Urban Air Pollution and Mortality in a Cohort of Norwegian Men

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We investigated the association between total and cause-specific mortality and individual measures of long-term air pollution exposure in a cohort of Norwegian men followed from 1972–1973 through 1998. Data from a follow-up study on cardiovascular risk factors among 16,209 men 40–49 years of age living in Oslo, Norway, in 1972–1973 were linked with data from the Norwegian Death Register and with estimates of average yearly air pollution levels at the participants' home addresses from 1974 to 1998. Cox proportional-hazards regression was used to estimate associations between exposure and total and cause-specific mortality. During the follow-up time 4,227 men died from a disease corresponding to an ICD-9 (*International Classification of Diseases, Revision 9*) code < 800. Controlling for a number of potential confounders, the adjusted risk ratio for dying was 1.08 [95% confidence interval (CI), 1.06–1.11] for a 10-μg/m^3 increase in average exposure to nitrogen oxides (NO_x) at the home address from 1974 through 1978. Corresponding adjusted risk ratios for dying from a respiratory disease other than lung cancer were 1.16 (95% CI, 1.06–1.26); from lung cancer, 1.11 (95% CI, 1.03–1.19); from ischemic heart diseases, 1.08 (95% CI, 1.03–1.12); and from cerebrovascular diseases, 1.04 (95% CI, 0.94–1.15). The findings indicate that urban air pollution may increase the risk of dying. The effect seemed to be strongest for deaths from respiratory diseases other than lung cancer. *Key words:* air pollution, cohort, epidemiology, long-term exposure, mortality, Norway. *Environ Health Perspect* 112:610–615 (2004). doi:10.1289/ehp.6684 available via *http://dx.doi.org/* [Online 20 January 2004]

The current understanding of the association between long-term exposure to air pollution and mortality is based on results from a few cohort studies, of which two studies have received a lot of attention (Dockery et al. 1993; Pope et al. 1995, 2002). Both of these studies have assessed air pollution exposure on an aggregated (not individual) level. All participants living in the same city were given a city-specific exposure level based on the available measurements. At least two other cohort studies have assessed exposure at an individual level (Beeson et al. 1998; Hoek et al. 2002). Results from these studies strengthen the evidence that urban air pollution is associated with increased risk of dying. Associations have varied and exposure measures have been rather crude. No single epidemiologic study can be the basis for determining a causal relation between air pollution and mortality (Health Effects Institute 2000), and there is still a strong need for exploring the associations between long-term air pollution and mortality further. For a long time Norway has had monthly updated registers for all citizens' home addresses and for deaths. This makes it possible to assess air pollution exposure at home addresses historically by geographical information systems and to link the information with information on deaths and causes of deaths for persons who have lived at these addresses. In this study we have estimated yearly air pollution levels at the home addresses for a cohort of 16,209 male citizens from 1974 to 1998 by geographical information systems (Gram et al. 2003; Håheim et al. 1996; Leren et al. 1975; Nafstad et al. 2003). The cohort was established in 1972–1973. The aim of the present study was to estimate associations between air pollution levels estimated at the participants' home addresses and the participants' risk of dying.

Materials and Methods

Study population. The study population has been described elsewhere (Håheim et al. 1996; Leren et al. 1975; Nafstad et al. 2003). Briefly, in 1972 all 40- to 49-year-old men living in Oslo, Norway (*n* = 25,915), were invited to participate in a population-based follow-up study of cardiovascular diseases. Those willing to participate (*n* = 16,209) met for a screening investigation between May 1972 and December 1973.

Health outcome. The National Death Register (Statistics Norway, Oslo, Norway) provided data on all deaths within the cohort including the cause of death according to the *International Classification of Diseases,* Revision 8 (ICD-8; Statistisk Sentralbyrå 1973), Revision 9 (ICD-9; Statistisk Sentralbyrå 1990), and Revision 10 (ICD-10; Statens Helsetilsyn 1998). The register was updated through 1998. The following outcomes were considered in the analyses: total deaths from diseases, deaths from respiratory diseases, deaths from lung cancer, deaths from ischemic heart diseases (including sudden death), and deaths from cerebrovascular diseases. The end points and the definition according to ICD-8, -9, and -10 classifications are listed in Table 1.

