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Personally measured weekly exposure to NO_2 and respiratory health among preschool children

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Personally measured weekly exposure to NO_2 and respiratory health among preschool children. K. Mukala, J. Pekkanen, P. Tiittanen, S. Alm, R.O. Salonen, J. Tuomisto. ©ERS Journal Ltd 1999.

ABSTRACT: Nitrogen dioxide is known as a deep lung irritant. The aim of this study was to find out whether the relatively low ambient air NO_2 concentrations in the northern city of Helsinki had an impact on the respiratory health of children.

The association between personal exposure to ambient air NO_2 and respiratory health was investigated in a 13-week follow-up study among 163 preschool children aged 3–6 yrs. Personal weekly average exposure to NO_2 was measured by passive diffusion samplers attached to the outer garments. Symptoms were recorded daily in a diary by the parents. Among 53 children, peak expiratory flow (PEF) was measured at home in the mornings and evenings. The association between NO_2 exposure and respiratory symptoms was examined with Poisson regression.

The median personal NO_2 exposure was 21.1 $\mu g \cdot m^{-3}$ (range 4–99 $\mu g \cdot m^{-3}$). An increased risk of cough was associated with increasing NO_2 exposure (risk ratio=1.52; 95% confidence interval 1.00–2.31). There was no such association between personal weekly NO_2 exposure and nasal symptoms, but a nonsignificant negative association was found between the exposure and the weekly average deviation in PEF.

In conclusion, even low ambient air NO_2 concentrations can increase the risk of respiratory symptoms among preschool children.

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Nitrogen dioxide is a major air pollutant both indoors and outdoors. It is formed in combustion processes, either directly or through secondary oxidation of nitric oxide. It may serve as a proxy of traffic-related air pollutants. NO_2 is an oxidant gas and a deep irritant in the lungs. There is toxicological evidence of pulmonary inflammation, deterioration of respiratory defence mechanisms and increased susceptibility to respiratory pathogens after NO_2 exposure [1–4]. The removal of inhaled NO_2 is limited in the upper airways, and according to dosimetric studies most of the inhaled NO_2 is retained in the lungs and deposited primarily in the large and small airways [2].

Suggested adverse health effects of NO_2 on humans include increased incidence and severity of respiratory infections, respiratory symptoms, reduced lung function and worsening of symptoms among subjects with asthma or chronic obstructive pulmonary disease [5]. According to epidemiological studies, the most susceptible population groups to the adverse effects seem to be small children and asthmatic subjects [1–4]. In these studies, however, the associations between the estimated NO_2 exposure and the prevalence of childhood respiratory symptoms and illnesses, illness duration or lung function have not been consistent [3, 5–9].

In many epidemiological studies, human exposure to NO_2 has been estimated by rather inaccurate methods, which might explain the difficulty in finding statistically significant associations between NO_2 and health effects. Furthermore, individual studies have usually focused on either indoor or outdoor exposure and not on the total NO_2 exposure. In indoor measurements, NO_2 concentrations have been measured most often with diffusion samplers or by classifying exposure on the basis of indoor sources such as the stove type and smoking status [10]. Outdoor exposure estimates have usually been based on fixed-site monitoring data or on diffusion sampler measurements outside the home. In two previous studies, in which personal monitoring of the total NO_2 exposure has been used, SAMET *et al.* [8] did not find a significant association between exposure and respiratory illness among children aged <18 months, whereas RUTISHAUSER *et al.* [11] found an increased frequency of respiratory symptoms with increasing NO_2 exposure among children <5 yrs of age.

In order to find out whether the relatively low ambient air NO_2 concentrations in the northern city of Helsinki had an impact on the respiratory health of children, personal weekly NO_2 exposure, and respiratory symptoms and peak expiratory flow (PEF) were measured among preschool children.

