Original article

Scand J Work Environ Health 2004;30(4):293–298

Exposure to urban nitrogen dioxide pollution and the risk of myocardial infarction

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Grazuleviciene R, Maroziene L, Dulskiene V, Malinauskiene V, Azaraviciene A, Laurinaviciene D, Jankauskiene K. Exposure to urban nitrogen dioxide pollution and the risk of myocardial infarction. *Scand J Work Environ Health* 2004;30(4):293–298.

Objectives This study attempted to determine whether long-term exposure to nitrogen dioxide (NO_2,), an indicator of motor vehicle exhaust, increases the risk of myocardial infarction (MI).

Methods A population-based case–control study was conducted among men aged 25–64 years and residing in Kaunas, Lithuania. The study included all cases of first-time myocardial infarction in 1997–2000. Interviews with patients treated in hospitals elicited information on smoking and other risk factors, including residential histories. A high response rate (77.4%) resulted in 448 cases and 1777 controls. Nitrogen dioxide (NO_2) was selected for analysis as an indicator of traffic-related air pollution. The annual air pollution levels were estimated for the residential districts; thereafter the data were linked to the home addresses of the cases and controls.

Results After adjustment for age, education, smoking, blood pressure, body mass index, marital status, and psychological stress, the risk of myocardial infarction was higher for the men exposed to medium [odds ratio (OR) 1.43, 95% confidence interval (95% CI) 1.04–1.96] and high (OR 1.43, 95% CI 1.07–1.92) NO_2 levels. The data suggested a stronger association among 55- to 64-year-old men. The risk of myocardial infarction increased by 17% among the 25- to 64-year-old men (OR 1.17, 95% CI 1.01–1.35) and by 34% among those aged 55–64 years (OR 1.34, 95% CI 1.08–1.67) from the first to the third tertile of NO_2 exposure.

Conclusions The results indicate that urban NO_2 pollution may increase the risk of myocardial infarction and that vehicle emissions may be of particular importance.

Key terms case-control study, long-term exposure, nitrogen dioxide.

In recent years, several epidemiologic studies have shown an association between short-term air pollution and cardiovascular deaths and hospital admissions (1–3). In a time-series study, the mean exposure to nitrogen dioxide (NO_2) over a period of 7 days was associated with an excess relative risk of ischemic heart disease (IHD) mortality (4). It was concluded that effect estimates increase as the duration of exposure to air pollution increases.

Some clinical studies of the last few decades have indicated that nonspecific adverse effects should be considered in research on the consequences of exposure to air pollutants (5). The evaluation of health risks of ambient air pollution (using NO_2 as an indicator) has thus far mainly been based on the results of animal and human experiments (6).

Within the body, NO_2, and the produced nitrogen dioxide ion (NO_2^-), is thought to be involved in oxidative stress, injury of the cell membrane, impairment of the function of alveolar macrophages and epithelial cells (7), reaction with lung tissue, and hemoglobin in erythrocytes and result in various injuries, carcinogenesis, and aging (8). NO_2 increases lipid peroxide formation, inhibits antioxidative enzymes (9), and exerts profound physiological effects on the lung, the liver, the immune system, and, especially, blood vessels (2). A few clinical studies have supported the hypothesis that NO_2 pollution may adversely affect health by causing airway inflammation, reducing lung function (10), and increasing blood coagulability (11). Similarly, the nonspecific effects of ambient air pollution exposure may be related to the pathological mechanisms linking air pollution

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to IHD. A 10-year follow-up study showed a significantly increased risk of IHD mortality for bus drivers working in an area with high traffic intensity (12). For professional drivers, motor exhaust exposure and the work environment have been proposed as possible risk factors for myocardial infarction (MI) (13). NO_2 pollution could serve as a predictor of hospital admissions for IHD or as an indicator of the frequency of outpatient visits associated with cardiovascular diseases (14–18). Patients with congestive heart failure are more susceptible to the harmful effects of ambient air pollution than the general population (19), and a significant positive association exists between daily deaths from all causes and short-term NO_2 exposure (20). We have not found any reports on the effects of long-term NO_2 exposure on first-time MI risk for the general population.

Traffic-related air pollution is currently a growing concern, and NO_2 may serve as a surrogate for traffic-related combustion products (21). Moreover, local-scale spatial variations in outdoor NO_2 concentrations have been shown to be reflected in similar variations in personal exposure (22).

