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Urban Air Pollution and Lung Cancer in Stockholm

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We conducted a population-based case-control study among men 40–75 years of age encompassing all cases of lung cancer 1985–1990 among stable residents of Stockholm County 1950–1990. Questionnaires to subjects or next-of-kin (primarily wives or children) elicited information regarding smoking and other risk factors, including occupational and residential histories. A high response rate (>85%) resulted in 1,042 cases and 2,364 controls. We created retrospective emission databases for NO_x/NO_2 and SO_2 as indicators of air pollution from road traffic and heating, respectively. We estimated local annual source-specific air pollution levels using validated dispersion models and we linked these levels to residential addresses using Geographical Information System (GIS) techniques. Average traffic-related NO_2 exposure over 30 years was associated with a relative risk (RR) of 1.2 (95% confidence interval 0.8–1.6) for the top decile of exposure, adjusted for tobacco smoking, socioeconomic status, residential radon, and occupational exposures. The data suggested a considerable latency period; the RR for the top decile of average traffic-related NO_2 exposure 20 years previously was 1.4 (1.0–2.0). Little association was observed for SO_2. Occupational exposure to asbestos, diesel exhaust, and other combustion products also increased the risk of lung cancer. Our results indicate that urban air pollution increases lung cancer risk and that vehicle emissions may be particularly important. (Epidemiology 2000;11:487–495)

Keywords: lung cancer, air pollution, case-control study, road traffic, NO_2, SO_2, smoking.

Epidemiologic studies from many countries have shown elevated risks of lung cancer in urban or industrially polluted areas, generally by up to 1.5 times, even when adjustment for smoking has been attempted.[1,2] Traffic-related air pollution is a growing concern today, but most of the available evidence relates to areas where motor vehicles were not the major source of air pollution. Nevertheless, studies on diesel-exposed occupational groups provide support for a causative role of traffic-related air pollution for lung cancer.[2] Recent population-based cohort studies with measured air pollution data have also indicated that lung cancer incidence is increased by 30–50% in areas with high ambient air pollution levels compared with areas with lower levels.[3–5]

A major deficiency of many previous studies is the lack of individual long-term data on air pollution exposure.[1] It is also unclear which sources of urban air pollution may be of importance. In many instances, the lack of individual-level air pollution data is likely to have obscured much of the true range of individual exposure. The resulting limited exposure contrast has also hampered analyses of interactions with smoking and other known risk factors for lung cancer, even when such information was available.

The present study was conceived with the specific aim of exploring the possible association of lung cancer and urban air pollution by using geographical information system (GIS) techniques to assign individual exposures to ambient air pollution from oxides of nitrogen (NO_x), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2) from defined emission sources. These pollutants were chosen as suitable indicators of air pollution from road traffic and heating, which constituted the main local sources of air pollution. Individual data on smoking, occupational exposures, and some other risk factors were also collected and used for evaluation of confounding and possible interactions.

Methods

Study Subjects

The study population comprised men 40 to 75 years of age who were residents of Stockholm County at any time between January 1, 1985 and December 31, 1990.

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Editors' note: See related editorial on page 485 of this issue.

TABLE 1. Response Rates and Vital Status of Lung Cancer Cases and Controls 1985–1990 in Stockholm, Sweden

Categories	Cases		Population Controls		Mortality-Matched Controls	
	No	%	No	%	No	%
Selected	1196	100	1441	100	1324	100
Non-response	154	13	167	12	234	18
Total included (response rate)	1042	87	1274	88	1090	82
Vital status of included individuals						
Alive at time of data collection	68	7	1001	79	117	11
Dead at time of data collection	974	93	273	21	973	89

An additional restriction was residence outside the county for at most 5 years between 1950 to 1990, a criterion approximately 70% fulfilled. In this study base, we identified 1,196 male lung cancer cases (ICD-7 code 162.1, diagnosed between January 1, 1985 and December 31, 1990) from the Stockholm County regional cancer registry, of whom 1,042 participated in the study (Table 1). Cases who were deceased and who were still alive were included. The diagnosis was based on histology for 78.3% and cytology for 20.4%.