Exposure assessment. Indicators of air pollution exposure considered in these analyses were sulfur dioxide and nitrogen oxides. The Norwegian Institute for Air Research has estimated average concentrations per year of these air pollutants at the home addresses of all participants from 1974 to 1998. Good emission data existed for the whole period, but concentration measurements were sparse and stability data existed only for short periods. Particles were not considered in this study because measurement methods changed during the period from measuring black soot from coal and heavy oil combustion to measuring size fractions of particles from traffic.

The model for SO_2 is based on detailed model calculations per square kilometer for the years 1979 and 1995. For the other years, the concentrations were calculated using the modeling results together with observed concentrations in central Oslo and emission data for industry, heating, and traffic. Observed NO_x concentrations were not available for all the years, so a new procedure had to be developed; the shape of the SO_2-concentration fields was determined from the detailed model calculations for SO_2, and the emissions levels were determined from the SO_2-measurements. We used this method to define separate dispersion fields (concentration divided by emission) for each year for heating and traffic. These measures were multiplied by the corresponding emissions of NO_x and added with a background contribution from other sources. Annual nitrogen dioxide fields were not calculated because ground level ozone concentrations were not measured. Addresses linked to 50 of the busiest streets were given an additional exposure based on estimates of annual average daily traffic. For many of the streets, the traffic changed considerably during the 25-year period because of changes in the main road network. More detailed descriptions of

the exposure estimates are given elsewhere (Gram et al. 2003).

The National Population Register (Skattedirektoratet, Oslo, Norway) includes home addresses for all Norwegians and is updated monthly. For a person who moved within Oslo, we used the average air pollutant concentration at the address where he lived the largest part of that year. The air pollution levels were linked to map references and then to the participants home addresses during the study period. All of the men lived in Oslo during the first years of the study, and about 90% were still living in Oslo in 1985. Air pollution exposures for persons moving from Oslo were assessed in a special way. Because Oslo is the largest city in Norway, with around 500,000 citizens, moving out of Oslo meant—with few exceptions—moving into a less-populated area with low levels of air pollution. Norway has had a network of background air pollution monitoring stations since the beginning of the 1970s, and values from these stations were used for the less-populated areas. For larger cities and industrial areas, we used available measurements to adjust background values; the annual variations were based on emission estimates from Statistics Norway. The concentration for one specific year was calculated as the region concentration multiplied by an emission index for that year and linked to the cohort information. We used the calculated values to estimate average exposure for different time windows and cumulative exposures. All available information was used in the modeling, and we were only able to evaluate the model for short periods during these 27 years (Gram F, unpublished data).

Covariates. Statistics Norway provided information on the highest level of education for each participant in the cohort: < 10 years, 10–12 years, and > 12 years of education, which reflects low, medium, and high education in Norway.

Information on all other covariates is based on the baseline screening of the cohort, which included a self-administered questionnaire, sampling of blood, and measurements of height and weight (Håheim et al. 1996; Leren et al. 1975). We used the following information in the present analyses: participants' age, smoking habits, leisure-time physical activity, occupation, height, weight, cholesterol, blood pressure, and risk groups for cardiovascular diseases. Smoking habits within the cohort were grouped as follows: nonsmoker, 1–9 cigarettes/day, 10–19 cigarettes/day, ≥ 20 cigarettes/day, smoker (no amount reported), and former smoker. Smoking reported as grams of tobacco per week (smoked as hand-rolled cigarettes or in pipes) was converted to cigarettes per day (0.8 g tobacco = 1 cigarette). Occupation was

Table 1. Causes of deaths, numbers of deaths, and incidences of deaths with 95% CIs according to the ICD-8, -9, and -10.

Causes of death	No.	Incidence (1,000/year)	95%CI
Total deaths (ICD-8 and -9 codes < 800; ICD-10 codes A00-R99)	4,227	11.57	11.23–11.92
Respiratory deaths (ICD-8 and -9 codes 460–519; ICD-10 codes J00-J99)	200	0.55	0.47–0.62
Lung cancer deaths (ICD-8 and 9 code 162; ICD-10 code C34)	382	1.05	0.94–1.15
Ischemic heart deaths (including sudden deaths, ICD-8 and 9 codes 410–414; ICD-10 codes I20-I25; ICD-8 code 795; ICD-9 code 798.1; ICD-10 code R96)	1,508	4.13	3.92–4.34
Cerebrovascular deaths (ICD-8 and 9 codes 430–438; ICD-10 codes I60-I69)	258	0.71	0.62–0.79

Table 2. Distribution (%) of selected covariates in a cohort of 40- to 49-year-old Oslo men according to 5-year average NO_x exposure at their home addresses, 1974–1978.