Material and methods

Study location

The study was conducted in years 1990–1991 in Helsinki, where the main sources of ambient air pollution are automotive traffic and energy production, and to a smaller

extent industry. At the street level, the most important source of pollution is traffic, which is responsible for practically all carbon monoxide emissions and >90% of the nitrogen oxides (NO_x) emissions. In 1991, the maximum 24-h average NO_2 concentration was 115 $\mu g \cdot m^{-3}$ (at 0°C).

Study design

This is a prospective panel study, in which the preschool children were followed for a total of 13 weeks. The study was divided into two periods in different seasons: a 6-week winter period and a 7-week spring period. The children′s personal weekly average exposure to NO_2 was assessed with passive diffusion samplers, *i.e.*, Palmes tubes [12], and their respiratory symptoms were recorded on daily diaries. PEF was recorded in a subsample of the study population. Simultaneous ambient air quality data from fixed-site monitoring stations were obtained from the Helsinki Metropolitan Area Council (YTV).

Selection of study subjects.

Eight municipal day care centres were selected from the city of Helsinki. Four day care centres were from the central area, where traffic density was high and air quality worse and the other four centres were from the suburban area with less traffic and better air quality. A baseline questionnaire was delivered to the parents of all 363 children, who were aged 3–6 yrs and attended the selected day care centres. The questionnaire included questions on the health status of the child, and the sociodemographic factors and housing conditions of the family. Two hundred and forty-six (68%) completed questionnaires were received, 118 from the central area and 128 from the suburban area. All children, whose parents returned the questionnaire and accepted the invitation for participation, were initially included in the study. A more detailed description of the selection of the study population has been published previously [13].

The study protocol was approved by the Ethical Committee of the National Public Health Institute. A written consent was obtained from the parents of the children.

Exposure assessment

For assessment of personal weekly exposure to NO_2, one Palmes tube was fixed to the outer garments of each child. The tube was changed weekly in the day care centre by the researchers. Only tubes that had been sampling for 168±24 h, were accepted for final analyses [14]. The absorbed NO_2 was analysed as nitrite with an ion chromatograph (Dionex 4000i; Dionex Corporation, Sunnyvale, CA, USA). A more detailed description about personal exposure measurement method and quality control of Palmes tubes is explained by ALM *et al.* [14]. The observed error limits of the method were ±6%, when duplicate measurements were conducted in the pilot phase [13]. To detect possible contamination during shipment and sampling, field blanks were placed inside day care centres [14].

Respiratory symptom assessment and lung function

In the beginning of the study, the parents were instructed to fill in symptom diaries. They were asked to record daily the presence of nasal symptoms, cough, eye symptoms, ear symptoms, difficulties in breathing, stomach-ache and fever. If the child had no symptoms on a particular day, this was marked in a separate question category of "no symptoms". To stimulate daily diary filling, new diaries were distributed and completed diaries were collected weekly in the day care centre, while changing the Palmes tubes [13].

In a subsample of the study population (aged 4–6 yrs), PEF was also recorded. Measurement of peak flow was chosen because it is the only measurement that can be easily made within a young child′s home. One of the researchers tested the children′s ability to perform a PEF manoeuvre, and those who could do it correctly and give reproducible recordings were included. In this study, the PEF measurements were made with the mini-Wright PEF meters (Airmed, Clement Clarke International Ltd., Essex, UK). PEF was recorded twice a day at home: morning-PEF after getting up and evening-PEF at bedtime. In the beginning of the study, the children and their parents were trained for the use of the mini-Wright peak flow meter according to the following protocol: 1) to perform the test standing, 2) to hold the meter lightly and horizontally, 3) not to interfere with the movement of the air flow marker, and 4) to repeat the test three times and to record the highest morning and evening PEF values in the diary.

