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Long term effects of residential NO_x exposure on total and cause-specific mortality and incidence of myocardial infarction in a Swedish cohort

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ABSTRACT

Background and aims: Exposure to air pollution has been linked to total and cardiopulmonary mortality. However, few studies have examined the effects of exposure over decades, or which time windows of long term exposure are most relevant. We investigated the long term effects of residential air pollution on total and cause-specific mortality and incidence of myocardial infarction in a well-characterized cohort of men in Sweden.

Methods: A cohort of 7494 men in Gothenburg was examined in 1970–1973 and followed subsequently to determine predictors of cardiovascular disease. We collected data on residential address and cause-specific mortality for the years 1973–2007. Each individual was assigned yearly nitrogen oxides (NO_x) exposure based on dispersion models. Using multivariable Cox regression and generalized additive models with time-dependent exposure, we studied the association between three different time windows of residential NO_x exposure, and selected outcomes.

Results: In the years 1973–2007, a total of 5669 deaths, almost half of which were due to cardiovascular diseases, occurred in the cohort. Levels of NO_x exposure decreased during the study period, from a median of 38 $\mu g/m^3$ in 1973 to 17 $\mu g/m^3$ in 2007. Total non-accidental mortality was associated with participants' NO_x exposure in the last year (the year of outcome) (HR 1.03, 95% CI 1.01–1.05, per 10 $\mu g/m^3$), with the mean NO_x exposure during the last 5 years, and with the mean NO_x exposure since enrolment (HR 1.02, 95% CI 1.01–1.04 for both). The associations were similar (HR 1.01–1.03), but generally not statistically significant, for cardiovascular, ischemic heart disease, and acute myocardial infarction mortality, and weaker for cerebrovascular and respiratory mortality. There was no association between NO_x exposure and incident myocardial infarction.

Discussion and conclusions: Long term residential exposure to NO_x at these relatively low exposure levels in Gothenburg was associated with total non-accidental mortality. The association was as strong for NO_x exposure in the last year as for longer exposure windows. The effect was near linear, and only marginally affected by confounders and effect modifiers. The improved air quality in Gothenburg has by these estimates led to a 6% decrease in excess non-accidental mortality during the study period.

1. Introduction

Long term exposure to air pollution has been associated with increased cardiopulmonary morbidity and mortality (Brook et al., 2010, WHO, 2013). Much of the evidence comes from American cohort studies – the Six Cities study (Dockery et al., 1993) and the American Cancer Society (ACS) study (Pope et al., 1995). There are also several European cohort studies reporting long term effects of air pollution on mortality (Hoek et al., 2002; Nafstad et al., 2004; Filleul et al., 2005; Elliott et al., 2007; Raaschou-Nielsen et al., 2012; Carey et al., 2013; Cesaroni et al., 2013), including the recent, multicenter European Study of Cohorts for Air Pollution Effects (ESCAPE) project (Beelen et al., 2014).

Several different mechanisms have been suggested for the health effects of air pollution, and have found support in

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experimental studies. They include low grade pulmonary and systemic inflammation leading to atherosclerosis and thrombosis, autonomic imbalance and arrhythmias, endothelial dysfunction and myocardial ischemia (Donaldson et al., 2005; Mills et al., 2005, 2007; Brook et al., 2010). In epidemiological studies, risk estimates are generally higher in longer term (conducted over months to years) compared to shorter term (involving days) studies (Brook et al., 2010). However, the majority of the risk increase seems to be manifested within 1–2 years of follow-up, indicating the importance of relatively rapid biological responses versus slower processes, such as the long term progression of atherosclerosis. Studies using exposure information from several decades are rare, however, and have been called for to further investigate this question (Brook et al., 2010).

Quantitative health risk assessments of long term effects of air pollution are often based on the results of the large ACS study (Forsberg et al., 2005; WHO, 2006). However, risk estimates vary between different studies, and it is still not clear which physical and chemical properties determine the toxicity of air pollution. The reason for different results might be methodological differences, such as variations in exposure assessment, exposure time windows, or confounder control, or there might be true differences between geographical areas. The levels and composition of air pollution, as well as other factors such as indoor infiltration rates, and the relative distribution of possible effect-modifying covariates (for example, diet, smoking habits, and physical activity) vary between populations.