Incidence density sampled controls were drawn in 1992 by random sampling from retrospective population registers covering Stockholm County, stratified on age (5-year categories) and calendar year of selection (1985 to 1990) of the cases. One control group (N = 1,274) was drawn from all individuals in the study population alive at the end of each selection year ("population" controls). As foreseen, more individuals in this group than among the cases were still alive at the time of data collection (Table 1). To allow an evaluation of possible bias from using proxy interviews for deceased individuals, primarily in our occupational analyses,[6] we recruited a second control group (N = 1,090), also frequency matched to the cases on vital status on December 31, 1990, using the Cause-of-Death Registry (mortality-matched controls). We excluded individuals who had died from smoking-related diagnoses[7] from this control group.[6]

Exposure Assessment

Data collection via postal questionnaire was performed from 1994 through 1996. The questionnaire was sent to living subjects, or to next-of-kin (primarily wives or children) for deceased study subjects. Several mail reminders, and follow-up telephone reminders and interviews ensured a high response rate (over 85%, Table 1). The questionnaire inquired about smoking and dietary intake of vegetables and fruits, as well as detailed occupational and residential histories. For the assessment of air pollution exposure, the addresses of all residences after 1950 inhabited for over 1 year were collected. When the questionnaire residence history from 1950 was not complete, parish offices and tax authorities provided additional data. For the classification of residential radon exposure, questions concerning building materials, house type, and ground contact of dwelling were also asked.[8] All collected data were truncated at the individual selection year.

The geocoding and air pollution exposure assessment methodology using GIS is described in detail elsewhere.[9] Briefly, the addresses were transformed into geographical coordinates using standard GIS computer software[10] in conjunction with a regional geographical address data base.[11] The reference point for assessment of air pollution exposure was a detailed regional emission database for 1993[12] (see also http://www.slb.mf.stockholm.se/) containing approximately 4,300 traffic-related line sources covering all roads with over 1,000 vehicles/24 hr (90% of the estimated emission from road traffic), as well as over 500 point sources (district heating facilities, industries, etc.). Limited diffuse emission sources (*eg*, air traffic and merchant vessels) are mapped as area sources, and population-density related sources (*eg*, local heating, work machines) as grid-sources (250 or 1,000 m grids).

In this study, the estimated contributions to the total ambient NO_x/NO_2 and SO_2 levels from the relevant sources were used as markers for air pollution from road traffic and residential heating, respectively, based on source-specific emission data. These sources form the major part of ambient NO_x/NO_2 and SO_2 levels, respectively, in Stockholm County. We assessed area-wide emissions of traffic-related air pollution (NO_x and NO_2 from road traffic) for three periods: the 1960s, 1970s, and 1980s. Data on the expansion of built-up areas in Stockholm County and the growth and distribution of road traffic was collected from 1960 through 1993 to reconstruct comparable historical emission databases based on the 1993 database. Similarly, for emissions of SO_2 from heating sources, three corresponding historical emission databases were reconstructed using data on the sulfur content in oil and the development of district heating (point sources) and other energy plants. Available SO_2 measurement data were also used to calibrate the model regarding average emission levels from grid-type sources (mainly local oil-fuelled residential heating).

Dispersion calculations for annual mean SO_2 and NO_x from these emission databases used a Gaussian model,[13,14] in resolutions up to 100 × 100 m. The NO_x concentrations were transformed to NO_2 data using a non-linear relation derived from measurements in Stockholm County in the early 1980s. The dispersion model calculations from the NO_x/NO_2 1980s database (extended for this purpose to include traffic-related as well as other sources to produce estimates of total NO_x/NO_2) was compared with actual measurements of NO_2 at six roof-top or background sites. The modeled values

in these points were within ±20% from observed annual means. As all available measurements for SO_2 were used for model calibration, a similar validation was not possible for SO_2, although the calibration as such implies that the model approaches the measured data.

Annual levels of SO_2 and NO_x/NO_2 were computed for each year between 1950 and 1990 by linear extrapolation and interpolation from the three database values, based on historical traffic counts for NO_2, and available trend data for SO_2 concentrations in Stockholm.[9] For main streets in the city center, street contributions of NO_x and NO_2 concentrations were added to the roof concentrations. These contributions were assessed by dispersion calculations with a street canyon model[14] and summarized in a 50% addition at street level and 20% at mid-facade.

Finally, the air pollution data for relevant time periods were linked to the nearly 11,000 individual address coordinates of the study subjects, yielding exposure indices for each of the three air pollution indicators for each year.