Data analyses

The following inclusion criteria were used for the final analyses: 1) a minimum of 60% of the diary data per season, 2) personal NO_2 measurement and diary data from the same study week, 3) complete diary data for every day of the week, 4) complete questionnaire data, and 5) the last week of both seasons were excluded, because there were only two children fulfilling the last four criteria. After applying these inclusion criteria, the final study material consisted of 13 weeks and 163 children, of which 76 were from the central area and 87 from the suburban area.

The corresponding inclusion criteria for the final analyses of the changes in lung function were as follows: 1) at least 60% of the PEF data per season, 2) PEF data for at least 5 $days \cdot week^{-1}$, 3) personal NO_2 measurement and PEF data from the same study week, and 4) complete questionnaire data. In addition, the first two days of each season were considered unacceptable for all analyses, due to a learning effect (*i.e.*, lower values in the first two days, after starting PEF follow-up). After applying these criteria, there were 53 children left for the final analyses of the changes in lung function.

The characteristics of the study population are shown in table 1. The groups of children, who were included in, or excluded from the final analyses of the questionnaire and diary data or included in the PEF follow-up, had very similar characteristics to each other.

Multivariate analysis. The association between NO_2 exposure and respiratory symptoms (cough and nasal symptoms) was examined with Poisson regression. The outcome variable was the prevalence of the symptom

Table 1. – Characteristics of the children included in and excluded from the final analyses of respiratory symptoms as well as those of the children in the subgroup with daily peak expiratory flow (PEF) follow-up

	Included %	Excluded %	PEF subsample %
Subjects n	163	77	53
Females	49	49	53
Age yrs	4.7±1.1	4.7±0.98	5.2±0.75
History of allergy[†]	29	23[‡]	30
Smoking at home	47	61[§]	53
Maternal smoking*	9[#]	12[$]	6
Parental education >12 yrs	60	45[+]	59
Pets with fur	16	14	9
Multifamily house	77	79	81
Gas stove	15	18	21
Living in the central area	47	48	55

Age results presented as mean±SD. [†]: history of allergy, skin symptoms, wheezing or asthma-like symptoms; *: not excluded if missing information on "mother's smoking", because "smoking at home" was used in the statistical models; [#]: n=154; [‡]: n=75; [§]: n=67; [$]: n=66; [+]: n=64.

during a follow-up week. The prevalence rates of different respiratory symptoms were calculated for each child as the proportion of the number of days with the symptom to the seven follow-up days per week. The association between the weekly average NO_2 exposure and the symptoms was assessed using symptoms from 1) the same week as the NO_2 measurement (lag0), and 2) the week starting 2 days after the start of NO_2 measurement (lag2). The lag2 analysis was performed to determine whether there was a delay in symptom outcome. In both lag0 and lag2 analyses, the personal weekly NO_2 exposure was divided into three categories using the 25th and 75th percentiles of the study population as cut-off points. Other categorizations were tested as well and the conclusions from the results remained consistent with those presented.

The crude estimate for NO_2 was obtained by regressing the health outcome only against NO_2. All potential confounders were then added one at a time into the crude model, and those confounders which changed the crude estimate of NO_2 by $\geq$10% were included into the final model. Allergy of the child, stove type, smoking (any family member smoking at home), parental education, day care centre, and season (only in analyses of cough) were included in the final model. Weekly average temperature, weekly average pollen count, and the weekly sum of the pollen count did not affect the NO_2 estimates, nor did the age or sex of the child. Consequently, these factors were not included in the final models. During the study periods, there were no epidemics of any respiratory diseases.

The effect modification of allergy, education, smoking and stove type was checked, including an interaction term with NO_2 in the model, one at a time. However, none of the interaction terms was statistically significant and therefore they were not included in the final model.

In two pollutant models the weekly average concentrations of ambient air pollutants (NO, NO_2, O_3, SO_2, total suspended particulate (TSP)) were included into the model together with Palmes NO_2, one at a time. Ambient air pollutants were included into the model both as continuous variables and as categorized variables using 25th and 75th percentiles as cut-off points, separately.