	No.	Average length of follow-up (years)	NO_x			
			0–9.99 µg/m³ (n = 6,74)	10–19.99 µg/m³ (n = 4,479)	20–29.99 µg/m³ (n = 3,082)	≥ 30 µg/m³ (n = 1,931)
Total	15,966	22.9	40.5	28.1	19.3	12.1
Education						
< 10 years	4,761	21.4	39.1	28.1	22.8	9.9
10–12 years	7,726	22.8	42.5	27.4	17.8	12.3
> 12 years	3,443	23.5	38.3	29.4	17.7	14.6
Occupation						
White collar	7,812	22.9	41.6	27.8	17.8	12.7
Blue collar						
Moderate physical work	4,678	22.4	40.6	27.7	20.0	11.8
Intermediate physical work	2,736	22.2	38.8	29.3	20.8	11.1
Vigorous physical work	592	21.9	37.5	29.9	22.0	10.6
Smoking habits						
Nonsmoker	3,031	23.8	42.0	28.7	17.2	12.2
1–9 cigarettes/day	1,543	22.7	42.1	26.9	19.4	11.6
10–19 cigarettes/day	4,361	21.7	39.0	28.0	21	11.5
≥ 20 cigarettes/day	3,007	21.3	37.0	28.2	21.9	12.9
Smoker, amount not reported	75	23.7	44.0	28.0	9.3	18.7
Former smoker	3,949	23.5	43.2	28.0	16.7	12.1
Leisure-time physical activity						
Sedentary	3,390	21.8	40.1	27.0	20.8	12.2
Moderate	9,497	22.6	40.3	28.0	19.6	12.1
Intermediate	2,803	23.2	42.1	29.9	16.2	11.8
Vigorous	254	24.0	40.2	25.2	20.9	13.8
Risk groups for cardiovascular diseases						
No symptoms or signs of cardiovascular diseases or diabetes	14,187	22.9	40.7	28.2	19.1	12.0
Symptoms of cardiovascular disease	721	21.3	38.4	29.0	20.9	11.7
Cardiovascular disease or diabetes	1,058	18.6	40.1	25.3	21.6	13.0
Age at inclusion (years)						
40–45	7,308	23.6	41.5	27.4	17.7	13.4
46–49	8,658	22.3	39.7	28.6	20.7	11.0

Information was missing on NO_x for 243 subjects, education level for 36 subjects, occupation for 148 subjects, and leisure-time physical activity for 22 subjects.

grouped into "blue collar" work, with moderate, intermediate, or vigorous physical activity at work, and "white collar" or sedentary work, whereas leisure-time physical activity was grouped as sedentary, moderate, intermediate, and vigorous. Risk groups for cardiovascular diseases were grouped as follows: no symptoms and signs of cardiovascular diseases or diabetes; symptoms and signs of cardiovascular diseases; reported cardiovascular disease; and diabetes.

Data linkage. All Norwegian citizens have a unique national identification number that is used in all the national registers. We used these identification numbers to link information from the cohort with information on home addresses, deaths, and education level.

Statistical methods. We calculated incidences of the studied death causes per 1,000 observation years starting at the beginning of

1974, the first year with information on air pollution exposure. We used Cox proportional hazard regression models to evaluate the association between incidence of death and the indicators of air pollution. For the analyses of time to death from a specific cause, we examined each participant's observation time at the end of the follow-up (1998), at the year when the person died from another cause, or the year the participant emigrated or moved to an address without information on air pollution exposure. We used average 5-year levels of exposure in most of the analyses. Air pollution levels were included as both continuous and categorical variables. The average exposure levels were skewed with little variation in the lower quartiles (range within first to second quartile: NO_x, 0–11 µg/m^3; SO_2, 0–9 µg/m^3). The exposure levels were therefore grouped as

follows: 0–9.99, 10.00–19.99, 20.00–29.99, and ≥ 30.00 µg/m^3. Furthermore, NO_x and SO_2 were never included in the same regression model because of potential colinearity problems. To study the functional form of the association between air pollution exposure and different causes of death, we also modeled the continuous exposures as smoothed cubic splines using S-PLUS, Release 6.0 for Windows (Insightful, Seattle, WA, USA) (Therneau and Grambsch 2000). Two extreme values (outliers) were excluded from the analyses because they did not fit any reasonable statistical distribution, they seemed unreasonably high, and they could have large effects when air pollution exposure was used as a continuous variable.

