

8. Epidemiologic studies

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Epidemiologic studies on the health effects of nitrogen oxides have mainly focused on nitrogen dioxide (NO_2). If exposure levels are given, they are generally expressed as NO_2 , although it is evident that exposure has also occurred to other oxides, primarily nitric oxide (NO). In view of the data available and the difficulties in separating effects of different nitrogen oxides, the discussion of the epidemiologic evidence relates mainly to NO_2 .

The epidemiologic evidence on NO_2 exposure covers a wide range of health effects, from acute annoyance reactions and lung function disturbances to chronic pulmonary diseases, such as asthma and chronic bronchitis. This review mainly focuses on studies relevant to the risk assessment of low-level exposure in the general environment (ie, on effects in sensitive parts of the population, such as diseases of the lower respiratory tract in children). The possible role of NO_2 exposure in the excess risk of allergic sensitization and lung cancer in urban areas is discussed only briefly because of the lack of specific exposure data, and therefore it is not used in the risk evaluation.

Much of the evidence relates to NO_2 exposure in ambient air, where NO_2 is only one of several components whose exposure may be correlated, and it is thus difficult to define etiologic relationships. Only studies providing data on actual NO_2 concentrations based on measurements or model calculations have been included in this review. Gas appliances are an important source of indoor NO_2 exposure, which can be a main contributor to total NO_2 exposure for people spending most of their time indoors. (See chapter 2.) Epidemiologic studies on NO_2 exposure from gas appliances have received particular attention, as concomitant exposure to other agents may be less important than in the outdoor environment; this situation facilitates the assessment of causal relationships.

Acute effects of short-term exposure are discussed first. Symptoms and diseases of the respiratory tract in children and adults are then considered. They were generally reported in relation to long-term exposure, but it cannot be excluded that short-term peaks were of importance. Pulmonary function disturbances are treated separately and include effects of both short-term and long-term exposures. A section on occupational exposure provides evidence of the effects of comparatively high NO_2 levels.

Acute effects

Several studies have investigated the relation between NO_2 levels in ambient air, often measured as hourly or daily averages, and acute health effects. These effects primarily include annoyance reactions and subjective symptoms reported in diaries and in hospital admissions. Studies on lung function which may represent both acute and chronic effects are reviewed later in a separate section.

A study of 158 adults suffering from chronic obstructive pulmonary disease or allergy (mainly allergic rhinitis and conjunctivitis) was performed in two areas near a coal-fired plant in Finland (1). The mean NO_2 concentrations in the areas were 28.3 and 25.3 $\mu\text{g}\cdot\text{m}^{-3}$ during the four-month study period with daily averages ranging up to 70 $\mu\text{g}\cdot\text{m}^{-3}$. There was a significant correlation ($P<0.01$) between daily NO_2 levels and symptom rates in the patients with chronic obstructive pulmonary disease. However, when adjustment was made for air temperature, which was inversely related to NO_2 levels and symptom rates, no clear association was seen.

A total of 128 elementary school-age children from a region in Pennsylvania with coal-fired power plants participated in an eight-month diary study on respiratory symptoms (2). The children were selected from an earlier cross-sectional study and divided into the following three groups: persistent wheeze, cough or phlegm, and no respiratory symptoms. The daily mean of maximum 1-h NO_2 concentrations in the region ranged from 12 to 79 $\mu\text{g}\cdot\text{m}^{-3}$ with an average of 40.5 $\mu\text{g}\cdot\text{m}^{-3}$. No differences in NO_2 concentrations were observed between days with high and low incidence rates of respiratory symptoms or illnesses. Respiratory illness on the preceding day was the most important predictor of current illness.

Weekly changes in air pollutant levels were compared with respiratory infections in children and adults diagnosed at municipal health centers and with absenteeism from day-care centers during one year in Helsinki, Finland (3). The annual average NO_2 concentration measured at one station was 47 $\mu\text{g}\cdot\text{m}^{-3}$. After standardization for temperature, no correlation was seen between the NO_2 levels and respiratory infections or absenteeism from day-care centers.

Approximately 200 student nurses in Los Angeles were included in a diary study extending over three years (4). Daily maximum 1-h NO_2 concentra-

tions measured at a station near the school averaged $244 \mu\text{g}\cdot\text{m}^{-3}$ (0.13 ppm) with a 75th percentile of $320 \mu\text{g}\cdot\text{m}^{-3}$ (0.17 ppm). In a logistic regression analysis controlling for temperature and serial correlation between days, an increase in $171 \mu\text{g}\cdot\text{m}^{-3}$ (0.091 ppm) corresponded to excess risks of phlegm [relative risk (RR) 1.08, $P<0.01$], sore throat (RR 1.26, $P<0.001$) and eye irritation (RR 1.16, $P<0.001$). The associations persisted also after adjustment for smoking and allergies.

A diary study of 162 children and adults in Oslo registered annoyance and symptoms on an hour-by-hour basis during two weeks (5). The estimated mean NO_2 exposure levels based on time activity patterns ranged from 10 to $53 \mu\text{g}\cdot\text{m}^{-3}$ for the different individuals, with maximum hourly concentrations of up to $188 \mu\text{g}\cdot\text{m}^{-3}$ for children and teenagers, and up to $163 \mu\text{g}\cdot\text{m}^{-3}$ for elderly persons. Fatigue, sneezing, sore/irritated throat, tight chest, annoying smell, and annoying noise were significantly associated with estimated NO_2 exposures, showing relative risks ranging from 1.17 to 2.45 in a comparison with a concentration of $100 \mu\text{g}\cdot\text{m}^{-3}$ with $10 \mu\text{g}\cdot\text{m}^{-3}$. The relative risks comparing different exposures were calculated from the regression coefficients in multiple regression analyses including symptoms the preceding hour, outdoor temperature, relative humidity, smoking, and the like.