Poisson regression was first implemented with the Procedure for Generalized Linear Models (PROC GENMOD) (SAS Institute Inc., Cary, NC, USA) [15]. However, this method assumed that the occurrence of respiratory symptoms during any follow-up week of the child was independent of the occurrence of symptoms in any other follow-up week. Consequently, the final analyses were performed by using the generalized estimating equations (GEE) approach, which took into account the intrasubject correlation [16]. The correlation of the responses from subjects was assumed to follow a first-order autoregressive process, *i.e.* the correlation weakens in time. Independent and exchangeable correlation structures were also tested to check the robustness of the results to the chosen correlation structure. However, the conclusions from the results were practically unchanged. The estimation was implemented with PROC GENMOD using GEE option.

To examine the changes in lung function, seasonal average morning PEF was first calculated for each child. After that the daily morning PEF deviations from the seasonal average morning PEF were calculated for each child. Thereafter, the weekly average morning PEF deviations of the child were calculated and used in the analysis. The same calculations were performed with evening PEF.

A linear multivariate regression model was used to examine the association between the personal NO_2 exposure and the weekly average PEF deviation. The dependence of the repeated measurements of the same child was accounted assuming the first-order autocorrelation structure for errors. The model was implemented by the Procedure for Mixed Linear Models (MIXED procedure) (SAS Institute Inc.) [15]. Least-squares means (*i.e.*, predicted PEF values) were calculated so that the coefficients across classification effects were defined to be proportional to those found in the present data.

Results

Exposure

The personal exposure monitoring reflected nearly all contributions of outdoor NO_x sources, because there are minimal NO_x sources in Finnish households due to widespread electric stoves and district heating. The median NO_2 exposures were low and their range was narrow as assessed by direct personal measurements with the Palmes tubes (fig. 1, table 2). The median exposure in the whole study population was 21.1 $\mu g \cdot m^{-3}$. The personally measured NO_2 concentrations were higher in the central area than in the suburban area during both seasons. There was little difference in the NO_2 level between winter and spring. The fixed-site ambient air concentrations of NO_2 were generally higher than the personal concentrations. The levels of O_3, SO_2 and TSP were low (table 2).

Prevalence and risk ratios of symptoms

The prevalence of different symptoms (*i.e.*, the proportion of the number of days with symptoms to the

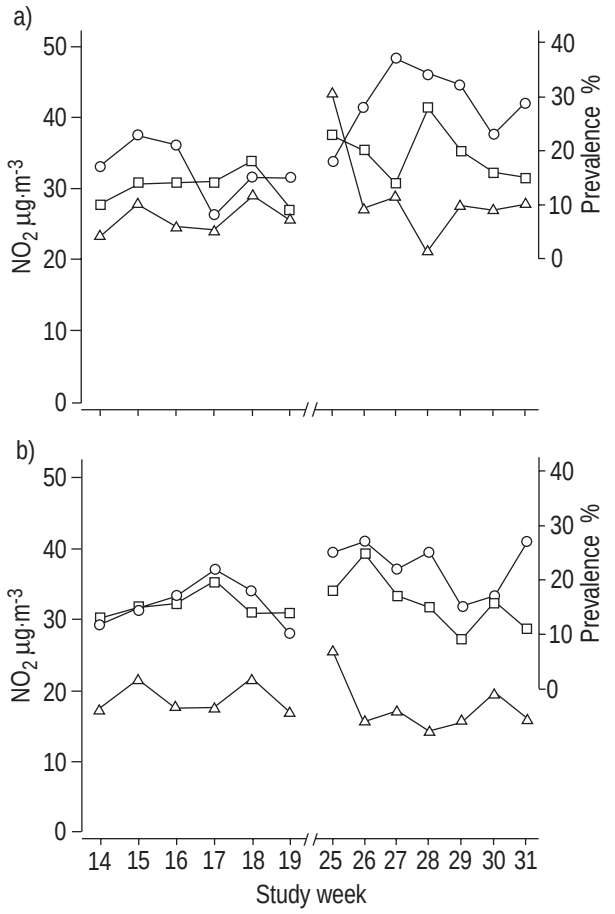

Fig. 1. – The median values of weekly personal NO_2 concentrations (△) and prevalences of cough (□) and nasal (○) symptoms in the central (a) and suburban (b) areas during the winter (weeks 14–19) and spring (weeks 25–31) seasons.