Our study was aimed at exploring the possible association between the MI risk and urban air pollution. NO_2 was chosen as the indicator of traffic-related air pollution because traffic constituted the main local source of air pollution. Individual data on smoking, education, blood pressure, body mass index (BMI), psychological stress, and other risk factors were collected so that we could evaluate the confounders and possible interactions.

Participants and methods

Study design and study base

The study was conducted in Kaunas, which is the second largest city in Lithuania and covers approximately 157.2 km^2. The city, with about 400 000 inhabitants, is situated in a valley and on a neighboring plain. The National Department of the Environment and has performed air pollution measurements at municipal ecological monitoring posts in the city of Kaunas since 1993. The monitoring has revealed that exposure to major ambient air pollutants differs significantly according to the residential district of the city. During the last decade, the concentration of sulfur dioxide (SO_2) decreased to almost one-tenth of the previous pollutant level, and total suspended particles (TSP) decreased to one-half of the previous pollutant level. The major air pollution source is exhaust emissions from vehicles, which account for over 70% of the total emissions.

We analyzed the effect of ambient NO_2 pollution on the risk of first-time MI within the municipality of Kaunas using a population-based case–control study design. The study base population comprised all 25- to 64-year-old men residing in the city. All hospitalized patients with a first-time MI from 1997 to 2000 were eligible for the study. More than 97% of the MI cases occurring among 25- to 64-year-olds hospitalized in the Kaunas area are treated in four cardiological departments. Specially trained staff identified the persons for MI registration in these departments.

Identification of the cases and controls

The cases were identified from two sources and were included at the time of the first-time MI occurrence. The sources were the coronary and intensive care units within the cardiovascular departments in all hospitals in Kaunas and the hospital discharge register. All 25- to 64-year-old surviving patients with first-time MI treated in Kaunas hospitals were considered eligible for the epidemiologic study. A case was a person with a clinical diagnosis coded I21 in the 10th revision of the International Classification of Diseases (ICD-10) in the hospital register. The criteria for MI included (i) certain symptoms according to the case history information, (ii) specified changes in blood levels of the enzymes creatine kinase and lactate dehydrogenase, and (iii) specified electrocardiographic changes. Altogether, 579 first-time MI cases were registered among the men of the age group in question; 448 (77.4%) of them were interviewed in the hospital during their first week of hospitalization.

Four random controls, stratified by gender and age, were selected for each case from the population registers of the 12 residential districts. Men were eligible as controls if a clinical diagnosis of IHD or angina pectoris was not recorded in their medical documents, and the respondents did not report chest pain complaints during the interview. Altogether 2500 controls were selected; of them, 517 (20.7%) refused to participate and 206 (8.2%) had chest pain complaints or a history of IHD. Altogether 1777 controls were included in the study (response rate 71.1%). Four controls per case were interviewed within 7 days of the case incidence.

Exposure assessment

We used Kaunas municipal ecological monitoring data to assess exposure to ambient NO_2. Of the four routinely monitored air pollutants (SO_2, NO_2, TSP, and formaldehyde), we selected NO_2 for analysis, since it could serve as an indicator of vehicle exhaust. The NO_2 measurements were taken from 12 municipal monitoring sites, one in each residential district of the city. The monitors were located outside, primarily near schools and kindergartens. We used all the daily measurements available for NO_2 (photometric method) to assess the

annual mean residential exposure, which was considered to reflect personal exposure for the cases and controls. The exposure parameter was applied in both continuous and categorical forms. We grouped the residential districts according to pollutant concentrations into three categories (tertiles). For the categorical analysis, the group of participants with exposure in the first tertile was used as the reference category (low exposure). The analysis for the continuous exposure parameter was conducted on the basis of an intertertile increase in the NO_2 concentration.

Data on risk factors

Trained physicians interviewed the cases and controls using identical standardized questionnaires, which included information on demographic, educational and psychological factors, health behavior, and a history of residence. Data on the participants' history of increased arterial blood pressure, diagnosed by a physician, was taken from the hospital records. BMI was calculated as weight (kg) divided by height squared (m^2). The respondent's perceived stress was measured by a set of seven questions, adapted from the L Reeder stress scale (23), as follows: (i) "In general I am tense and nervous", (ii) "I do not worry very much about my job", (iii) "My daily activities are very trying and stressful", (iv) "I seldom experience tension in my family relations", (v) "There is a great amount of nervous strain connected with my daily activities", (vi) "I often find tension in my relations with other people", and (vii) "At the end of the day I am completely exhausted mentally and physically".