Another Norwegian study was performed in Grenland, an industrially polluted area where three groups of subjects were followed on an hour-by-hour basis for four months (6). The three groups included a population sample of adults ($N = 312$), as well as adults ($N = 67$) and children ($N = 18$) with pulmonary disease. Estimated NO_2 exposures based on time activity patterns and indoor and outdoor measurements showed median levels of 14 and $13 \mu\text{g}\cdot\text{m}^{-3}$ for the population sample and subjects with pulmonary disease, respectively, with maximum hourly concentrations up to 334 and $214 \mu\text{g}\cdot\text{m}^{-3}$, respectively. The results showed a rather incoherent picture comparing NO_2 exposures with subjective symptoms in multiple regression analyses including outdoor temperature, relative humidity, and some air pollution components. Estimated NO_2 exposures seemed to correlate with symptoms from the upper respiratory tract and fatigue or stress in the population sample. NO_2 concentrations giving rise to a 50% increase in relative risk compared with an assumed background of $5 \mu\text{g}\cdot\text{m}^{-3}$ were estimated to be 42 and $229 \mu\text{g}\cdot\text{m}^{-3}$, respectively, for these two types of symptoms. The results for subjects with pulmonary disease were less consistent.

Daily counts of children's visits to physicians for croup symptoms and obstructive bronchitis in five German cities were compared with air pollution data for more than two years (7). Altogether 6630 cases of croup and 4755 cases of obstructive bronchitis were recorded. The median NO_2 levels in the five

cities ranged from 14 to $55 \mu\text{g}\cdot\text{m}^{-3}$. Physicians' visits for croup were correlated to daily concentrations of both NO_2 and suspended particulates. No significant effect of temperature or humidity on disease rates was observed after control for seasonal and other cyclical patterns. An increase in NO_2 concentration from 10 to $70 \mu\text{g}\cdot\text{m}^{-3}$ was estimated to result in a relative risk of 1.28. No corresponding association was seen for obstructive bronchitis.

A diary study during five weeks included 449 subjects believed to be sensitive to air pollution from answers to a questionnaire on asthma symptoms, other respiratory symptoms, annoyance, and the like (8). The subjects lived in 43 Swedish towns with average NO_2 concentrations ranging between about 10 and $40 \mu\text{g}\cdot\text{m}^{-3}$ during the observation period. Annoyance and symptoms from the respiratory tract were related to daily NO_2 concentrations ($P<0.001$) but not to sulfur dioxide, soot, temperature, or humidity. The daily symptom rate increased from 13.5 to 27.4% for days with NO_2 at less than $10 \mu\text{g}\cdot\text{m}^{-3}$ to days with NO_2 at more than $50 \mu\text{g}\cdot\text{m}^{-3}$. The associations became stronger when only days preceded by a symptom-free day were included in the analysis.

Studies on mortality in relation to variations in air pollution levels (eg, during smog episodes) are generally difficult to interpret because of high correlations between different pollutants (9, 10).

Symptoms and diseases of the respiratory tract in children

Symptoms and diseases of the respiratory tract are very common in children. A subdivision is often made into conditions affecting the lower and upper respiratory tract. Studies on lower respiratory tract symptoms include questions on persistent cough, wheezing, and colds going to the chest. The predominant illnesses affecting the lower respiratory tract among children are bronchitis, asthma, and pneumonia. Symptoms of the upper respiratory tract used in epidemiologic investigations include runny nose, cold, sore throat, earache, stuffiness of the head, and the like. Most studies on noninfectious environmental causes of respiratory diseases in children have focused on symptoms and diseases of the lower respiratory tract that may represent critical effects for some types of exposures, such as environmental tobacco smoke.

The design and results of the epidemiologic studies on NO_2 exposure and respiratory symptoms or diseases are summarized in table 8.1 on pages 60-63. Most of the studies were based on comparisons between children from homes with and without gas appliances. The design was often cross-sectional in which exposures and health effects were measured at the same time, for example via questionnaires to

parents. However, a few longitudinal studies exist, both of cohort and case-referent design. As is evident from the table, several of the studies included NO_2 measurements based on indoor, outdoor or personal monitoring. In a few studies time activity patterns were also considered in the estimates of NO_2 exposure. The assessment of the respiratory diseases of the children was generally based on parental reports in questionnaires without any attempts for validation. Information on potential confounding factors, such as parental smoking habits and socioeconomic status, was also obtained from the questionnaires.

The studies on gas appliances and respiratory diseases in children give somewhat inconsistent results. Figure 8.1 shows relative risks (odds ratios) for respiratory diseases or symptoms associated with gas stoves or measured NO_2 exposure in 13 studies. The relative risks and 95% confidence intervals were sometimes estimated from the data given in the original publications (11). A few of the investigations provide statistically significant excess risks (12, 13, 14, 15, 16), while the others fail to do so. However, the confidence intervals were wide in many of the "negative" studies, often having point estimates of relative risks (odds ratios) exceeding 1, which means that the studies do not provide strong evidence against an effect. Only one study showed a clear ex-

posure-response relationship (16), however, most of the investigations did not attempt such analyses.

Recently a meta-analysis has been performed of the studies on NO_2 exposure, mostly originating from domestic gas appliances, and lower respiratory tract illnesses in children (11). In order to combine the results, the relative risk associated with long-term exposure to a $30 \mu\text{g}\cdot\text{m}^{-3}$ increase in the NO_2 level was calculated (comparable to the increase resulting from exposure to a gas stove). If no measurement data were given in the original studies, the exposure was estimated from information on the use of gas stoves. The relative risks for lower respiratory tract illnesses in the 11 included studies ranged from 0.63 to 1.53, with an overall estimate of 1.18 and a 95% confidence interval of about 1.1-1.3 (depending on the method of analysis). In other words, the overall evidence is consistent with an excess risk of about 20% for lower respiratory tract illness in children in association with long-term exposure to an NO_2 increase of $30 \mu\text{g}\cdot\text{m}^{-3}$.