number of follow-up days during the study period) in the whole study population, was as follows: nasal symptoms 21.1%, cough 15.7%, breathing difficulties 0.6%, ear symptoms 0.3%, and eye symptoms 1.7%. Because of the low prevalence of breathing difficulties and eye and ear symptoms, these were not included in further analyses. The weekly average NO_2 exposures and the weekly prevalence of cough and nasal symptoms in winter and spring are shown in figure 1.

Cough

The overall prevalence of cough during the study period was 16.6% in the central area and 15.0% in the suburban area. The seasonal prevalence of cough (*i.e.*, the proportion of the number of days with cough to the number of follow-up days per season) tended to increase with increasing personal NO_2 exposure in the central area during the winter season and in the suburban area during both seasons (table 3). However, in the central area the highest prevalence of cough during the spring season was found in the lowest NO_2 category. The seasonal prevalence of cough remained quite similar in different NO_2 categories when the lag2 data was used instead of the lag0 data (table 3).

The prevalence of cough (seasons together) was higher in the second and third NO_2 category. The association between NO_2 exposure and cough was, however, statistically significant only in the highest category at lag0 (table 4). With lag2 data, the risk was slightly lower and statistically nonsignificant. The adjusted risk ratio (lag0 data) in the highest NO_2 category was slightly reduced, if SO_2 or ozone was added into the model (risk ratio (RR)=1.50, 95% confidence interval (CI) 1.00–2.26 and RR=1.47, 95% CI 0.96–2.25, respectively) and slightly increased when TSP was added into the model (RR=1.55, 95% CI 1.01–2.40).

Table 2. – The weekly average NO_2 concentrations from personal exposure monitoring and the corresponding concentrations of other pollutants from fixed site monitoring stations in the central and suburban areas during the winter and spring seasons

	Central area	Suburban area
Personal NO_2		
Winter*	26 (10–60)	18 (4–78)
Spring†	28 (10–69)	17 (4–99)
Ambient NO_2		
Winter	47 (41–55)	41 (22–60)
Spring	40 (34–76)	33 (19–66)
SO_2		
Winter	27 (11–73)	22 (8–54)
Spring	15 (10–27)	9 (3–18)
O_3		
Winter	14 (6–30)	28 (17–43)
Spring	33 (17–42)	53 (31–58)
TSP		
Winter	66 (39–89)	35 (18–63)
Spring	58 (29–132)	46 (32–83)

Data are presented as medians with ranges in parentheses in µg·m^{-3}. TSP: total suspended particulate. *: number of tubes 229/279 (six weeks) in the central and suburban areas, respectively; †: number of tubes 285/369 (seven weeks) in the central and suburban areas, respectively.

Nasal symptoms

The overall prevalence of nasal symptoms during the study period was 23.8% in the central area and 18.9% in the suburban area. In both areas, the seasonal prevalence of nasal symptoms was higher in spring than in winter. The seasonal prevalence of nasal symptoms was slightly higher when symptoms with 2-day lag were considered (table 3).

Because there was a seasonal difference in the association between NO_2 exposure and nasal symptoms, the two seasons were analysed separately. There was no increase in the risk of lag0 nasal symptoms with increasing NO_2 exposure (table 4). The risk of lag2 nasal symptoms tended to increase in higher NO_2 categories during the winter season, but the association was not statistically significant. During the spring season, however, there was a nonsignificant association between increase in the personal NO_2 exposure and reduction of the risk of nasal symptoms both with lag0 and lag2 data.