Four response options for each question [this describes me very well (1), fairly well (2), not very well (3), not at all (4)], scored 1–4, were used to define stress. We defined the stress measure as the sum of the scores so that the potential values for stress ranged from 7 to 28. Values from 15 to 28 were considered to represent "no stress", and those from 7 to 14 were labeled "stress". The participants were divided according to educational level into the following three categories: ≤8 years of schooling, secondary education, and university education.

Statistical analyses

We calculated the age-adjusted MI incidence rate per 1000 of the population per year for three NO_2 exposure categories. We calculated the crude odds ratios (OR) and their 95% confidence intervals (CI) for MI across the NO_2 exposure categories. The population-attributable risk (PAR) was calculated as $PAR=[(R_p–R_o)/R_p]\times100$, where R_p was the incidence of MI in the total 25- to 64-year-old male population, and R_o was that in the first tertile of NO_2 exposure.

We then examined the distribution of several known MI risk factors among the cases and controls across different exposure categories. The effect of ambient NO_2 exposure on MI risk was estimated using multivariate logistic regression. We adjusted the crude effects of NO_2 for the following potential confounding factors: age, education, marital status, smoking, blood pressure, BMI, and stress. For all the epidemiologic and statistical analyses, we used SPSS version 10.0 (SPSS Inc, Chicago, IL, USA).

Results

The mean NO_2 concentration was 20.0 (SD 5.4) $\mu g/m^3$ for the study period. During this time, 579 first-time nonfatal MI cases were registered. The age-standardized incidence of MI/1000 was 2.4. This index varied from district to district and reached the highest value in the central district with heavy traffic and a high ambient NO_2 concentration. Ambient air monitoring data showed fluctuation in the annual mean concentrations of NO_2 in the other districts as well.

According to the NO_2 concentrations in the residential districts, the following three areas of different exposure were determined: (i) a low-exposure area with NO_2 concentrations below 17 $\mu g/m^3$, a medium-exposure area (17–19 $\mu g/m^3$), and a high-exposure area, where NO_2 concentrations exceeded 19 $\mu g/m^3$. We assessed the age-standardized incidence of MI in these areas (table 1). In the area with low NO_2 exposure, the

Table 1. Distribution of the study population and first-time cases of myocardial infarction (MI) across the nitrogen dioxide (NO_2) exposure categories.

NO_2 tertiles	Concentration ($\mu g/m^3$)		Population at risk (N)	Myocardial infarction				
	Mean	SD		N	1000/1000 person-years	SD	OR[a]	95% CI
1 (low)	13.1	3.16	69 660	115	2.1	0.39	Reference	·
2 (medium)	18.7	0.73	81 231	189	2.4	0.36	1.41	1.11–1.79
3 (high)	24.7	3.06	111 939	275	2.6	0.32	1.49	1.19–1.86

[a] χ^2 for trend 11.586, df=2, P=0.0066.

incidence of MI was 2.1/1000, in the moderate-exposure area it was 2.4/1000, and in the high-exposure area the incidence was 2.6/1000. The crude odds ratio in the high NO_2 exposure area was 1.49 (95% CI 1.19–1.86, χ^2 for trend P=0.007 in comparison with the values of the low-exposure area). The relative importance of NO_2 exposure in the entire male population aged 25–64 years, estimated by calculating the PAR, was found to be 12.5%.

To assess whether the effect of NO_2 exposure increased with age, we calculated the age-standardized MI incidence in the 25–44, 45–54, 55–64 and 25–64 year age groups. The results showed that the MI incidence increased with increasing exposure level only among the men aged 55–64 years as follows: 4.4 in the first NO_2 tertile, 5.9 in the second NO_2 tertile, and 7.1 in the third NO_2 tertile (P for χ^2 trend 0.006). The PAR was 26.8%.

To investigate whether the characteristics of the MI cases and selected controls differed, we compared the distribution of potential MI risk factors in these two groups (table 2). There were significant differences with respect to age, education, marital status, smoking, blood pressure, BMI, psychological stress, and residential exposure. A greater proportion of the cases than the controls lived in areas of medium and high NO_2 exposure, and the MI proportion increased as the pollution level increased. The crude odds ratios for MI were found to be higher in the second and third tertile of NO_2 exposure.