A few studies focused on outdoor exposure to NO_2 or $\text{NO}_2 + \text{NO}$ (NO_x) (17-22). The design and results of these studies are also summarized in Table 8.1. In general, increased risks of respiratory diseases and symptoms were observed in children related to comparatively low outdoor NO_2 concentrations. How-

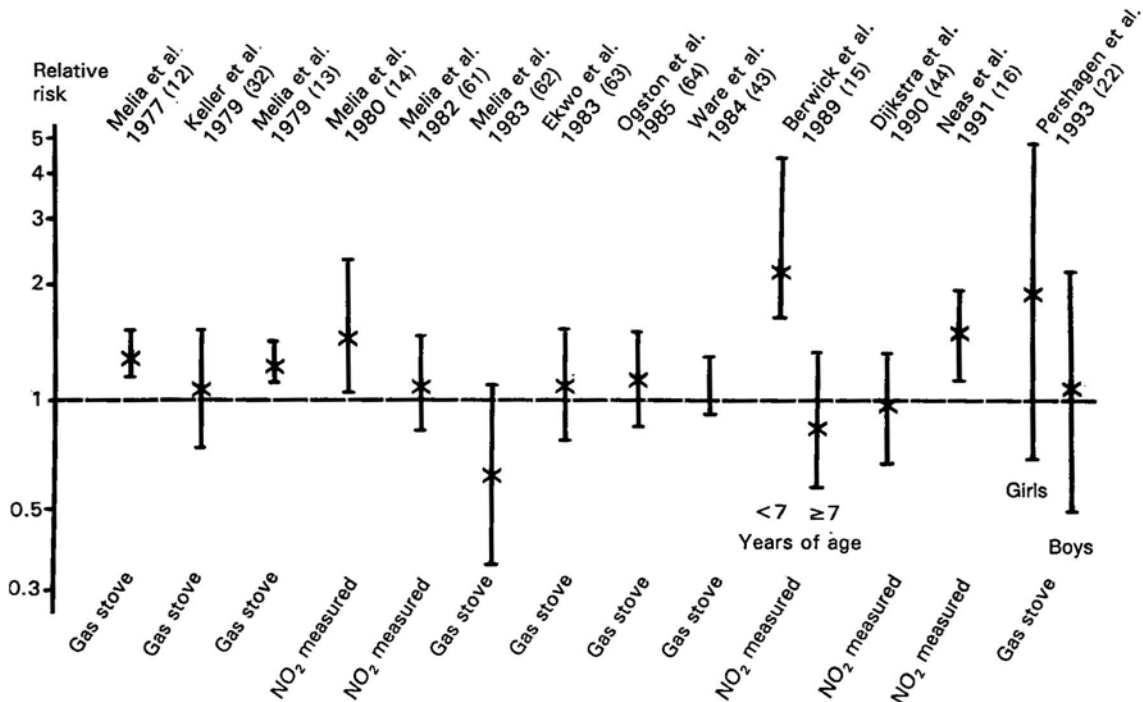


Figure 8.1 Relative risk for lower respiratory tract illness among children in relation to domestic gas appliances or measured indoor concentrations of nitrogen dioxide (NO_2) (bars indicate 95% confidence intervals).

Table 8.1. Summary of the design, exposure, and results of epidemiologic studies on nitrogen dioxide (NO₂) and respiratory illness in children. [RI = respiratory illness (bronchitis, asthma, pneumonia, chest illness), LRS = lower respiratory tract symptoms (colds going to the chest, persistent cough, wheezing, breathlessness), RS = respiratory symptoms, OR = odds ratio (range in parenthesis indicates 95% confidence interval), RR = relative risk (range in parenthesis indicates 95% confidence interval), SO₂ = sulfur dioxide, TSP = total suspended particulates, ETS = environmental tobacco smoke, NO_x = nitrogen dioxide + nitric oxide, max = maximum]

Country	Number/age	Exposure
England & Scotland	5758 children, 6-11 years	Gas cooking
England & Scotland	4827 children, 5-10 years	Gas cooking
England	808 children, 6-7 years	Gas cooking, one week NO ₂ measurement: 34 (range 11-353) µg·m ⁻³ in kitchen with electric cookers, 210 (range 10-596) µg·m ⁻³ in kitchen with gas cookers, 26 (range 6-70) µg·m ⁻³ in bedroom without gas, 57 (range 8-318) µg·m ⁻³ in bedroom with gas
England	337 children, 5-6 years	Gas cooking, weekly average NO ₂ concentrations 17-549 µg·m ⁻³ in living rooms and 9-302 µg·m ⁻³ in bedrooms
Scotland	1565 infants, <1 year	Gas cooking
United States Ohio	176 children, <12 years	Gas cooking, 38 µg·m ⁻³ not exposed, 94 µg·m ⁻³ exposed (annual mean)
United States (six cities)	8120 children, 6-10 years	Outdoor air pollution, gas stove; geometric mean NO ₂ level (24-h): indoor ranging from 3.6 (electric) and 14.7 (gas) to 41.4 (electric) and 54.3 (gas) µg·m ⁻³ in different cities; short-term peaks of 1100 occurred in kitchens; geometric mean outdoor levels ranged from 5.9 to 41 µg·m ⁻³ in the six cities
United States (six cities)	10106 children, 6-10 years	Gas stove
United States (six cities)	1567 children, 7-11 years	Weekly measurements of indoor NO ₂ during 1983-1988 (annual mean) ranged from 16 to 43 µg·m ⁻³ (with NO ₂ source in household)
United States, Ohio	Approximately 300 children, 9-11 years	Industrial area; schoolyear mean NO ₂ levels 54 and 37 µg·m ⁻³ in high and low exposure areas
United States, Tennessee	Preschool children	Trinitrotoluene plant [low exposure/high exposure area (NO ₂ in µg·m ⁻³): 24-h 43/37-91 (mean), 75/120-333 (99th percentile); 1-h 43/27-94 (mean), 113/188-692 (99th percentile)]
United States, Iowa	1355 children, 6-12 years	Gas cooking
United States, Pennsylvania	4071 children, 5-14 years	Coal-fired power plant: gas cooking stove, no NO ₂ concentrations reported
United States, Connecticut	121 children, <13 years	Two-week NO ₂ measurements, house average for all rooms: 6 µg·m ⁻³ no source, 41 µg·m ⁻³ kerosene heater only, 31 µg·m ⁻³ gas stove only, 90 µg·m ⁻³ kerosene heater+gas stove