Data Analysis

The occupational history included information on company names and locations, occupations, and work tasks for work periods of at least 1 year. We classified occupations according to the Nordic occupational code (NYK-83).[15] Classification of overall exposure to known or suspected occupational lung carcinogens used a published job-exposure matrix and was based on an individual's entire occupational history.[16,17] An occupational hygienist evaluated exposure to specific occupational carcinogens including diesel exhaust, other combustion products, and asbestos for each work period, case-by-case, assigning an intensity class and a probability of exposure for each work period and substance. We calculated the cumulative exposure for each factor as the product of the intensity, the probability, and the duration of exposure, summed over all work periods in the occupational history.[6] Subjects were also categorized as to predominantly blue or white collar work and approximate educational level implied by their occupational history, by matching NYK-83 job titles to Swedish socioeconomic level (SEI) codes.[18,19] The resulting socioeconomic variable represents a cross-classification of blue/white collar and low/high educational level. We estimated radon exposure for each residence from an equation predicting radon levels based on geographical radon risk level, building material and house type, obtained by regressing 9,002 measured houses from a nationwide Swedish radon study[8] on these variables. Time-weighted average radon exposure was calculated over all available residences 30 to 3 years before end of follow-up.

We controlled confounding from smoking by a categorical variable (never; former smokers since >2 years; current smokers of 1–10, 11–20, and >20 cigarettes daily on average) and continuous variables for years since quitting among former smokers and average amount smoked among current smokers, respectively (set to 0 for other subjects). Missing values for seven former smokers and two smokers of 1–10 cigarettes were replaced by the average corresponding value among controls.

Geocoded air pollution information was available from 1950 to each subject's selection year, with at most 5 years of missing values for any individual, mainly due to residency outside Stockholm county and to less complete address data in early years. Since we considered extrapolation far back from the 1960s air-pollution database to be uncertain, we used only a 30-year period before the selection year to estimate air-pollution exposure for each individual (*ie*, 1955–1984 to 1960–1989 for selection year 1985 to 1990, respectively). We excluded the selection year since annual exposure values were used and individual exposure in the selection year varies depending on a subject's exact selection date. In the 30-year study period for air pollution exposure thus defined, geocoded data were missing for only 159 residential exposure years (0.16%) among all 3,406 individuals; 75 individuals with at most 4 of 30 years missing. We calculated time-weighted average exposures over the study period and specific time windows.[20,21] Exposure-response relations were very similar for NO_x and NO_2 and only results for NO_2 are presented, since routine monitoring of this pollutant is more widespread. Furthermore, the correlation between the 30-year estimated traffic-related averages of the two pollutants was 0.98.

We estimated relative risks (RR) and 95% confidence intervals (CI) by odds ratios from multiple unconditional logistic regression, using the program Stata®.[22] The full models were adjusted for matching variables (age and selection year) and potential confounders: smoking, radon, socioeconomic grouping, work in risk occupations and occupational exposure to diesel exhaust, other combustion products and asbestos. Categorical variables were coded with indicator (dummy) variables. Results using either control group were similar and we combined the two groups to provide optimal statistical stability. We calculated attributable risks based on category-specific relative risks according to standard formulae.[21]

Results

Relative risks for lung cancer associated with some risk factors are shown in Table 2. Smoking-related RRs ranged up to 34.6 (95% CI = 23.2–51.6) for current smokers with more than 20 cigarettes per day of average consumption. With adjustment for age in narrow 5-year intervals, used in the case-control matching, exposure intensity rather than duration was more strongly related to lung cancer risk among current smokers, and among former smokers the RR decreased with longer duration since quitting smoking (detailed data not shown). The RR associated with residential radon exposure was 1.13 (95% CI = 0.83–1.55) per 100 Bq/m,^{3} assigning category means (see Table 2) as individual exposure level. Relative risks for three specific occupational exposures

TABLE 2. Relative Risk of Lung Cancer (and 95% Confidence Interval) Associated with Smoking, Radon, Socioeconomic Status, Some Occupational Exposures and Employment in Risk Occupations