All of the registered covariates were evaluated in the Cox proportional hazard model for inclusion in the final statistical models. We used different modeling strategies. The first strategy was to only include covariates that changed the log-likelihood test of the model significantly ($p < 0.05$). We specified different models for each of the health outcomes. The second strategy was to perform analyses with a core covariate set (education, occupation, smoking habits, leisure-time physical activity, risk group of cardiovascular diseases, and age at inclusion), which was the same for all the health outcomes. With all covariates in the model, we detected deviations from the proportional hazard rates assumption for two of the variables (education and risk groups for cardiovascular diseases), and we had to perform the analyses stratified for these variables (Harrell 2001). Risk ratios and confidence intervals (CIs) showed only minor variation between the first and second approach. This was also the case if the analyses were performed without education and risk groups for cardiovascular diseases in the model. Only results from the second approach are presented.

Our main focus was on air pollution exposure during the first 5 years of follow-up. We also performed analyses with yearly averages and with later 5-year periods; NO_x and SO_2 were also treated as time-dependent variables in the Cox regression models, representing average exposure for the last 5 years before death. Each time a risk set was created for a new death case with 5 years of exposure, the average air pollutant variable for each individual in the risk set was recomputed as the mean of the yearly exposures the last 5 years before the death occurred.

Results

Table 1 presents the number of deaths and the incidences of different causes of death within the cohort during the observational period. Death from ischemic heart diseases was the dominating cause of death ($n = 1,508$; incidence rate 4.13/1,000 observation years), but

Table 3. Mean levels of systolic blood pressure, serum cholesterol, height, and weight among 16,209 Oslo men 40–49 years of age at the baseline screening in 1972/1973 according to 5-year average NO_x exposure at their home addresses, 1974–1978.

		NO_x			
	No.	0–9.99 µg/m^3 ($n = 6,474$)	10–19.99 µg/m^3 ($n = 4,479$)	20–29.99 µg/m^3 ($n = 3,082$)	≥ 30 µg/m^3 ($n = 1,931$)
Systolic blood pressure (mmHg)	15,966	136.0	135.3	136.2	135.3
Cholesterol (mmol/L)	15,961	6.4	6.4	6.4	6.4
Height (cm)	15,845	177.5	177.4	177.1	177.6
Weight (kg)	15,842	77.8	78.1	77.9	77.8

Information was missing on NO_x for 243 subjects, serum cholesterol for 5 subjects, height for 121 subjects, and weight for 124 subjects.

Table 4. Incidences and aRRs (95% CIs) for total deaths among 16,209 men 40–49 years of age living in Oslo in 1972 according to selected conditions registered at baseline (Cox regression[a]).

	Incidence (1,000/year)	aRR (95% CI)
Education (years)		
< 10	15.97	1 (reference)
10–12	10.85	0.78 (0.73–0.84)
> 12	7.86	0.66 (0.60–0.74)
Occupation		
White collar	9.94	1 (reference)
Blue collar		
Moderate physical work	12.38	1.08 (1.00–1.17)
Intermediate physical work	14.01	1.06 (0.97–1.16)
Vigorous physical work	13.77	0.97 (0.83–1.15)
Smoking habits		
Nonsmoker	5.78	1 (reference)
1–9 cigarettes/day	12.11	1.82 (1.58–2.09)
10–19 cigarettes/day	15.78	2.49 (2.22–2.78)
≥ 20 cigarettes/day	18.20	2.86 (2.55–3.21)
Smoker, amount not reported	6.77	1.12 (0.62–2.04)
Former smoker	7.32	1.18 (1.04–1.33)
Leisure-time physical activity		
Sedentary	14.69	1 (reference)
Moderate	11.47	0.88 (0.82–0.95)
Intermediate	9.16	0.79 (0.71–0.88)
Vigorous	6.37	0.72 (0.52–1.00)
Risk groups for cardiovascular diseases		
No symptoms or signs of cardiovascular diseases or diabetes	10.42	1 (reference)
Symptoms of cardiovascular disease	17.44	1.39 (1.22–1.59)
Cardiovascular disease or diabetes	27.29	2.69 (2.44–2.95)
Age at inclusion (years)		
40–45	8.50	1 (reference)
46–49	14.43	1.65 (1.55–1.76)

[a]For two of the variables (occupation and risk factors for cardiovascular disease) there was a deviation from the proportional hazard rate assumption when all covariates were included in the model simultaneously.

as many as 200 men were registered as having died from a respiratory disease other than lung cancer (incidence rate, 0.55/1,000 observation years).