Results	Comments	References
RI and LRS (one or more symptoms): OR=1.31 children < age 8; girls P<0.05; boys P=0.30	Not adjusted for parental smoking	Melia et al, 1977 (12)
RI and LRS (one or more symptoms): OR=1.25 boys (P<0.05), 1.19 girls (P=0.07)	Adjusted for parental smoking	Melia et al, 1979 (13)
RI and LRS (one or more symptoms) associated with NO ₂ level in bedroom (P<0.1); later estimated by Hasselblad et al (11) that a 30 µg·m ⁻³ increase in bedroom corresponds to RR = 1.53 (1.04-2.24)	Adjusted for smoking and social class	Melia et al, 1980 (14)
RI or LRS (one or more symptoms) not associated with NO ₂ level in living room or bedroom; later estimated by Hasselblad et al (11) that a 30 µg·m ⁻³ increase in bedroom corresponds to RR = 1.11 (0.83-1.49)	Positive association found for relative humidity (P<0.05); adjusted for parental smoking	Melia et al, 1982 (61)
At least one episode of RI: RR = 1.14 (0.86-1.50)	Adjusted for parental smoking and type of heating	Ogston et al, 1985 (64)
LRS (one or more symptoms): OR=1.10 (0.74-1.54)	No adjustment for parental smoking	Keller et al, 1979 (32)
Doctor diagnosed RI before age 2 years: OR = 1.12 (1.00-1.26) for homes with gas stove compared to homes with electric stove	Adjusted for parental smoking and social class	Speizer et al, 1980 (42)
Doctor diagnosed respiratory disease before age 2 years: OR = 1.11 (0.99-1.28); history of bronchitis: OR = 0.86 (0.74-1.00)	Adjusted for smoking and parental education	Ware et al, 1984 (43)
Cumulative incidence of LRS (one or more symptoms) with a 30 µg·m ⁻³ difference in NO ₂ : OR = 1.4 (1.1-1.7) total; OR = 1.7 (1.3-2.2) girls; OR = 1.2 (0.4-1.5) boys	Adjusted for parental history of LRI education, single parent family status, and measured levels of respiratory particles	Neas et al, 1991 (16)
RR = 2.25 (P = 0.04) for wheezing and dyspnea comparing high and low exposure areas	School year mean levels of SO ₂ and TSP 77 and 55 µg·m ⁻³ in high exposure area and 21 and 52 µg·m ⁻³ , respectively, in low exposure area	Mostardi et al, 1981 (17)
Higher rate of acute respiratory disease in area of high exposure compared with low exposure area (RR = 1.4, P=0.0004)	Adjusted for education, crowding, smoking by parents and paternal bronchitis; mean TSP concentration exceeded 75 µg·m ⁻³ in low exposure area	Love et al, 1982 (18)
Hospitalization for RI before age 2 years: RR=2.4 (P=0.001)	RR=9.25 (P<0.0006) gas+parental smoking	Ekwo et al, 1983 (63)
No association between gas cooking stove and RI, RS or serious respiratory illness before 2 years of age	Younger age, male gender, and low socioeconomic status independent risk factors for most RS and RI; significant trend for RI with number of current parental smokers	Schenker et al, 1983 (66)
LRS (two or more symptoms) with a 30 µg·m ⁻³ NO ₂ difference: OR = 2.25 (1.69-4.79) age <7 years; OR = 0.84 (0.59-1.42) age >7 years	Adjusted for socioeconomic status and history of respiratory illness	Berwick et al, 1989 (15)

(continued)

Table 8.1. Continued.

Country	Number/age	Exposure
The Netherlands	128 children suffering from bronchitis, asthma, frequent coughs and allergy; 103 controls; aged 6 years	NO ₂ levels in kitchen 144 µg·m ⁻³ , living room 80 µg·m ⁻³ , bedroom 50 µg·m ⁻³ and ambient air 45 µg·m ⁻³
The Netherlands	775 children, 6-12 years of age	Weekly average NO ₂ concentrations about 20, 40 and 60 µg·m ⁻³ in homes without kitchen geyser, with kitchen geyser and flue, and with kitchen geyser but no flue, respectively
Japan	About 1500 schoolchildren, 6-14 years of age	Outdoor air pollution: annual mean NO ₂ concentrations 20 - 60 µg·m ⁻³ in different study areas
Israel	3374 second and fifth grade schoolchildren	NO _x concentrations in ambient air: Hadera: 6-10 ppb (monthly average), 37-128 ppb (max concentration 30 min) Ashdod: 8-33 ppb (monthly average), 38-528 ppb (max concentration 30 min)
Switzerland	1225 children, 0-5 years of age	Personal sampling (weekly) NO ₂ levels ranging from 25 to 52 µg·m ⁻³ (outdoor) and from 11 to 34 µg·m ⁻³ (indoor) in four towns during one year of study
Hong Kong	362 primary schoolchildren, 7-13 years of age	Personal sampling during two weeks: mean concentration 34.5 µg·m ⁻³ for boys and 35.7 µg·m ⁻³ for girls
Sweden	199 children with hospital treated wheezing, bronchitis or asthma and 351 population controls; 4 months - 4 years of age	Outdoor air pollution, gas stove: estimated time-weighted 99th percentile outdoor NO ₂ level 20 - 205 µg·m ⁻³ for different study subjects (mean 55 µg·m ⁻³)

ever, three of the studies were performed near fossil fueled power plants or in industrial areas with a complex exposure environment (17, 19, 20), and therefore it is difficult to assess the etiologic role of NO₂.