Peak expiratory flow

In the spring season in the crude model, both morning and evening PEF deviations were at their lowest in the highest NO_2 category. After adjusting for confounders

Table 3. – The seasonal prevalence rates (*i.e.*, the proportion of the number of days with symptoms to the number of follow-up days per person) of cough and nasal symptoms in different categories of weekly average NO_2 exposure

		Winter season			Spring season		
	Personal NO_2 concentration $\mu g \cdot m^{-3}$	Follow-up weeks n	Cough %	Nasal symptoms %	Follow-up weeks n	Cough %	Nasal symptoms %
Symptoms of the same week							
Central area	<16.2	12	7.1	16.7	16	34.8	34.8
	16.2–27.2	112	11.5	20.7	99	16.6	29.6
	≥27.7	85	15.0	15.8	136	20.5	26.5
Suburban area	<16.2	83	6.5	16.2	140	14.6	28.4
	16.2–27.2	159	17.0	13.2	163	14.9	17.7
	≥27.7	16	25.9	22.3	26	26.9	17.6
Symptoms with a 2-day lag							
Central area	<16.2	11	13.0	20.8	15	27.6	39.1
	16.2–27.2	103	12.1	18.9	86	19.1	29.9
	≥27.7	78	14.1	17.2	128	19.5	25.2
Suburban area	<16.2	79	6.0	14.7	133	14.7	28.4
	16.2–27.2	146	16.5	15.4	155	15.7	19.1
	≥27.7	15	28.6	24.8	27	29.1	20.1

there was a negative trend both in morning and evening PEF deviations. In winter there was no clear association between NO_2 exposure and PEF (table 5).

Discussion

A significantly increased risk of cough was found among preschool children, who were exposed to low ambient air NO_2 concentrations in Helsinki. During the spring season, there was also a trend of lower PEF values with increasing personal NO_2 exposure.

Respiratory health effects caused by indoor NO_2 exposure have been studied extensively among children [17–20]. The exposures have been assessed either by categorizing the study population, *e.g.*, by stove type or measuring indoor NO_2 concentrations with passive diffusion samplers in the kitchen, bedroom or living room of dwellings. Many of these studies have shown or suggested associations between NO_2 exposure and respiratory illness. HASSELBLAD *et al.* [21] performed a meta-analysis of studies on gas stove homes and found a combined odds ratio (OR) of 1.2 (95% CI 1.1–1.3) for respiratory illness in children, when the NO_2 concentration in the bedrooms varied 15–122 $\mu g \cdot m^{-3}$. In the USA six city study, NEAS *et al.* [20] found an increased risk (OR=1.4, 95% CI 1.14–1.72) of lower respiratory symptoms (shortness of breath, persistent wheeze, chronic cough, chronic phlegm and bronchitis) among children of 7–11 yrs of age (annual mean NO_2 16–43 $\mu g \cdot m^{-3}$). SAMET *et al.* [8], however, did not find any significant association between the NO_2 exposure and the respiratory health of children <18 months of age.

Epidemiological studies focused on outdoor NO_2 exposures have shown inconsistent results. Increased respiratory symptoms have been reported consistently among children living near busy roads [22–26]. The exposure assessments in these studies are usually based on home address, and only a few studies [25, 26] have used NO_2 dispersion models. BRAUN-FAHRLÄNDER *et al.* [6] did not find a significant association between the six-week average NO_2 concentration (range 11.1–51.3 $\mu g \cdot m^{-3}$) outdoors and the incidence of respiratory symptoms among Swiss children aged 0–5 yrs. RUTISHAUSER *et al.* [11] found, in the same age group of Swiss children, a

Table 4. – The risk ratio (RR) and 95% confidence interval (CI) for cough and nasal symptoms in different categories of weekly average NO_2 exposure