Distribution of air pollution exposure within the cohort has been described in more detail elsewhere (Gram et al. 2003; Nafstad et al. 2003). The yearly averages of SO_2 levels were reduced with a factor of 7 during the study period (from 16.0 $\mu g/m^3$ in 1974 to 2.4 $\mu g/m^3$ in 1995), whereas NO_x varied between 11.5 and 21.7 $\mu g/m^3$ without any clear downward or upward trends. The 5-year median average level of exposure for NO_x at the participants' home address during 1974–1978 was 10.7 $\mu g/m^3$, varying from 0.7 to 168.3 $\mu g/m^3$; quartiles for NO_x were divided at 6.8, 10.7, and 20.4 $\mu g/m^3$; and median levels within the quartiles of NO_x exposure were 3.8, 9.3, 15.4, and 28.8 $\mu g/m^3$. The corresponding 5-year median average exposure for SO_2 was 9.4 $\mu g/m^3$, varying from 0.2 to 55.8 $\mu g/m^3$; quartiles were divided at 4.5, 9.4, and 23.0 $\mu g/m^3$; and median levels within the quartiles were 2.5, 6.2, 14.7, and 31.3 $\mu g/m^3$. The Pearson's correlation coefficient between yearly NO_x and SO_2 levels was 0.63 (95% CI, 0.60–0.66).

Table 2 presents the distributions of categorical covariates that in some way were significantly associated with the risk of dying. Most of the participants had sedentary work and only 21% had intermediate or vigorous physical activity during work time. A sedentary or moderate physical leisure-time lifestyle was common (80.7%). About 70% of the participants had ≥ 10 years of education, and a large proportion of the participants reported that they were smokers or former smokers (56.3% current smokers, and 24.7% former smokers). Table 2 also demonstrates how the covariates were distributed according to the NO_x levels at the participants' home addresses. Most covariates were evenly distributed at all NO_x levels, whereas there was a tendency for the participants with the highest level of education to have the highest NO_x exposure. The mean level of systolic blood pressure, cholesterol, height, and weight were about the same in different strata of NO_x (Table 3).

Several of the core covariates, including smoking habits, were significantly associated with the risk of dying (Table 4). Crude and adjusted risk ratios (aRRs) were similar except for occupation (results not shown). The association between mortality and categories of occupation was weakened when education was included in the same model. Table 5 shows the incidence and risk ratios for the different causes of death that were considered in the analyses according to average exposure to NO_x from 1974 to 1978 and adjusted for the core covariates and corresponding figures for SO_2. Exposures to NO_x and SO_2 were

divided into four exposure levels in model 1 and included as continuous variables (per 10 $\mu g/m^3$) in model 2. The risk of dying from a disease increased with increasing levels of NO_x exposure. The effect was clearest for deaths from a respiratory disease other than lung cancer, both when the analyses were performed with NO_x as a categorical variable and as a continuous variable. The aRR was 1.71 (95% CI, 1.09–2.68), contrasting the highest and lowest categories of NO_x exposure (model 1), and aRR 1.16 (95% CI, 1.06–1.26) per 10 $\mu g/m^3$ increase in NO_x exposure (model 2). We used a smoothed cubic spline that described the relationship between NO_x and the log risk of death to examine if air pollution levels could be included in the analyses as a continuous variable. For respiratory mortality, there was a monotone increase in risk with increasing exposure levels up to 50 $\mu g/m^3$. For the

82 persons with higher exposure levels, the risk ratios became unstable with wide confidence limits but still in accordance with a linear trend. A similar but somewhat weaker trend was seen for the risk of dying from lung cancer. No clear dose–response pattern was seen between deaths from ischemic heart diseases and NO_x exposure when NO_x was included in the model as a categorical variable. Even so, the aRR increased [1.08 (95% CI, 1.03–1.12) per 10 $\mu g/m^3$ NO_x] when the analyses were performed with NO_x as a continuous variable. For cerebrovascular diseases, there was no clear association or trends between the health outcome and increasing NO_x exposure. For SO_2, there were, in general, no clear and meaningful associations between mortality and increased exposure; it was not the higher exposure levels but exposure between 10.00 and 19.99 $\mu g/m^3$ that mainly increased risk ratios.