Variable	Cases	Controls	RR*	95% CI*
Smoking†,‡,§,‖				
Never smokers**	36	705	1	
Former smokers	273	844	6.19	4.30–8.90
Current smokers				
1–10 cig/day	143	313	8.45	5.70–12.5
11–20 cig/day	348	363	18.4	12.7–26.6
>20 cig/day	242	139	34.6	23.2–51.6
Estimated residential radon exposure‡,§,‖,¶				
Below 78 Bq/m^3 (cat. mean 68)**	272	579	1	
78–93 Bq/m^3 (cat. mean 85)	265	587	0.94	0.74–1.19
93–116 Bq/m^3 (cat. mean 106)	280	572	1.08	0.85–1.37
Above 116 Bq/m^3 (cat. mean 147)	225	626	1.07	0.83–1.39
Broad socioeconomic groupings†,§,‖,¶				
Unskilled blue collar**	291	488	1	
Skilled blue collar, farmer	352	677	0.92	0.73–1.15
Unskilled white collar	136	333	0.87	0.65–1.16
Skilled white collar	263	866	0.74	0.58–0.95
Occupational exposure to diesel exhaust†,‡,‖,¶,††				
None or low**	970	2262	1	
High (≥2.38 mg-years/m^3 NO_2)	72	102	1.41	0.97–2.05
Occupational exposure to other combustion products†,‡,‖,¶,††				
None or low**	969	2268	1	
High (≥23.9 μg-years/m^3 benzo(a) pyrene)	73	96	1.47	1.01–2.14
Occupational exposure to asbestos†,‡,‖,¶,††				
None or low**	909	2189	1	
High (≥0.89 fiber-years/mL)	133	175	1.47	1.10–1.97
Employed in risk occupations†,‡,§,¶				
Never**	721	1802	1	
Ever	321	562	1.15	0.95–1.41

* All RRs adjusted for age, selection year, and exposure to traffic related air pollution.
† Additionally adjusted for radon.
‡ Additionally adjusted for socioeconomic grouping.
§ Additionally adjusted for occupational exposure to diesel exhaust, other combustion products, and asbestos.
‖ Additionally adjusted for employment in risk occupations.
¶ Additionally adjusted for smoking.
** Referent category.
†† Dichotomization of a cumulative exposure variable.

(diesel exhaust, other combustion products, and asbestos) were in the range 1.4–1.5. After adjustment for these exposures, the remaining relative risk for employment in risk occupations was 1.15 (Table 2). Low socioeconomic status was independently associated with increased risk. Variables for vegetable and fruit consumption were strongly protective in models that were adjusted only for the matching variables age and selection year (down to RR 0.3 for highest *versus* lowest consumption). These effects, however, largely disappeared when other risk factors (particularly smoking and socioeconomic status) were entered into the model. The dietary variables did not further confound the relation between air pollution and lung cancer. In addition, some subjects had missing dietary data, and thus we did not include the dietary variables in the final air pollution models.

The initial air pollution analyses utilized data covering the entire defined 30-year exposure period (Table 3). After we adjusted for the potential confounders identified, we found a weak effect for the 30-year average traffic-related NO_2 exposure, whereas we found no increase in risk of lung cancer associated with long-term average SO_2 exposure. In models incorporating both pollutants, the estimated effect of NO_2 was stronger.

We further investigated time windows and lags for calculating the individual mean exposure. Continuous and dichotomized NO_2 variables (representing linear component of trend and risk from extreme exposure, respectively) showed stronger positive associations with lung cancer risk than SO_2 variables, rather consistently regardless of time window used and particularly when early exposure (*ie*, 3rd decade before selection) was included. With a 20-year lag (*ie*, using a 10-year average over 21–30 years ago), the effects for traffic-related NO_2 exposure thus appeared stronger than for average exposure over the whole 30-year period, and showed a clearer dose-response (Table 4). When we examined exposures in the three different decades of the exposure period separately and jointly in regression models,[21] the results indicated that the earliest decade, 20 years before the selection year, was particularly important for lung cancer risk from traffic-related air pollution. The relative risk from traffic-related NO_2 exposure 21–30 years ago appeared relatively independent of smoking habits, *ie*, suggestive of an almost multiplicative interaction between the risks from these exposures. Heavy smokers constituted an exception, where no risk from traffic-related air pollution was indicated, although the confidence inter-

TABLE 3. Relative Risk of Lung Cancer (and 95% Confidence Interval) Associated with Long-Term (30-Year) Averages of Two Exposure Indicators for Air Pollution (NO_2 for Traffic-Related Air Pollution and SO_2 for Air Pollution from Heating)