One study included communities near a trinitrotoluene plant, where NO₂ exposures dominated, although total suspended particulate concentrations were comparatively high in one of the areas (18). These communities had been investigated earlier, when the exposure levels were higher, and an excess bronchitis morbidity in children had been indicated (23). In the later study the respiratory disease rates in pre-school children were increased in the designated high-exposure area during a period characterized primarily by high peak concentrations of NO₂ (1-h 99th percentile 692 µg·m⁻³). Similar but less pronounced effects were seen in schoolchildren.

Two studies concerned areas where motor vehi-

cles constituted the primary source of environmental NO₂. A significant association was found between measured NO₂ levels outdoors and daily respiratory symptom rates (cough, sore throat, runny nose, etc) among preschool children in a Swiss study (21). Increased symptom rates were suggested already at six-week average levels exceeding 30 µg·m⁻³; however, no information was provided on short-term peak exposures. The other study was performed in Stockholm, Sweden, and showed a statistically significant excess risk of wheezy bronchitis in girls having an estimated mean time-weighted outdoor NO₂ level of exposure exceeding 70 µg·m⁻³ as the 99th percentile of 1-h values (22). This level corresponds to a winter half-year mean of 27 µg·m⁻³. No comparable relation was seen for the boys. An excess risk in homes with gas stoves was also observed for the girls only. This finding is supported by the results of some other

Results	Comments	References
No clear associations between measured NO ₂ exposure and RI; however, suggested excess OR for some symptoms such as persistent cough and asthma in relation to measured NO ₂ levels in living rooms and bedrooms	Adjusted for parental respiratory symptoms, indoor humidity, parental education, bedroom heating and maternal smoking	Hoeck et al, 1984 (65)
LRS compared with 0-20 µg·m ⁻³ : 20-40 µg·m ⁻³ : RR= 0.84 (0.48 - 1.47); 41-60 µg·m ⁻³ : RR= 0.83 (0.36 - 1.93); >60 µg·m ⁻³ : RR= 0.96 (0.40 - 2.31)	Adjusted for home dampness, ETS exposure and parental education, association with ETS [RR=2.06 (1.6-3.66)] and dampness	Dijkstra et al, 1990 (44)
Correlation between annual mean NO ₂ concentration and wheezing in children with positive skin reaction to house dust extract (P<0.01), but not for children with negative skin reactions; correlation for "subacute phlegm" in both skin reaction groups (P<0.05)	Air pollution from oil-fired power station also included SO ₂ and particulates	Kagamimori et al, 1986 (19)
Ashdod compared with Hadera: RR=2.66 for asthma (P=0.04), RR=2.30 for bronchitis (P=0.01)	Adjusted for socioeconomic status, parental smoking and respiratory disease; Ashdod is an industrial polluted area and no distinction was made in the effect of different components (SO ₂ , NO _x , TSP, etc)	Goren & Hellmann, 1988 (20)
RS in relation to outdoor levels: <30 µg·m ⁻³ : 0.31 symptoms/day; 30-49 µg·m ⁻³ : 0.39 symptoms/day; >50 µg·m ⁻³ : 0.41 symptoms/day; P<0.001 for trend; no association between indoor levels and respiratory symptoms	Adjusted for parental smoking, nationality, socioeconomic status, history of serious respiratory problems, etc	Ruitshauser et al, 1990 (21)
No association between NO ₂ concentrations and LRS		Koo et al, 1990 (37)
RI associated with estimated outdoor NO ₂ exposure of girls (P=0.02) but not of boys; gas stove in homes: RR=1.9 (0.7 - 5.0) for girls and 1.1 (0.5-2.2) for boys	Adjusted for asthma, heredity and maternal smoking	Pershagen et al, 1993 (22)

investigations (12, 16). However, most of the studies on NO₂ exposure and respiratory disease in children did not look at boys and girls separately.

Allergic sensitization in children

A few studies indicate that sensitization to aeroallergens, such as pollen and animal dander, is more common among children living in urban areas (24, 25) or near roads with heavy traffic (26). This has also been confirmed for adults (27, 28). It is possible that outdoor air pollution may have contributed to these findings; however, other differences between urban and rural areas should also be considered in the interpretation, such as personal habits and the indoor environment. NO₂ levels were reported only in one

study (25), in which the hourly average concentration of 190 µg·m⁻³ was exceeded on 20 and 27 occasions during the two years of study at one station in the investigated town. No measurement data were available for the rural area used as comparison.

Symptoms and diseases of the respiratory tract in adults

A number of studies have investigated symptoms and diseases of the respiratory tract in adults in relation to NO₂ exposure. The design has been cross-sectional, with particular emphasis on symptoms or diseases of the lower respiratory tract. Most of the studies focused on outdoor air pollution, NO₂ being used as the indicator of pollution mainly originating from

motor vehicles. Tobacco smoking is the primary determinant of some important symptoms and diseases of the lower respiratory tract, such as persistent cough, phlegm production and chronic bronchitis, and, to avoid confounding, only nonsmokers were included in some of the studies. A disadvantage with such a design is that interactions between NO_2 exposure and smoking cannot be assessed.

Respiratory symptoms were studied via questionnaires to 3873 nonsmokers in two communities in California with mean hourly NO_2 concentrations of 96 and 43 $\mu\text{g}\cdot\text{m}^{-3}$ (0.051 and 0.023 ppm) during 1963-1967 (29). No difference in the prevalence of cough (with and without phlegm) was seen between the two areas.

The prevalence of chronic respiratory disease assessed via questionnaire tended to be higher among both nonsmokers and current smokers working as traffic officers in a study of 268 policemen from Boston, Massachusetts (30). The mean NO_2 concentration during the year of study was 103 $\mu\text{g}\cdot\text{m}^{-3}$ (0.055 ppm) with maximum hourly levels of up to 564 $\mu\text{g}\cdot\text{m}^{-3}$ (0.33 ppm).