To remove the effect of differences in the prevalence of independent variables, we adjusted the crude odds ratios for the following identified predictors of first-time MI: age, education, smoking, blood pressure, BMI, marital status, psychological stress, and residential exposure to NO_2 (table 3). After full adjustment, the MI risk remained significantly higher for the 25- to 64-year-old men in the second and third tertiles of NO_2 exposure (OR 1.43, 95% CI 1.04–1.96, and OR 1.43, 95% CI 1.07–1.92, respectively). Using a continuous exposure variable, we estimated that the MI risk increased by 17% among the 25- to 64-year-old men (adjusted OR 1.17, 95% CI 1.01–1.35) and by 34% among the 55- to 64-year-old men (adjusted OR1.34, 95% CI 1.08–1.67) from the lowest to the highest tertile of NO_2 exposure.

Table 2. Distribution of potential risk factors for myocardial infarction among the cases and controls, crude odds ratios (OR) and 95% confidence intervals (95% CI).

Risk factors	Cases (N=448)		Controls (N=1777)		Crude OR	95 % CI
	N	%	N	%		
Age groups						
25–44 years	65	14.5	340	19.1	·	·
45–54 years	158	35.3	636	35.8	1.30	0.94–1.81
55–64 years	225	50.2	801	45.1	1.47	1.07–2.01
Marital status						
Married	394	87.9	1490	83.8	·	·
Single	54	12.1	287	16.2	0.71	0.51–0.98
Education						
University	132	29.5	438	24.1	·	·
Secondary	217	48.4	1003	56.4	0.71	0.56–0.91
8 years	99	22.1	346	19.5	0.89	0.66–1.21
Smoking						
Nonsmoker	107	23.9	609	34.3	·	·
Current smoker	245	54.7	908	51.1	1.54	1.19–1.99
Former smoker	96	21.4	260	14.6	2.10	1.52–2.90
Blood pressure						
<140/90 mm/Hg	246	54.9	1400	78.8	·	·
140/90 mm/Hg	140	31.3	319	17.9	1.95	1.95–3.20
≥160/100 mm/Hg	62	13.8	58	3.3	6.08	4.08–9.08
Body mass index						
Normal (20.1–25.0 kg/m^2)	221	49.3	928	52.2	·	·
Increased (25.1–30.0 kg/m^2)	130	29.0	555	31.2	0.98	0.77–1.26
Obesity (>30.0 kg/m^2)	97	21.7	294	16.6	1.39	1.05–1.84
Psychological status						
No stress	293	65.4	1550	87.2	·	·
Stress	155	34.6	227	12.8	3.61	2.82–4.62
Traffic in district						
Not busy	224	50.0	1018	57.3	·	·
Busy	224	50.0	759	42.7	1.34	1.08–1.66
NO_2 exposure						
1st tertile	86	19.2	467	26.3	·	·
2nd tertile	151	33.7	526	29.6	1.56	1.15–2.11
3rd tertile	211	47.1	784	44.1	1.46	1.10–1.94

Table 3. Adjusted odds ratios (OR) for myocardial infarction among the men aged 25–64 years and among those aged 55–64 years by nitrogen dioxide (NO_2) exposure.

NO_2 exposure	25- to 64-year-old men				55- to 64-year-old men			
	Adjusted [a]		Adjusted [b]		Adjusted [a]		Adjusted [b]	
	OR	95% CI	OR	95% CI	OR	95 % CI	OR	95 % CI
1st tertile	Reference	·	Reference	·	Reference	·	Reference	·
2nd tertile	1.43	1.05–1.94	1.43	1.04–1.96	2.12	1.32–3.43	1.97	1.20–3.24
3rd tertile	1.37	1.03–1.82	1.43	1.07–1.92	1.98	1.24–3.16	2.07	1.28–3.35
Intertertile change	1.14	1.00–1.30	1.17	1.01–1.35	1.35	1.09–1.68	1.34	1.08–1.67

[a] Adjusted for age, smoking, blood pressure, body mass index.
[b] Adjusted for age, smoking, blood pressure, body mass index, psychological stress, marital status, education.