Symptoms	Personal NO_2 concentration $\mu g \cdot m^{-3}$	Symptoms of the same week (lag0)			Symptoms with a 2-day lag		
		Weeks n	Crude RR (95% CI)	Adjusted* RR (95% CI)	Weeks n	Crude RR (95% CI)	Adjusted* RR (95% CI)
Cough	<16.2	251	1	1	238	1	1
	16.2–27.2	533	1.18 (0.87–1.60)	1.23 (0.89–1.70)	490	1.23 (0.93–1.63)	1.28 (0.96–1.72)
	≥27.7	263	1.45 (1.03–2.05)	1.52 (1.00–2.31)	248	1.39 (1.00–1.93)	1.43 (0.96–2.14)
Nasal symptoms in winter season	<16.2	95	1	1	90	1	1
	16.2–27.2	271	1.01 (0.63–1.64)	0.99 (0.58–1.68)	249	1.07 (0.72–1.61)	1.07 (0.69–1.66)
	>27.7	101	0.97 (0.54–1.76)	0.89 (0.44–1.82)	93	1.16 (0.68–1.96)	1.18 (0.63–2.22)
Nasal symptoms in spring season	<16.2	156	1	1	148	1	1
	16.2–27.2	262	0.82 (0.62–1.09)	0.76 (0.56–1.02)	241	0.81 (0.62–1.06)	0.77 (0.57–1.02)
	>27.7	162	0.84 (0.59–1.18)	0.68 (0.46–1.01)	155	0.77 (0.53–1.12)	0.66 (0.44–1.00)

*: adjusting for allergy, stove type, smoking, parental education and day care centre. Cough also adjusted for season.

Table 5. – The least-square means* of morning and evening peak expiratory flow (PEF) deviations in different categories of weekly average NO_2 exposure

Personal NO_2 concentration $\mu g \cdot m^{-3}$	Morning PEF			Evening PEF		
	Week n	Crude†	Adjusted#	Week n	Crude†	Adjusted#
Winter						
<16.2	27	0.04	0.3	30	0.06	0.3
16.2–27.2	73	-0.9	-1.0	70	-1.5	-1.5
≥27.7	37	1.6	1.5	38	2.2	2.0
Spring						
<16.2	38	0.7	1.9	38	0.6	1.2
16.2–27.2	81	0.8	1.1	85	0.9	1.0
≥27.7	59	-0.3	-1.5	62	-0.6	-1.0

*: least-square means are predicted PEF values obtained from the estimated regression models; †: crude refers to the model where there is only one independent variable, namely NO_2, and where observations are assumed to be independent; #: adjusted refers to the model, which is adjusted for city area, stove type, education, smoking, allergy and first-order autocorrelation.

statistically significant positive trend between the weekly outdoor NO_2 concentration (range 25–52 $\mu g \cdot m^{-3}$) and the respiratory symptoms, but not between the weekly indoor NO_2 concentration (range 11–34 $\mu g \cdot m^{-3}$) and the respiratory symptoms. KOO *et al.* [27] found no association between the exposure and lower respiratory symptoms among children aged 7–13 yrs, when the personally measured two-week mean NO_2 concentration for males was 34.5 $\mu g \cdot m^{-3}$ and for females 35.7 $\mu g \cdot m^{-3}$. In Sweden, PERSHAGEN *et al.* [25] showed a significant association of the 99th percentile 1 h NO_2 concentration (range 20–205 $\mu g \cdot m^{-3}$) with hospital treated wheezing bronchitis among females aged 4 months–4 yrs, but there was no such association among males. In East Germany, VON MUTIUS *et al.* [28] found that an increased risk of developing upper respiratory symptoms (cough, running nose, hoarseness) in childhood was associated with moderate levels of NO_x both in winter and summer months (NO_x maximum concentration range 49–502 $\mu g \cdot m^{-3}$ in a high pollution season and 89–261 $\mu g \cdot m^{-3}$ in a low pollution season).

