% CI	OR[c]	95% CI	OR[c]	95% CI
Males																
Outdoor NO_2 concentration, 10 ppb[d] increase	0.96	0.75–1.22	1.13	0.81–1.60	1.15	0.76–1.79	1.28	0.83–2.08	1.46	0.86–2.69	1.11	0.69–1.89	1.41	0.87–2.45	1.27	0.72–2.45
Indoor NO_2 concentration, 10 ppb increase	1.05	0.85–1.28	1.04	0.77–1.38	0.98	0.68–1.39	0.88	0.59–1.29	0.91	0.58–1.41	0.77	0.48–1.20	0.92	0.60–1.39	0.78	0.45–1.30
Parental smoking habits	0.92	0.60–1.39	0.67	0.38–1.18	1.30	0.65–2.72	1.02	0.49–2.22	1.38	0.58–3.65	1.21	0.53–2.97	0.99	0.45–2.31	1.14	0.43–3.35
Use of unvented heater in winter	0.96	0.57–1.63	0.60	0.29–1.23	0.54	0.23–1.28	0.63	0.26–1.56	0.60	0.21–1.69	0.71	0.25–1.98	0.64	0.24–1.70	0.71	0.21–2.31
Females																
Outdoor NO_2 concentration, 10 ppb increase	0.95	0.75–1.19	1.27	0.89–1.83	1.32	0.81–2.25	1.15	0.68–2.20	1.00	0.58–1.74	1.14	0.65–2.09	1.14	0.63–2.13	0.95	0.45–2.05
Indoor NO_2 concentration, 10 ppb increase	1.10	0.89–1.35	1.42	1.06–1.90	1.90	1.30–2.83	1.60	1.06–2.44	1.23	0.78–1.92	1.63	1.06–2.54	1.67	1.06–2.66	1.18	0.62–2.18
Parental smoking habits	1.04	0.68–1.60	1.06	0.55–2.09	0.61	0.26–1.44	0.57	0.23–1.48	0.48	0.19–1.28	0.63	0.24–1.75	0.45	0.16–1.24	0.63	0.17–2.47
Use of unvented heater in winter	0.83	0.49–1.38	1.04	0.46–2.40	0.62	0.21–1.89	1.07	0.31–4.01	2.71	0.69–13.75	1.15	0.31–4.86	1.03	0.27–4.49	1.10	0.21–6.61

[a] The first survey (1992) only.

[b] Odds ratios adjusted for seven variables including respiratory diseases under 2 years of age, feeding methods in infancy, and parental history of allergic diseases, using the logistic regression model.

[c] Odds ratios adjusted for history of allergic diseases in addition to above seven variables.

[d] Parts per billion.

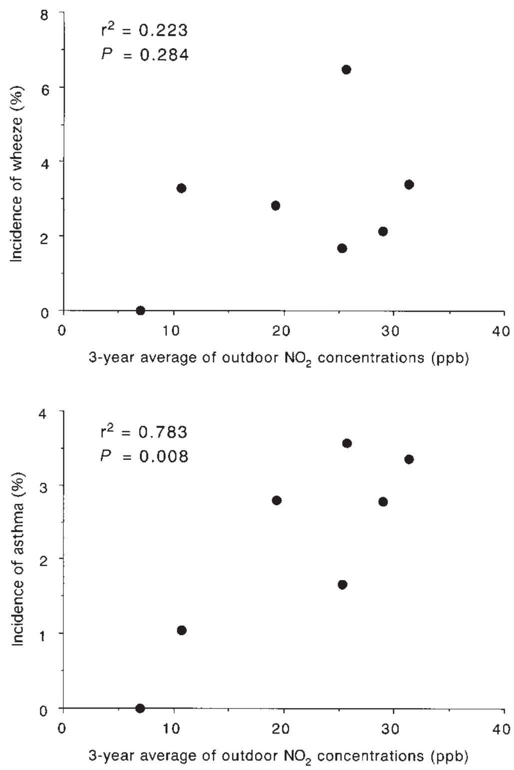

Figure 2 Incidence rates of wheeze or asthma and outdoor nitrogen dioxide (NO_2) concentration for each community

on the annual cumulative incidence of respiratory symptoms during the prior year. However, they did not refer to the rates of newly developed asthma during the study period. In a study of children living in eight areas of Japan for 5 years, the incidence of asthma tended to increase in areas with an annual mean NO_2 concentration >0.03 parts per million (ppm), although the effects of confounding factors, including allergy, were not considered.[20]