Questionnaires were distributed to more than 5000 individuals living in two Californian communities exposed to different levels of photochemical oxidants, including NO_2 (31). The annual means of daily maximum hourly concentrations of NO_2 were 60 and 211 $\mu\text{g}\cdot\text{m}^{-3}$ in the two areas. The prevalence of cough, sputum production, and wheezing was increased in the high pollution area among the nonsmokers, while for smokers the excess was primarily seen for wheezing.

No increase in respiratory symptoms or disease rates was found for adults from homes with cooking gas in the study by Keller et al (32), as discussed in the section on lower respiratory tract illness in children.

Respiratory symptoms were recorded for 708 non-smoking adults in Maryland and related to exposure to environmental tobacco smoke and gas cooking (33). Symptom rates were significantly increased for chronic cough (with and without phlegm) in subjects from households using gas cooking after adjustment for socioeconomic status. An earlier study, based on the same group but also including smokers, indicated that the effects were less pronounced among smokers (34).

More than 100 housewives living at different distances from a major traffic artery in Tokyo answered a questionnaire on respiratory symptoms, smoking habits, and the use of kerosene heaters (35). NO_2 concentrations measured in ambient air during 7 d ranged from 68 to 129 $\mu\text{g}\cdot\text{m}^{-3}$ within 20 m from the roadside and from 45 to 80 $\mu\text{g}\cdot\text{m}^{-3}$ up to 150 m from the road. Personal samplers indicated that the use of kerosene heaters was the main determinant of NO_2 exposure. Increased prevalence rates of persistent

cough and phlegm were determined for women living closest to the road, particularly for the nonsmokers and those not using kerosene heaters. The effects were less clear in relation to kerosene heater use.

A total of 7445 Seventh-day Adventists who were nonsmokers from California were included in a study on chronic obstructive disease symptoms in relation to exposure to photochemical oxidants (36). About 20% of the population was estimated to be exposed to NO_2 at 94 $\mu\text{g}\cdot\text{m}^{-3}$ (0.05 ppm) or higher during 4900 h a year. No association between estimated NO_2 exposure and respiratory symptoms was seen in a multiple regression analysis including gender, age, race, education, passive smoking, and the like. On the other hand, symptom rates were significantly associated with exposure to total oxidants, sulfur dioxide, and, most strongly, total suspended particulate.

Respiratory symptom rates were compared with NO_2 exposure measured by personal samplers during two weeks among 319 women from Hong Kong (37). The mean NO_2 level of 36 $\mu\text{g}\cdot\text{m}^{-3}$ was influenced by occupational exposure, cooking fuels (liquid petroleum gas and kerosene), ventilation, and incense burning in the home. Among the 312 nonsmokers the symptom rates were associated with NO_2 exposure for allergic rhinitis and chronic cough. A significant trend ($P<0.01$) was also seen between the number of respiratory symptoms and the NO_2 levels.

A questionnaire on annoyance and respiratory symptoms was answered by more than 6000 subjects living in towns near 55 measurement stations for air pollution in Sweden (38). Winter half-year average NO_2 levels ranged between about 10 and 30 $\mu\text{g}\cdot\text{m}^{-3}$ in the different towns. Statistically significant correlations ($P<0.01$) were seen between the NO_2 levels and annoyance due to bad smell, irritation, and dust or soot pollution of the air. Similar effects were observed in nonsmokers, ex-smokers, and smokers. With regard to respiratory symptoms, the highest correlation appeared for throat irritation and irritating or unproductive cough during the last three months ($P<0.01$). Weaker correlations were generally found between symptom rates and concentrations of sulfur dioxide and soot.

Increased lung cancer rates have been reported for urban areas, with smoking standardized relative risks on the order of 1.5 or lower in a comparison with rural areas (39). Coal combustion was a major source of air pollution in many of the environments under study. If exposure data were given, they were often expressed as concentrations of sulfur dioxide or particulates, although it is clear that the levels of nitrogen oxides were also increased. The lack of specific information on NO_2 exposure makes the evidence unsuitable for risk estimation.

Pulmonary function

Pulmonary function studies in relation to NO_2 have been performed on children and adults after both short-term and long-term exposures. Most of the investigations included measures of obstructive impairment, such as forced expiratory volume in 1 s ($\text{FEV}_{1.0}$), forced vital capacity (FVC), and peak expiratory flow (PEF). Recent studies tend to focus on effects in the smaller airways. A thorough description of different measures and tests of pulmonary function and their significance is given in chapter 5. Although most of the studies were cross-sectional, some also included longitudinal follow-up of lung function. Unfortunately, very few investigations focused on asthmatics or other subjects who may be particularly sensitive to airway irritants.

Two studies looked at acute effects on pulmonary function in children in relation to NO_2 levels in the ambient air (2, 40). In the first study there was a correlation between daily NO_2 levels and PEF, while the second failed to show such an association. The hourly average NO_2 concentrations in the first study ranged between about 10 and 400 $\mu\text{g}\cdot\text{m}^{-3}$, and the daily means of the hourly maximum concentrations were between 12 and 79 $\mu\text{g}\cdot\text{m}^{-3}$ in the second study.

An early study on children living near a trinitrotoluene plant indicated a small decrease in pulmonary function ($\text{FEV}_{1.0}$) in comparison with the $\text{FEV}_{1.0}$ of control children (41). The winter half-year mean NO_2 concentrations at different stations in the high exposure area ranged from 117 to 205 $\mu\text{g}\cdot\text{m}^{-3}$ (0.062–0.109 ppm) and the corresponding TSP levels (total suspended particulates) were also increased (63–96 $\mu\text{g}\cdot\text{m}^{-3}$). Later studies showed slight decreases in pulmonary function measures associated with gas cooking or estimated NO_2 exposure in some groups (42–44) but not in others (16, 45, 46). Lung function growth measured over a two-year period was not associated with NO_2 exposure in one study (44). No consistent differences in NO_2 levels were evident between the six later studies showing or not showing associations. It should be noted that the effects were small in the studies showing statistically significant results (ie, only a few percent decrease in the flow rates or less).