Variable	Cases	Controls	One Pollutant* RR‡	One Pollutant* 95% CI‡	Both Pollutants† RR‡	Both Pollutants† 95% CI‡
NO_2 from road traffic						
Continuous variable (per 10 $\mu g/m^3$)			1.05	0.93–1.18	1.08	0.93–1.27
Quartiles and 90th percentile						
<15.20 $\mu g/m^3$§	242	609	1		1	
≥15.20 to <19.85 $\mu g/m^3$	276	575	1.18	0.93–1.49	1.22	0.93–1.61
≥19.85 to <25.06 $\mu g/m^3$	252	600	0.90	0.71–1.14	0.96	0.72–1.30
≥25.06 to <30.55 $\mu g/m^3$	160	351	1.05	0.79–1.40	1.13	0.81–1.58
≥30.55 $\mu g/m^3$	112	229	1.17	0.84–1.62	1.28	0.87–1.88
SO_2 from heating						
Continuous variable (per 10 $\mu g/m^3$)			1.00	0.96–1.05	0.98	0.92–1.04
Quartiles and 90th percentile						
<41.30 $\mu g/m^3$§	245	606	1		1	
≥41.30 to <52.75 $\mu g/m^3$	254	598	1.06	0.83–1.35	1.00	0.77–1.31
≥52.75 to <67.14 $\mu g/m^3$	272	579	0.98	0.77–1.24	0.92	0.69–1.22
≥67.14 to <78.20 $\mu g/m^3$	152	359	0.90	0.68–1.19	0.85	0.61–1.20
≥78.20 $\mu g/m^3$	119	222	1.00	0.73–1.37	0.92	0.63–1.34

Estimated time weighted average air pollution exposure 1–30 years before end of follow-up.
* Estimate obtained when only one pollutant was entered into the regression model.
† Estimate obtained when the corresponding variable for the other pollutant (SO_2 or NO_2) was entered separately into the same regression model as a confounder. For example, point estimates 1.08 (NO_2) and 0.98 (SO_2) for the continuous air pollution variables are obtained from the same model, and similarly for the categorical variable results.
‡ Adjusted for age, selection year, smoking, radon, socioeconomic grouping, occupational exposure to diesel exhaust, other combustion products, and asbestos and employment in risk occupations.
§ Referent category.

val is compatible with a similar RR in this group (Table 5).

Despite high exposure levels in the early years of the study period, heating-related SO_2 showed little effect in any time window. The results were different from those obtained for NO_2, despite the fact that the 30-year averages of estimated individual SO_2 and NO_2 exposure showed some correlation (Pearson's correlation 0.64). Correlations were highest in the early years; for annual averages, they were around 0.7 for the years 1950–1968 and 0.5 for the years 1969–1990 and similar for cases and controls.

When the two different control groups were evaluated separately, results were similar. The point estimates for the 90th percentile of 10-year average traffic-related NO_2 exposure 20 years before selection were 1.45 for "population" controls and 1.49 for mortality-matched controls as compared with 1.44 (95% CI = 1.05–1.99) when

TABLE 4. Relative Risk of Lung Cancer (and 95% Confidence Interval) Associated with 10-Year Averages of Two Exposure Indicators for Air Pollution (NO_2 for Traffic-Related Air Pollution and SO_2 for Air Pollution from Heating) Lagged 20 Years

Variable	Cases	Controls	One Pollutant* RR‡	One Pollutant* 95% CI‡	Both Pollutants† RR‡	Both Pollutants† 95% CI‡
NO_2 from road traffic						
Continuous variable (per 10 $\mu g/m^3$)			1.10	0.97–1.23	1.15	0.97–1.35
Quartiles and 90th percentile						
<12.78 $\mu g/m^3$§	243	608	1		1	
≥12.78 to <17.35 $\mu g/m^3$	264	588	1.15	0.91–1.46	1.19	0.91–1.56
≥17.35 to <23.17 $\mu g/m^3$	250	601	1.01	0.79–1.29	1.11	0.83–1.48
≥23.17 to <29.26 $\mu g/m^3$	165	346	1.07	0.81–1.42	1.19	0.86–1.66
≥29.26 $\mu g/m^3$	120	221	1.44	1.05–1.99	1.60	1.07–2.39
SO_2 from heating						
Continuous variable (per 10 $\mu g/m^3$)			1.01	0.98–1.03	0.99	0.95–1.02
Quartiles and 90th percentile						
<66.20 $\mu g/m^3$§	239	612	1		1	
≥66.20 to <87.60 $\mu g/m^3$	270	581	1.16	0.91–1.47	1.07	0.83–1.40
≥87.60 to <110.30 $\mu g/m^3$	259	593	1.00	0.79–1.27	0.90	0.67–1.19
≥110.30 to <129.10 $\mu g/m^3$	151	360	0.92	0.70–1.21	0.80	0.58–1.12
≥129.10 $\mu g/m^3$	123	218	1.21	0.89–1.66	0.95	0.64–1.39