Discussion

This study suggested an increase in the risk of MI in association with traffic-related air pollution. The exposure assessment was based on ambient NO_2 concentrations in the residential district of the participants. Because actual exposures are always to pollutant mixtures, our findings should be critically appraised, especially with respect to concentrations below the current guidelines. Moreover, an assessment of long-term exposure effects requires treatment of potential confounders. Therefore, we used two methods to examine the association between NO_2 pollution and MI risk. First, we analyzed the association between NO_2 pollution and the MI incidence rate of the general population. Then, we employed a case–control study design and used a logistic regression to adjust for confounders. We used the standardized case-register technique to cover all MI events in the city population over 4 years. The application of common diagnostic criteria for MI should have contributed to an even and high quality of diagnosis through the whole case registration period.

The method used to find and ascertain the cases was comparable to that of MI registries set up in accordance with principles adopted in the MONICA program of the World Health Organization (24). However, there were several sources of error that may have caused a misclassification of the clinical diagnosis. These errors include diagnostic errors in silent cases and coding errors or other clerical errors in the recording of data. However, these errors were probably not related to residential exposure, and thus they did not bias the odds ratio estimates of the exposure areas. In our study, the age-adjusted MI incidence per 1000/year was calculated using all incident nonfatal cases. As we included only hospitalized cases of first-time MI in the study, our sample was not necessarily representative of all first episodes of MI. Therefore, some misclassification may have occurred with respect to the potential confounding factors, particularly the history of chronic diseases. Using questionnaire data gathered for 77% of all the registered MI events would have some effect on the misclassification of potential confounding factors.

As a representation of long-term exposure to air pollution, daily data on ambient NO_2 concentrations were recorded for a 5-year period. The ambient air pollution levels in Kaunas were relatively low, the mean concentration being 20.0 μg/m^3 for NO_2, 13.0 μg/m^3 for SO_2, 2.70 μg/m^3 for formaldehyde, and 111.0 μg/m^3 for TSP.

An increased incidence of MI was found for the men aged 25–64 years and exposed to ambient NO_2 levels below the levels of current guidelines. An excess risk of MI was found for the men aged 55–64 years, but not for those aged 25–44 or 45–54 years. The relative importance of NO_2 exposure for the entire 25- to 64-year-old male population, estimated as the population attributable risk, was found to be 12.5%, while it was 26.7% for the age group of 55–64 years. These results confirm the data of studies showing that the air pollution effects are stronger among older men (19, 25). Our results concerning an increased MI risk in relation to increasing levels of NO_2, as a traffic-related pollution indicator, are consistent with the findings reported for urban drivers (26). A study (13) that investigated the association between MI risk and work duration among 45- to 70-year-old urban professional drivers showed an exposure-response pattern. It was concluded that the work environment for urban bus and taxi drivers contributed to an increased MI risk (13). An increased MI risk has also been reported for plant and machine operators and assemblers (27). In Toronto, where concentrations of ambient air pollutants are low, 4.83 avoidable admissions for respiratory and cardiac diseases were attributable to NO_2 exposure, assessed on the basis of a single pollutant model (14). The strongest effect of NO_2 exposure was shown for IHD and heart failure admissions (10). The studies provided indirect support for our conclusion that exposure to ambient NO_2 levels below current guidelines may increase MI risk. The most important source of error and possible bias in our study—as has been the case in most studies in which exposure was based on place of residence—was the possible misclassification of exposure. We estimated exposure to pollutants using the average measures for the entire residential district. True personal exposure depends upon a several exposure pathways, time spent indoors versus outdoors, time spent at work, and migration. Nevertheless, factors expected to contribute to differences between area-wide and individual exposure were probably not related to the exposure assessment, the result being an underestimation of the effects of air pollution. Insufficient control of occupational exposures and other environmental risk factors could have also influenced the observed associations.

The results of our study revealed that adjustment for age, education, marital status, smoking, blood pressure, BMI, and psychological stress somewhat reduced the excess MI risk associated with NO_2, but the risk remained consistent for the men 25 to 64 years of age. Older men experienced stronger effects at the same level of NO_2 exposure than the younger ones did. These results suggest that air pollution could be particularly harmful to older men, who are more susceptible because of degenerative changes in the respiratory and cardiovascular systems.

In conclusion, the relation between long-term ambient NO_2 pollution and MI incidence showed a strong association and a dose–response relationship. The largest contribution to the excess risk among the men aged 25–64 years came from the group aged 55–64 years. However, we could not exclude the possibility that these

findings may be attributable also to other environmental risk factors and traffic-related combustion products.

Acknowledgments

Research for this paper was supported by the Lithuanian State Science and Studies Foundation.

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Received for publication: 7 July 2003