Table 5. Incidences and aRRs (95% CIs) for deaths caused by different diseases among 16,209 men 40–49 years of age living in Oslo in 1972 according to average exposure to NO_x and SO_2 at their home address during 1974–1978.

Deaths	NO_x incidence (1,000/year)	aRR (95% CI)	SO_2 incidence (1,000/year)	aRR (95% CI)
Total deaths				
Model 1				
0–9.99 $\mu g/m^3$	10.61	1 (reference)	10.99	1 (reference)
10–19.99 $\mu g/m^3$	10.55	0.95 (0.88–1.03)	13.87	1.23 (1.13–1.33)
20–29.99 $\mu g/m^3$	14.21	1.22 (1.12–1.32)	11.72	0.97 (0.89–1.07)
≥ 30 $\mu g/m^3$	12.26	1.18 (1.07–1.30)	9.98	0.95 (0.86–1.05)
Model 2				
per 10 $\mu g/m^3$		1.08 (1.06–1.11)		0.98 (0.96–1.01)
Respiratory diseases				
Model 1				
0–9.99 $\mu g/m^3$	0.41	1 (reference)	0.45	1 (reference)
10–19.99 $\mu g/m^3$	0.50	1.13 (0.78–1.65)	0.70	1.49 (1.04–2.14)
20–29.99 $\mu g/m^3$	0.74	1.55 (1.05–2.27)	0.74	1.32 (0.89–1.98)
≥ 30 $\mu g/m^3$	0.72	1.71 (1.09–2.68)	0.45	1.05 (0.66–1.68)
Model 2				
per 10 $\mu g/m^3$		1.16 (1.06–1.26)		1.03 (0.93–1.14)
Lung cancer				
Model 1				
0–9.99 $\mu g/m^3$	0.97	1 (reference)	0.99	1 (reference)
10–19.99 $\mu g/m^3$	0.89	0.85 (0.65–1.11)	1.11	1.07 (0.82–1.40)
20–29.99 $\mu g/m^3$	1.28	1.16 (0.89–1.52)	1.20	1.03 (0.77–1.38)
≥ 30 $\mu g/m^3$	1.25	1.30 (0.94–1.78)	0.95	0.98 (0.71–1.35)
Model 2				
per 10 $\mu g/m^3$		1.11 (1.03–1.19)		1.00 (0.93–1.08)
Ischemic heart diseases				
Model 1				
0–9.99 $\mu g/m^3$	3.96	1 (reference)	4.11	1 (reference)
10–19.99 $\mu g/m^3$	3.67	0.88 (0.77–1.01)	4.85	1.16 (1.02–1.33)
20–29.99 $\mu g/m^3$	5.05	1.17 (1.01–1.34)	3.89	0.85 (0.72–1.00)
≥ 30 $\mu g/m^3$	4.09	1.09 (0.92–1.30)	3.26	0.87 (0.73–1.03)
Model 2				
per 10 $\mu g/m^3$		1.08 (1.03–1.12)		0.95 (0.91–0.99)
Cerebrovascular diseases				
Model 1				
0–9.99 $\mu g/m^3$	0.67	1 (reference)	0.63	1 (reference)
10–19.99 $\mu g/m^3$	0.61	0.88 (0.64–1.21)	0.85	1.36 (0.99–1.87)
20–29.99 $\mu g/m^3$	0.95	1.32 (0.96–1.82)	0.84	1.24 (0.86–1.77)
≥ 30 $\mu g/m^3$	0.58	0.85 (0.54–1.34)	0.62	1.05 (0.70–1.56)
Model 2				
per 10 $\mu g/m^3$		1.04 (0.94–1.15)		1.02 (0.93–1.12)

Model 1 exposure is categorized in four intervals, and model 2 is categorized per 10 $\mu g/m^3$ increase in exposure (Cox regression); aRRs were adjusted for education, occupation, smoking habits, leisure-time physical activity, risk group of cardiovascular diseases, and age at inclusion.

Other analytical approaches, including cumulative air pollution exposures, exposures the 5 last years before death, and inclusion of height, weight, blood pressure, and cholesterol in the regression models, gave quite similar associations between air pollution exposures and health outcomes (results not shown). We also analyzed data according to more recent 5-year time windows for NO_x exposure, excluding cases of death occurring before or during the time windows used in the analyses. This reduced the number of deaths and observation years included in the analyses (Table 6). Even so, for a 10-$\mu g/m^3$ increase in NO_x exposure during the different time windows the risk estimates were quite stable also if shorter time windows for exposure were used in the analyses. The risk estimates for respiratory deaths increased somewhat, whereas they were reduced for lung cancer. None of the changes were statistically significant.