One study found an increased prevalence of bronchial hyperreactivity among schoolchildren in an urban area of Switzerland, primarily in those children without asthma or other allergic diseases (47). Average NO_2 levels during a 10-month period in the urban and rural comparison areas were 36 and 26 $\mu\text{g}\cdot\text{m}^{-3}$, respectively.

Acute effects on pulmonary function in adults from NO_2 exposure was assessed in four studies. A preliminary investigation of eight asthmatics and six nonasthmatics from Toronto, Canada, compared daily pulmonary function measurements and NO_2 exposure based on personal sampling (48). The av-

erage NO_2 level during the 40 d study period was 37 $\mu\text{g}\cdot\text{m}^{-3}$, and the corresponding particulate concentration 106 $\mu\text{g}\cdot\text{m}^{-3}$. The daily decrease in pulmonary function was associated with NO_2 exposure, but was statistically significant only for the asthmatics. A small study on asthmatics suggested a drop in FVC and PEF at indoor NO_2 levels above 564 $\mu\text{g}\cdot\text{m}^{-3}$ (0.3 ppm) in association with meal preparation on a gas stove (49). No corresponding effects were seen for nonasthmatics. In the studies by Clench-Aas & Bjerknes Haugen (6) and Clench-Aas et al (5), described in the section on acute effects, no consistent associations between hourly air pollution measurements and PEF values were observed.

Long-term exposure to NO_2 and effects on pulmonary function in adults have been investigated in a few studies. Two discussed previously also included data on pulmonary function in relation to domestic gas appliances, one showing no effect (32) and the other, with nonsmokers only, indicating a reduced $\text{FEV}_{1.0}$ (33). Use of gas for cooking showed a suggestive association with low $\text{FEV}_{1.0}$ (RR 1.82, $P = 0.08$) in a case-referent study on 213 nonsmoking women from Michigan (50). The NO_2 levels measured during one week in the homes of 97 nonsmoking Dutch women were negatively associated with several pulmonary function parameters, including $\text{FEV}_{1.0}$ and FVC (51). However, no significant association was found between NO_2 exposure and pulmonary function decline during 17 years. The estimated personal exposure on a weekly average basis ranged from 11 to 125 $\mu\text{g}\cdot\text{m}^{-3}$.

No effects on pulmonary function were seen in the studies by Cohen et al (29) and Speizer & Ferris (30) from California and Massachusetts, respectively, in relation to outdoor NO_2 levels. The study by Detels et al (31), also described earlier, on two communities in California, showed no consistent differences between the areas in pulmonary function tests associated with small airways. However, the prevalence of subjects with a poor $\text{FEV}_{1.0}$ or FVC was increased ($P < 0.01$) in the high-pollution area, both among the nonsmokers and among the smokers. In a follow-up of the nonsmokers after five to six years a greater deterioration in pulmonary function was observed in the high-exposure area, particularly for tests associated with small airways (52).

Occupational exposures

Investigations on occupational groups provide evidence of health effects related to high levels of NO_2 . Silo-filler's disease, resulting from short-term exposure to very high NO_2 concentrations (up to several hundred milligrams per cubic meter) in newly filled silos, is characterized by pulmonary edema, which can be fatal, and sometimes with a later development

of bronchiolitis obliterans (53). Case reports are also available on similar effects from other occupational groups, such as firemen (54) and welders (55). NO_2 levels ranging from several hundred to several thousand micrograms per cubic meter can be found for bus garage workers and miners, mainly from diesel engine exhaust, which also gives rise to particulate emissions. One study on salt miners showed no excess symptom prevalence or airway obstruction (56), while another study on bus garage workers indicated increased symptom rates but no effects on pulmonary function (57). A study on British coal miners with average NO_2 exposures of only about 40-150 $\mu\text{g}\cdot\text{m}^{-3}$ found no excess of respiratory symptoms or decline in $\text{FEV}_{1.0}$ (58).

A few studies have provided evidence of acute effects in the lower respiratory tract among ice-hockey players, cheerleaders, and referees after exposure to increased NO_2 concentrations resulting from malfunctioning ice-resurfacing machines in closed arenas (59, 60). Symptoms included cough, hemoptysis and dyspnea, which developed within 48 h after the exposure. No pulmonary function disturbances could be detected after 10 d or two months. Unfortunately, no NO_2 measurements were taken during the episodes, but levels were reported at 5600-7500 $\mu\text{g}\cdot\text{m}^{-3}$ (3-4 ppm) 2 d later.

Summary and concluding remarks

NO_2 -induced health effects can result from both short- and long-term exposures. The health effects related to the two types of exposure are often different in character, acute conditions being associated with short-term exposures and more chronic diseases being related to long-term exposures. Furthermore, the epidemiologic methodology is generally quite different for the study of acute reversible conditions and chronic health effects. Thus it is pertinent to separate effects occurring after short-term and long-term exposure in the evaluation. However, it should be realized that it is sometimes difficult to determine whether observed health effects result from short-term or long-term exposure, such as in cross-sectional studies on respiratory symptoms or pulmonary function.

Short-term exposure

The epidemiologic evidence under evaluation for short-term exposure to NO_2 is based on 11 studies focusing on annoyance and symptoms reported in diaries, on hospitalization for respiratory diseases, or on pulmonary function problems. Six of the studies included children and seven included adults; often subjects believed to be particularly sensitive to air pollution, such as asthmatics, were used. As a rule, daily health effect measures were compared with estimated or measured NO_2 levels, which were

mostly used as an indicator of ambient air pollution. The average NO_2 concentrations in the different studies were on the order of 10-50 $\mu\text{g}\cdot\text{m}^{-3}$, with maximum hourly concentrations ranging up to several hundred micrograms per cubic meter of air. Seven of the studies provided some evidence of association between NO_2 exposure and health effects after control for outdoor temperature, which is generally a strong risk factor. The reporting of results in these studies was often based on regression or correlation coefficients, and therefore determining the threshold or lowest effect levels is difficult.