Estimated time weighted average air pollution exposure 21–30 years before end of follow-up.
* Estimate obtained when only one pollutant was entered into the regression model.
† Estimate obtained when the corresponding variable for the other pollutant (SO_2 or NO_2) was entered separately into the same regression model as a confounder. For example, point estimates 1.15 (NO_2) and 0.99 (SO_2) for the continuous air pollution variables are obtained from the same model, and similarly for the categorical variable results.
‡ Adjusted for age, selection year, smoking, radon, socioeconomic grouping, occupational exposure to diesel exhaust, other combustion products and asbestos and employment in risk occupations.
§ Referent category.

TABLE 5. Relative Risk of Lung Cancer (and 95% Confidence Interval) According to Level of Individual Smoking Habits and Exposure to Traffic-Related NO_2 (as an Indicator of Air Pollution from Road Traffic) 20 Years Previously

Exposure to NO_2 from Road Traffic*		Never-Smoker	Former Smoker	Current Smoker (Average Consumption, Cigarettes/Day) 1–10	11–20	21 or More
Below 90th percentile (29.3 $\mu g/m^3$)	RR†	1	6.31	8.81	18.8	38.7
	95% CI	(ref)	4.25–9.38	5.76–13.5	12.6–28.2	25.1–59.6
Cases/controls		30/629	238/774	129/288	307/331	218/121
Above 90th percentile (29.3 $\mu g/m^3$)	RR†	1.68	9.95	12.0	27.9	28.8
	95% CI	0.67–4.19	5.71–17.3	5.60–25.7	15.3–51.0	13.9–59.6
Cases/controls		6/76	35/70	14/25	41/32	24/18
RR and 95% CI within smoking stratum	RR†	1.68	1.58	1.36	1.48	0.74
	95% CI	0.67–4.19	1.01–2.45	0.68–2.74	0.90–2.44	0.38–1.45

* Estimated time weighted 10-year average exposure lagged 20 years, *ie*, exposure 21–30 years before end of follow-up.
† Adjusted for age, selection year, smoking, radon, socioeconomic grouping, occupational exposure to diesel exhaust, other combustion products and asbestos and employment in risk occupations.

using both control groups. For the continuous variable, the estimates were 1.090 and 1.109, respectively, as compared with 1.096 (95% CI = 0.97–1.23). Thus, both control groups appeared to produce valid and equivalent results and were combined in the analyses.

Confounding from smoking seemed adequately controlled with the categorical variable, with only minor additional effect of adding continuous variables for average amount among current smokers and time since quitting among former smokers. A continuous variable for duration of smoking had no further effect on confounding control, probably because little correlation of air pollution exposure with smoking duration remained after stratification for age in 5-year intervals, smoking dose and subdivision of smokers into current and former smokers. A minor positive confounding effect by smoking included alone in the models tended to be balanced by minor negative confounding when adding the other risk factors.

Discussion

This study suggests an increased risk of lung cancer from traffic-related air pollution, assessed by individual annual estimates of traffic-related ambient NO_2 concentrations at the place of residence over a 30-year period, based on emission data and dispersion modeling. The clearest results were found for a time window covering the first of the three investigated exposure decades, *ie*, approximately 20 years in the past, which points to a considerable latency period. No effect was discernible for SO_2 related to residential heating, neither for long-term average levels, nor for past time windows. This finding appears somewhat paradoxical, as SO_2 levels were high in the past and NO_2 levels low, whereas in recent years SO_2 levels have decreased and NO_2 levels increased appreciably. Despite these contrasting temporal trends, however, the estimated exposures to heating-related SO_2 and traffic-related NO_2 showed reasonably high correlation, mainly due to geographical covariation. Nonetheless, traffic-related NO_2 rather than heating-related SO_2 was consistently the stronger risk indicator, with a suggestion of a 20-year latency period, a pattern that would seem to argue against a spurious association.