Discussion

We found that home address NO_x exposure, which was estimated using a geographical information system, was associated with the risk of dying in a cohort of Oslo men. The associations were robust for different analytical approaches and adjustments for different covariates. The effect was strongest for respiratory deaths other than lung cancer [aRR 1.16 (95% CI, 1.06–1.26) for a 10-$\mu g/m^3$ increase in NO_x exposure at the participants' home address during 1974–1978]. Increased NO_x exposure was also associated with deaths from lung cancer and ischemic heart diseases. The effects were smaller and the dose–response relation less clear for ischemic deaths. Analyses with more recent time windows for exposure that excluded men who died early in the follow-up gave similar results. High correlation between exposure levels for different years made it difficult to use these findings to explore latency in time between exposure and diseases. However, the findings indicated stable risk estimates that did not depend on a few cases of death. A small group of participants

had NO_x levels > 50 $\mu g/m^3$, which was clearly higher than the rest. Analyses with and without these persons showed that they did not change the overall effects, and they were kept in the analyses.

Different approaches have been used to estimate exposure in studies of long-term air pollution exposure and mortality. This has varied from attributing all citizens in one city the same level of exposure (Dockery et al. 1993; Pope et al. 1995, 2002) to using geographical information systems, including air pollution monitoring and information on emissions to estimate more or less individual exposure (Beeson et al. 1998; Bellander et al. 2001; Hoek et al. 2001, 2002; Langholz et al. 2002; Raaschou-Nielsen et al. 2001; Reynolds et al. 2002). In the present study we used the last approach and developed a model that estimates individual home address air pollution exposure by historical data on air pollution measurements and emission and by meteorologic and topographic observations. To obtain the best results, we included all available information in the model (Nafstad et al. 2003). This reduced our ability to evaluate accuracy of the model. Even if we found reasonable agreement for shorter time intervals, we considered that our information was not sufficient to give overall estimates of accuracy and precision. To assess the accuracy and precision of estimates of air pollution levels at more than 16,000 addresses during 27 years would have been unrealistic. Thus, we cannot exclude the possibility of some misclassification of exposure, as will be the case in most similar studies. However, we see no reason to expect systematic misclassification because exposure was assessed independently from all the other data. We believe this model is best for estimating long-term average exposure. We also expect the accuracy to be quite good for estimating exposure for men moving out of Oslo into areas with lower pollution. Another general problem is that home address exposure may not correctly measure true individual exposure because people do not stay home all the time

and often stay indoors when they are at home. However, adults, in general, spend much of their time in their home environment; this was probably even more common during the 1970s when people were less mobile and often worked near their homes. Furthermore, there were few indoor sources of NO_x, and studies have found a strong correlation between indoor and outdoor exposure levels under such conditions (Emenius 2003; Magnus et al. 1998). We therefore believe that home address NO_x levels are a reasonable way of estimating long-term NO_x exposure of these subjects.

Our 27-year follow-up study of 16,209 middle-aged men living in one city has several strengths. It ensures a large number of observational years and many deaths and it reduces problems with age variation and between-city heterogeneity. This study also ensures a plausible relationship in time between these conditions and disease development and a low chance of reporting bias. Air pollution exposure was estimated independently. Systematic misclassification in home address exposure related to the outcomes is therefore unlikely, and random misclassification would probably dilute the associations between exposure and outcome. We have no reason to believe that the Oslo men not willing to participate would have a different health effect from air pollution exposure. The study included information on most conditions that we considered potential confounders. NO_x exposure was quite evenly distributed for different categories of these conditions, including smoking, which was very common among Norwegian men in the 1970s. This reduces the chance of confounding. Furthermore, we have adjusted for these conditions in several ways in the analyses, and these adjustments gave only minor changes in associations between air pollution exposure and outcomes. It is impossible, however, to fully exclude the possibility of confounding and misclassification of exposure in this type of study. Consistent findings from different cohort studies will therefore be important to increase the understanding of the associations between mortality and long-term air pollution exposure (Health Effects Institute 2000). The associations between SO_2 exposure and mortality give further support to this view. The lack of dose–response relations and the fact that primarily moderate levels of exposure increased the risk of death should be confirmed in other studies before speculating too much about possible explanations.