A possible cause for the lack of consistency in epidemiological studies concerning health effects of NO_2 is misclassification of exposure.

With regard to exposure assessment, the present study differs from many previous NO_2 exposure studies. Children in this study were mostly asymptomatic and indoor sources of NO_x (*e.g.*, gas stove) were scarce. The total exposure of 163 children aged 3–6 yrs was assessed by using direct measurements of the personal weekly average NO_2 concentration for 13 weeks. In this way, it was attempted to minimize exposure misclassification, which usually reduces the power of the study to find an association between the exposure and health outcome. As in many cities, the children in this study were exposed not only to NO_2 outdoors, but were in fact exposed to a complex mixture of air pollutants. The possible modifying effect of the co-pollutants (*e.g.*, particles, O_3) on the health effects of NO_2 is poorly understood [2], but in the present analyses they did not seem to have a major role.

The nonsignificantly increased risk of nasal symptoms after a 2-day lag in the winter season might be partly owing to both the NO_2 exposure and the northern climatic conditions. Nasal discharge is a common symptom among physically active children when entering a warm indoor environment from a cold outdoor environment. There is no clear explanation for the decreased risk of nasal symptoms when the NO_2 exposure increased in the spring season. Nasal symptoms are quite nonspecific, and they may be attributed to a variety of causes, *e.g.*, pollen. In this study, however, the pollen counts did not change the risk estimates. The finding that personal NO_2 exposure was significantly associated with cough, but not with nasal symptoms, might be at least partially related to the physicochemical properties of the pollutant, which limit its removal in the upper airways and make it an irritant of the lower airways [1–4].

In this study, the trend of lower PEF values with increasing personal NO_2 exposure was nonsignificant. There have been no clear associations between low NO_2 concentrations and PEF values in previous studies. No association was found between the daily 1 h maximum NO_2 concentration (mean 40.5 $\mu g \cdot m^{-3}$, range 12–79 $\mu g \cdot m^{-3}$) and PEF among elementary school children [7], nor between the indoor NO_2 concentration (9.9% over 60 $\mu g \cdot m^{-3}$) and PEF among children aged 6–12 yrs [19]. Among Dutch children (6–12 yrs of age), however, a decrease in PEF was noticed two weeks after an air pollution episode in January 1987 (1-h maximum NO_2 concentration 250 $\mu g \cdot m^{-3}$) [29]. After a later air pollution episode in February 1991, no such association could be shown between NO_2 (1-h maximum 127 $\mu g \cdot m^{-3}$) and PEF among children aged 7–12 yrs [30].

In the present study, the use of weekly average morning and evening PEF deviations might have been a too crude and insensitive way to estimate changes in lung function, which might have weakened the association. PEF analysis measures the change of the calibre of larger airways as well as the coordination and strength of respiratory musculature, and NO_2 is a deep lung irritant. The reliability of PEF measurements in this age group is not unambiguous. The maturation of the children's lungs continues up to school age, and the resistance of peripheral airways constitutes a great part of the total airway resistance in children <6 yrs. In two studies, where the reproducibility of the PEF measurement was assessed, the coefficient of variation was 7.8% among healthy children <5 yrs of age [31] and 8.8% among asthmatic children (mean±SD age 6.0±2.7 yrs) [32]. To clarify the association between NO_2 exposure and lung function, more epidemiological studies are needed, especially on short-lasting peak exposures, because it has been suggested that the short-lasting peaks might actually be more harmful than the somewhat elevated long-term average exposures to NO_2 [1–4].

In conclusion, a significantly increased risk of cough was found among preschool children in association with relatively low personal NO_2 exposures in Helsinki. As the well-known indoor sources of NO_x could have only a small contribution to the personal NO_2 exposure, this finding must be associated with the main outdoor sources, *i.e.*, automotive traffic. Further elucidation of the respiratory health effects of NO_2, including personal monitoring of peak exposures, is needed.

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