The controls in this study were selected from population registers with complete coverage of the study base from which the cases emanated. The response rate was high, over 85% among both cases and controls. Differential misclassification of air pollution exposure between cases and controls is not likely, since residential data on street address and years are unlikely to be affected by differential reporting bias, data was collected from several sources to obtain complete residential histories for virtually all subjects, and air pollution modeling is independent of case-control status. Non-differential misclassification, on the other hand, is probable and would tend to bias estimates for continuous variables and the top category of categorical variables toward the null.[21] The stronger effect seen in the time window analysis with 20-year lag suggests the possibility of decreased misclassification of biologically relevant exposure when an appropriate time window is specified. Nonetheless, the exposure indicators used in this study are still likely to be subject to non-systematic measurement error if they do not exactly correspond to the "true" exposure but are proxies for one or several components of the complex air pollution mix. Notwithstanding, a major strength of the present study lies in the long-term air pollution exposure assessment, which was based on detailed historical emission data and was performed individually for a 30-year residence period for each subject. Misclassification of true individual exposure is thus likely to be less serious than in many previous studies with cruder, non-individual exposure assessment. Furthermore, the emission data allowed us to partition exposure according to sources

and use source-specific NO_2-levels as an indicator of traffic-related air pollution and source-specific SO_2 as an indicator of air pollution from residential heating. The individual exposure contrast appears to have been sufficient to evaluate variations in risk - the ratio between the 90th and 25th percentiles was 2.0 to 2.3 for NO_2 and 1.9 to 2.0 for SO_2 (Tables 3 and 4), and the 30-year average ranged 11-fold for NO_2 and almost 18-fold for SO_2.

Expected relative risks for lung cancer were found for smoking[7,23] and radon,[8,24] and increased RRs were obtained for some well-known and suspected occupational risk factors, suggesting that questionnaire data were of good quality. Detailed results regarding occupational exposure are published elsewhere.[6] In crude analyses, protective effect estimates were obtained for vegetable and fruit consumption, but were no longer clearly apparent after detailed adjustment for other known risk factors. This confounding may partly reflect inadequate dietary reporting from proxies, leading to misclassification of these variables. The dietary variables did not confound the relation between air pollution and smoking. It is possible that overall dietary differences in our data, and possible confounding of air pollution associations, was described better by the socioeconomic and occupational variables. For the effect associated with traffic-related NO_2, minor positive confounding from smoking tended to be balanced mainly by negative confounding when adding the other exposures. The degree of confounding was modest. Thus, although imprecision in measuring confounders may limit confounding control, residual confounding of importance seems unlikely in this study.

Not many studies of ambient air pollution and lung cancer risk have investigated several pollutant measures and few have considered both NO_2 and SO_2. Consistent with our results, two ecological studies have suggested that NO_2 rather than SO_2 is associated with regional differences in lung cancer mortality or incidence.[25,26] Similarly, a case-control study suggested that nitrogen oxides and carbon monoxide (city center, largely traffic-related), or ozone and particulates (incinerator area) were more likely to be responsible for the increased risk found in that study than SO_2 (iron foundry area).[27,28] In a U.S. cohort study conducted among Seventh-Day Adventists in California, a strong relation for lung cancer incidence and mortality to 20-year averages of respirable particles (PM_{10}) was observed among men; among women it was weaker.[29,30] Associations were similar also for ozone and SO_2 among men and appeared stronger for SO_2 among women. The gender differences appeared to be partially due to differences in exposure, mainly that males spent more time outdoors, particularly in the summer.[29,30] For NO_2 exposure, a weak relation to lung cancer incidence was observed in one-pollutant models (*eg*, RR 1.5, 95% CI = 0.7–3.1 per 1.98 ppb NO_2 among men), and slightly stronger effects on lung cancer mortality (RR 1.8, 95% CI = 0.9–3.6 among men and 2.8, 1.1–6.9 among women, per 1.98 ppb NO_2). These estimates weakened further when other pollutants, including SO_2, were introduced into the models. In the U.S. Six Cities study, the risk gradient across the six cities was more strongly associated with fine and sulfate particulate levels than with either SO_2 and NO_2 levels; the two latter were similarly correlated with risk.[4]