Our study supports findings from other cohort studies that urban air pollution may increase mortality (Beeson et al. 1998; Dockery et al. 1993; Hoek et al. 2002; Pope et al. 1995, 2002). It is difficult to compare associations between specific outcomes and exposures because of differences in design, local conditions, exposure assessment methods, and

Table 6. aRRs (95% CIs) for deaths caused by different diseases according to average NO_x for home address in different 5-year periods.

Deaths per 10 $\mu g/m^3$ increase in NO_x	1974–1978 aRR (95% CI)	1979–1983 aRR (95% CI)	1984–1988 aRR (95% CI)	1989–1993 aRR (95% CI)
Total deaths	1.08 (1.06–1.10) (n = 3,821)	1.08 (1.06–1.10) (n = 3,329)	1.08 (1.06–1.11) (n = 2,614)	1.08 (1.05–1.12) (n = 1,503)
Respiratory diseases	1.14 (1.07–1.22) (n = 177)	1.14 (1.06–1.23) (n = 160)	1.16 (1.08–1.25) (n = 140)	1.23 (1.13–1.35) (n = 86)
Lung cancer	1.07 (1.01–1.14) (n = 353)	1.06 (0.99–1.14) (n = 305)	1.07 (0.99–1.15) (n = 242)	1.05 (0.93–1.17) (n = 143)
Ischemic heart diseases	1.07 (1.03–1.11) (n = 1,250)	1.07 (1.04–1.11) (n = 1,059)	1.06 (1.01–1.11) (n = 771)	1.07 (1.00–1.15) (n = 379)
Cerebrovascular diseases	1.03 (0.94–1.12) (n = 258)	1.01 (0.92–1.11) (n = 220)	1.01 (0.92–1.12) (n = 188)	1.02 (0.89–1.16) (n = 118)

Values exclude deaths that occurred before or during the NO_x time window used in the analyses (Cox regression). aRRs were adjusted for education, occupation, smoking habits, leisure-time physical activity, risk group of cardiovascular diseases, and age at inclusion.

which air pollutants have been measured. In this study we did not include indicators on human exposure to particulate matter, which most often has been shown to be associated with adverse health effects. Urban air pollution is always a mixture of pollutants. We believe that air pollution components assessed in this study and similar studies are exposure indicators only; it is difficult to conclude from such studies which air pollutant causes which health effects. Even so, we believe that the contrasting effect between SO_2 and NO_x found in this study is interesting and might indicate that traffic-related air pollution is important.

Respiratory mortality other than lung cancer was the cause of death most strongly associated with NO_x exposure. Other studies have also shown that exposure to different air pollutants is associated with respiratory health effects (Archer 1990; Clancy et al. 2002; De Leon et al. 2003; Hedley et al. 2002; Lebowitz 1996; Pope 2000; Sunyer et al. 2002). A large proportion of the respiratory deaths is expected to be chronic obstructive pulmonary disease (COPD). Both COPD and lung cancer have been shown to be related to environmental conditions including tobacco-smoke exposure (Mannino 2002). It therefore seems biologically reasonable that urban air pollution may increase the risk of developing these diseases. As for the risk of death from lung cancer, the association was well in accordance with the risk of developing lung cancer, as shown by Nafstad et al. (2003).

Several time-series studies have found associations between ischemic heart diseases and deaths, and biological mechanisms for explaining these findings have been developed (Dockery 2001; Magari et al. 2002; Peters et al. 1997, 2001; Pope 1991). This includes inflammation of the lung by cytokine release, which also affects the cardiovascular system and alterations in autonomic cardiac function (Pope 2000). Even if there was a statistically significant association between NO_x exposure and deaths from ischemic heart disease, the dose–response relation was not clear and warrants caution in our conclusions. We have no good explanation for this finding except that some other studies have also shown that the association between indicators of air pollution

exposure and cardiovascular outcome is weaker than between such exposures and respiratory outcomes (Archer 1990; Clancy et al. 2002; De Leon et al. 2003). These exposures may also primarily affect the risk of developing acute cardiac events and, to a lesser extent, contribute to the development of chronic heart diseases. These findings illustrate that no single epidemiologic study can be the basis for determining a causal relation between air pollution and mortality (Health Effects Institute 2000).

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