In our study, the prevalence of wheeze and asthma decreased over the study period in all districts. In a British cohort, more than two-thirds of the children with a history of wheeze or asthma by age 7 experienced no attacks at age 11.[21] Our subjects were observed from ages 9–10 to ages 11–12. The remission of wheeze or asthma may be due to growth. On the other hand, some children first reported wheezing or asthmatic symptoms during the study period. The incidence rates were higher in areas with high concentrations of outdoor NO_2. The relationships between outdoor NO_2 and the incidence of wheeze or asthma remained significant, even after adjustment for potential confounding factors such as history of allergic diseases and indoor NO_2 concentration. Respiratory symptoms were evaluated by a standardized questionnaire in the first survey, and a simple questionnaire in the second and third surveys because the latter were easy to complete. The difference in questionnaires might lead to potential bias in responses.[22] However, the two questionnaires included the same questions about respiratory symptoms, and the definitions of wheeze and asthma were unified. Therefore, we have considered that misclassification due to the difference in questionnaires is minimal.

In cohort studies, a substantial number of subjects may be inevitably lost to follow-up primarily because of out-migration. Forastiere *et al.*[23] obtained responses from 84.6% of the primary subjects after a 3.5-year interval in a cohort of children. We were able to follow up 842 children (93.0% of the subjects in the first survey) for 2 years, which satisfied the purpose of our study.

To evaluate the health effects of outdoor air pollution, the potential involvement of indoor air pollution also should be considered.[11–13] The use of gas cooking stoves often has been considered as a major indoor source of NO_2.[11,13] Several studies have shown that a gas stove in the home is a risk factor for respiratory symptoms and diseases in children,[6,24] while others have failed to demonstrate such effects.[25,26] In Japan, almost all homes use gas appliances for cooking, and the use of unvented heaters in winter is usually considered a source of indoor air pollution.[12,16] The present study also showed that indoor NO_2 concentrations were higher in homes with unvented compared to vented heaters. However, neither prevalence nor incidence of respiratory symptoms was significantly associated with type of heater.

A few studies have included measurements of NO_2 in the subjects' homes. Neas *et al.*[14] demonstrated an association between indoor NO_2 concentrations and increased incidence of lower respiratory symptoms in children. Infante-Rivard[25] found a dose-response relationship between personal exposure to

Table 5 Odds ratios (OR) and 95% CI[a] for various risk factors on the incidence of wheeze or asthma for the follow-up period

	Incidence of wheeze			Incidence of asthma		
Factors	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Sex, boy versus girl	1.10	0.45–2.80	0.839	2.08	0.75–6.72	0.181
History of allergic diseases	2.91	1.12–8.52	0.035	7.96	2.15–51.61	0.007
Respiratory diseases under 2 years of age	2.95	0.89–8.39	0.054	2.86	0.85–8.29	0.065
Breastfeeding in infancy	0.18	0.03–0.62	0.021	0.60	0.36–1.07	0.118
Parental history of allergic diseases	0.88	0.35–2.21	0.792	1.02	0.38–2.83	0.967
Outdoor NO_2 concentration, 10 ppb[b] increase	1.76	1.04–3.23	0.049	2.10	1.10–4.75	0.042
Indoor NO_2 concentration, 10 ppb increase	0.73	0.45–1.14	0.178	0.87	0.51–1.43	0.592
Parental smoking habits	0.50	0.20–1.20	0.116	0.51	0.19–1.35	0.168
Use of unvented heater in winter	2.90	0.91–10.48	0.083	1.26	0.36–4.62	0.718

[a] Odds ratios adjusted for all variables using the logistic regression model.

[b] Parts per billion.

NO_2 and asthma, but NO_2 measurements were conducted in only 140 children. In other studies, indoor NO_2 exposure has been minimally associated with either respiratory symptoms or illnesses.[26,27] Most of these studies have been conducted in only one area, and few studies have considered the potential effects of various environmental factors, including outdoor air pollution. Braun-Fahrländer *et al*.[15] reported that NO_2 measured outdoors but not indoors was associated with the duration of respiratory symptoms in children.

In this study, valid measurements of indoor NO_2 concentrations were obtained in 905 homes from seven different communities in both winter and summer, although each measurement was carried out on only one day. Then, we estimated the effects of outdoor and indoor NO_2 together using multiple logistic models. The relationships between the prevalence of respiratory symptoms and indoor NO_2 concentration were significant among girls, but not among boys. We have previously reported that pulmonary function measurements were associated with indoor NO_2 among girls only.[16] Neas *et al*.[14] found a stronger effect of indoor NO_2 on respiratory symptoms among girls than among boys. In other studies, a gas stove in the home appeared to be a risk factor for respiratory illnesses, primarily among girls and young women.[6,11,24] Melia *et al*.[24] suggested that girls would be more likely to spend more time in the kitchen. Pershagen *et al*.[6] also found an increased risk associated with a gas stove in girls only, but they suggested that environmental exposure did not differ between boys and girls, since 90% of their subjects were under 2 years. Constitutional factors linked to sex may be of importance in respiratory symptoms or diseases.