An overall evaluation indicates that the epidemiologic evidence of effects following short-term exposure to NO_2 is inconclusive, mainly because etiologic relations specifically involving NO_2 are difficult to define in complex ambient air exposure situations. However, some recent studies suggest that acute annoyance reactions and symptoms from the respiratory tract may occur at NO_2 concentrations currently found in urban areas in Sweden. Studies on pulmonary function have shown inconsistent results, but effects on sensitive individuals such as asthmatics have been investigated only to a limited extent.

Long-term exposure

Most studies on effects of long-term exposure to NO_2 have focused on the indoor environment, where gas appliances constitute a major source. Altogether 15 studies are available on symptoms and diseases of the lower respiratory tract in children in relation to gas appliances in residences. The average NO_2 concentrations measured in such residences (excluding kitchens) range from about 40 to 80 $\mu\text{g}\cdot\text{m}^{-3}$ in the different studies, but short-term peaks in kitchens can exceed 1000 $\mu\text{g}\cdot\text{m}^{-3}$. Long-term average NO_2 concentrations outdoors were generally lower than in the homes with gas appliances. A meta-analysis of the studies shows a statistically significant increase in risk of about 20% for lower respiratory tract illness in association with gas appliances, which contributed an average of about 30 $\mu\text{g}\cdot\text{m}^{-3}$ to the indoor NO_2 levels.

The few studies on respiratory diseases in children and outdoor NO_2 exposure are more difficult to interpret because of the complex exposure environments. One study on children living near a trinitrotoluene plant and exposed to average outdoor NO_2 levels of about 40-90 $\mu\text{g}\cdot\text{m}^{-3}$ and two studies in urban areas with average concentrations of about 30 $\mu\text{g}\cdot\text{m}^{-3}$ indicate increased disease rates. One-hour peak exposures of up to 700 $\mu\text{g}\cdot\text{m}^{-3}$ were encountered near the trinitrotoluene plant.

Studies on long-term exposure to NO_2 and pulmonary function in children provide inconsistent results. An early study of children living near a trinitrotoluene plant and exposed to outdoor NO_2 levels of between 100 and 200 $\mu\text{g}\cdot\text{m}^{-3}$ indicated a small decrease in pulmonary function. Later inves-

tigations on children exposed primarily via domestic gas appliances showed statistically significant effects in three studies but not in another three studies. If NO_2 levels were reported, they were similar to those given in the previous section on lower respiratory tract illnesses.

The studies on long-term exposure to NO_2 and symptoms or diseases of the respiratory tract in adults mostly concerned areas where motor vehicles constituted a major contributor to outdoor levels. Increased prevalence rates were observed in nonsmokers in four studies with average NO_2 concentrations in the "exposed" areas ranging from about 30 to 100 $\mu\text{g}\cdot\text{m}^{-3}$, but no corresponding effects were seen in two studies of populations exposed to similar concentrations. In two studies the prevalence of lower respiratory tract symptoms was related to gas-cooking or measured personal NO_2 exposure (36 $\mu\text{g}\cdot\text{m}^{-3}$) but not in a third study.

Two studies on pulmonary function showed no effect in relation to long-term average NO_2 levels of about 100 $\mu\text{g}\cdot\text{m}^{-3}$ in urban air, while, in a third study, a small decrease was apparent among nonsmokers and smokers. Three studies on nonsmokers indicated a decreased pulmonary function in relation to the use of gas for cooking or measured indoor NO_2 levels, but another study showed no such effect.

In the interpretation of the epidemiologic evidence on long-term exposure to NO_2 , it is necessary to consider the possible influence of various types of bias. Primarily two types of bias are of interest, misclassification and confounding. The methods used in the different studies to estimate NO_2 exposure result in some misclassification. Personal monitors were rarely used, and, if so, only during short measurement periods. The role of short-term peaks and long-term low-level exposure remains unclear. To the extent that the misclassification is unrelated to the outcome under study, it will tend to dilute any association. Nondifferential misclassification of health effects, resulting, for example, from poor quality in the questionnaire information or pulmonary function measurements with regard to specificity, will have the same consequences.

Uncontrolled confounding must also be considered in the interpretation of the findings. The meta-analysis on domestic gas appliances and low respiratory tract illnesses in children showed a relative risk of only 1.2. Important risk factors for low respiratory tract illnesses, such as parental smoking and socioeconomic status, were often controlled in the studies. However, it cannot be ruled out that residual confounding from these factors and other risk factors which were not controlled contributes to explaining the observed association. Confounding by other environmental factors is of particular concern in the studies on outdoor exposure to NO_2 .

In conclusion, an overall assessment of the epidemiologic evidence on long-term exposure suggests

that gas appliances in the home are associated with an increased risk of lower respiratory tract illness in children. Average indoor NO_2 concentrations in the studies were on the order of 40–80 $\mu\text{g}\cdot\text{m}^{-3}$, but short-term exposure peaks exceeding 1000 $\mu\text{g}\cdot\text{m}^{-3}$ also occurred. The observed excess risk is low, and it cannot be ruled out that it is caused by bias, such as uncontrolled confounding. Some supporting evidence is provided by studies on pulmonary function in children and lower respiratory tract symptoms and pulmonary function in adults, but the data are not consistent.

The epidemiologic findings on outdoor NO_2 exposure are difficult to interpret because of the complex exposure environments. Inconsistent evidence of health effects, similar to those reported for domestic gas appliances, is available at long-term average outdoor concentrations ranging from about 30 to 100 $\mu\text{g}\cdot\text{m}^{-3}$. In a comparison of exposure-response relationships with the studies focusing on indoor measurements, it is necessary to consider time activity patterns, which indicate that personal exposures are probably more influenced by indoor levels in most populations under study. Another complexity is the role of high short-term exposures for the reported health effects; this role is currently unclear.

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