Earlier studies used quantitative or semi-quantitative data on measured total ambient air pollution levels, whereas our study uses source-specific contributions from road traffic and residential heating emissions to population NO_2 and SO_2 exposure, respectively. If other emission sources are important in other localities, total NO_2 and SO_2 are likely to have a different interpretation as proxies for air pollution exposures. Furthermore, the use of fixed site monitors, as in the two cohort studies mentioned above, is likely to entail important non-differential misclassification of exposure, in particular for gaseous pollutants, such as SO_2 and NO_2, where local variation in emissions may produce sizeable variations in exposure levels.

When a restriction to NO_x/NO_2 from road traffic is made, as in this study, it is likely to represent not only traffic-related NO_x/NO_2 emissions but also may be a good proxy for other components of vehicle exhausts, including components of diesel exhaust and possibly fine or ultrafine particles, which have been suggested to be particularly important for mortality. For example, a study from Finland in an area where traffic is a main source of pollutants found correlation coefficients of 0.55–0.94 between NO_2 and various particulate measures including PM_{10}, black smoke and number concentrations of fine and ultra-fine particles.[31] We were not able to make direct analyses of particulate air pollution in this study because of lack of historical measurements, past emission data and validated dispersion models for particulates.

Interestingly, our study gives evidence for lung cancer risk related to several combustion sources, smoking being by far the strongest risk factor. In addition, we found an increased risk for occupational diesel exposure and occupational exposure to other combustion products,[6] providing some support for the relation with traffic-related air pollution reported here.

Lag or induction times for an effect of air pollution on lung cancer risk have not often been considered. An ecological study in an area with very low smoking rates investigated the effect of opening a steel mill that became the major air pollution source and found increased lung cancer mortality rates within 15 years.[32] Two case-control studies found increased risks associated with air pollution indices at the last place of residence, but since the average duration of residence was 30 years or more, these indices may represent both recent and long-term exposure.[27,33] Another case-control study suggested a stronger effect by ambient air pollution when allowing for a latency period of 20 years than when lifetime exposure was considered.[34] Most other case-control studies did not investigate this aspect of exposure in detail.[1]

Of the approximately 10 cohort studies on ambient air pollution and lung cancer, the majority are older studies using an urban/rural exposure contrast.[1] Individual estimates of air pollution exposure were only made in one

study, based on interpolation from fixed site monitoring stations.[3,29,30,35] Most cohort studies observed increased risk of lung cancer in the order of 1.5, surprisingly consistent and similar to the case-control studies.[1] Two recent U.S. studies with aggregate measured air pollution data suggest that the risk may be associated with fine or sulfate particulates.[45] In the third study, with individual exposure estimates, an effect of particulates, as well as ozone, was seen mainly in males, whereas a strong effect of SO_2 was seen in both genders.[29,30] NO_2 showed less of an association. One often-emphasized advantage of cohort studies is that because exposure information is collected before disease occurrence, differential bias in the exposure assessment is very unlikely. This advantage does not really apply in relation to our case-control study, however. Detailed exposure assessment using the methodology we have employed is unlikely to be affected by case-control status and represents a substantial improvement over most previous attempts to estimate long-term exposure to air pollution for individuals.

Some previous studies have suggested a multiplicative interaction between air pollution exposure and smoking, while others have been more consistent with an additive relation.[36] Our results are more compatible with a multiplicative interaction, except among heavy smokers, where no clear effect of traffic-related air pollution was evident. Similar weaker effects among heavy smokers have been observed for occupational arsenic[37] and residential radon[38,39] exposure. Possible explanations include a thickening of the bronchial mucosa,[40] a selection bias similar to the "healthy worker survivor effect" for maintaining high tobacco consumption, or chance.

Since exposure is widespread, the public health impact of a 50% increase in lung cancer risk among heavily exposed in the general population from traffic-related air pollution, as suggested by this study, may be important, and lower risk increases at more common moderate exposures potentially play a large role, too. An attributable risk calculation based on exposure above the 25th percentile suggests that the proportion of lung cancer among smoking and non-smoking males 40–75 years old in Stockholm County related to traffic-related air pollution exposure 20 years earlier could be as high as 10%.

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