Outdoor NO_2 exposure was also reported to be a risk factor for wheezing bronchitis in only girls.[6] In our study, outdoor NO_2 concentration was not significantly associated with the prevalence of respiratory symptoms in either boys or girls. The incidence of wheeze and asthma was higher among boys than girls, although the sex-related difference was not significant. Since wheeze and asthma had arisen in only a small number of our subjects, the incidence should be further evaluated in more large-scale cohort studies.

Environmental tobacco smoke (ETS) has been shown to increase the incidence of asthma and wheezing in childhood.[28] However, Chinn and Rona[29] found that ETS exposure was associated with wheezing but not with diagnosed asthma. In the present study, parental smoking was not related to either wheeze or asthma in children. This may be because we did not evaluate the effect of ETS exposure, but only parental smoking habits. Breastfeeding in infancy was strongly associated with a low incidence of wheeze. Wilson *et al*.[30] showed the protective effect of breastfeeding against respiratory illness during childhood.

A history of allergic diseases was also associated with the incidence of wheeze and asthma. Half of the subjects had a history of allergic diseases, among which atopy and allergic rhinitis were dominant. In a British cohort, atopy had an influence on the incidence of wheezing during adulthood.[21] No increase in allergic diseases was observed with increasing levels of air pollution in the International Study of Asthma and Allergy in Childhood (ISAAC).[2,9] The comparisons between eastern and western European populations showed a higher prevalence of infectious airway diseases and a lower prevalence of allergic diseases in eastern areas with high levels of sulphur oxides and suspended particles.[31,32] A recent report from Germany found no effect of air pollution on the development of allergies.[33] The present study showed no difference in the prevalence of allergic diseases in relation to districts and indoor NO_2 concentrations.

On the other hand, several studies using the ISAAC questionnaire have shown that air pollution from heavy traffic has adverse effects on the respiratory health of children living in urban areas.[7,34,35] Traffic-related NO_2 has been shown to be associated with the prevalence of asthma and respiratory symptoms in children.[7,36] Our study districts in urban communities were intersected by major trunk roads, and the high NO_2 concentrations were derived primarily from automobile exhaust.[12] Exposure to NO_2 has been assumed to influence asthma in two ways: by decreasing the threshold of allergens in the development of asthma and worsening the morbidity of existing atopy or asthma.[5,37] Our findings are consistent with the latter possibility, in that the incidence of wheeze and asthma was associated with NO_2 exposure and allergic diseases. Atopic children would be expected to have a greater risk of respiratory symptoms with exposure to NO_2 than non-atopic children.[38] Accordingly, it is possible that NO_2 directly causes airway inflammation and cellular damage in the human body.[39]

Pilotto *et al*.[40] suggested that repeated exposure to short-term peaks of NO_2 is more important in pathogenesis than long-term exposure to lower levels of NO_2. However, the NO_2 monitors used in epidemiological studies can obtain only average concentrations over the measurement periods.[6] In this study, outdoor NO_2 levels were assessed using only 3-year average concentrations. Therefore, our results may underestimate the effects of NO_2 exposure. The presence of other pollutants, such as particulates, ozone, and formaldehyde, in the outdoor and indoor environment should be also considered.[4,9] Fine particles have been reported to be associated with the prevalence of bronchitis, but not with asthma.[41] Outdoor NO_2 concentration may act as a surrogate for the real cause of the health effects. The association between respiratory symptoms and air pollutants other than NO_2 should be further evaluated.

In conclusion, this study showed that the incidence of wheeze and asthma increased among children living in areas with high concentrations of outdoor NO_2. This relationship remained significant even after adjustment for various factors, such as indoor NO_2 concentration. These findings suggest that air pollution, including NO_2, may be particularly important for the development of wheeze and asthma in urban districts. Indoor NO_2 concentrations were associated with the prevalence of respiratory symptoms among girls, but not among boys. The relationship between indoor NO_2 and the incidence of wheeze or asthma was not significant either. The incidence and prognosis of respiratory symptoms should be further evaluated in a longitudinal study for many more years.

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