To assess the long term health risks of ambient air pollution in the Nordic environment, we have investigated the effects of yearly residential outdoor nitrogen oxides (NO_x) exposure on total and cause-specific mortality, as well as incident myocardial infarction (MI), over several decades and in different exposure time windows, in a well-characterized, large cohort of men in Gothenburg, Sweden.

2. Material and methods

2.1. Study population

The Multifactor Primary Prevention Study started in 1970 (Wilhelmsen et al., 1972) and was originally an intervention trial against smoking, hypercholesterolemia, and hypertension in a random third ($n=10{,}004$) of all men in the city of Gothenburg born between 1915 and 1925, except for 1923. An initial screening was performed in 1970–1973, with 7494 participants (participation rate 75%), and a second examination in 1974–1977 ($n=7121$). Ten years after the first examination, a subsample of 20% of the intervention group, and a control group, were re-examined. No significant differences in risk factors or outcomes were found between the groups (Wilhelmsen et al., 1986). Consequently, any changes brought about by the intervention were taking place in the general population as well, and the present study group (the intervention group) is therefore considered to be representative of the background population of the city.

For the 7494 men participating in the 1970–1973 screening, individual yearly addresses for the entire study period (1970–2007) were retrieved (for 1970–1978 from the National Archives and for 1978–2007 from Statistics Sweden) and assigned geographical coordinates. All addresses were manually checked and corrected for inconsistencies, such as spelling mistakes. Some of the older addresses were located and assigned using maps in the city archives.

The study period was defined as January 1st, 1973, to December 31st, 2007, during which time all participants were followed based on their unique Swedish personal identification number. We obtained data on cause-specific mortality according to the International Classification of Diseases (ICD)-8, ICD-9, and ICD-10 from the Swedish national register on cause of death and examined total non-accidental mortality, cardiovascular mortality, death from ischemic heart disease (IHD), death from acute MI, death from cerebrovascular diseases, and death from respiratory diseases excluding lung cancer (Table 1). For incident MI, we combined data from the hospital discharge register, the Gothenburg Registry of Myocardial Infarctions, and the national register on cause of death (Table 1). The study was reviewed and approved by the Gothenburg Ethics Committee.

Table 1
International Classification of Diseases (ICD) codes and numbers of deaths from selected causes and incident myocardial infarctions in the cohort during the study period.

Cause of death	Number	% of deaths
Total mortality	5669	100
Non-accidental (ICD8 and ICD9 001-779 and ICD10 A00-R99)	5457	96
Cardiovascular (ICD8 and ICD9 400-440 and ICD10 I10.0-I70)	2465	43
Ischemic heart disease (ICD8 and ICD9 410-414, ICD10 I20-I25)	1584	28
Myocardial infarction (ICD8 and ICD9 410, ICD10 I21, I22)	953	17
Cerebrovascular disease (ICD8 and ICD9 430-438, ICD10 I60-69)	442	8
Respiratory disease (ICD8+9 460-519, ICD10 J00-J99)	373	7
Incident myocardial infarction (ICD8 and ICD9 410, ICD10 I21)	1722	n.a.

n.a.=not applicable.

At baseline, the year 1973, participants were middle aged, with ages evenly distributed between 48 and 58 years (Table 2). Over half of the participants were initially smokers, but a relatively large fraction (9.4% of the cohort) quit between the first and the second screening. Around half were employed in white collar jobs, and half in blue collar jobs. Most (58.3%) reported a moderate amount of physical activity in their leisure time. Almost a quarter (24%) reported a family history of coronary events, and 15.6% said that they were feeling constantly stressed. Only 2% had a diagnosis of diabetes mellitus. The median body mass index (BMI) was 25.2 kg/m^2, with very few participants being underweight or obese. Systolic and diastolic blood pressures were relatively high on average, and were found to be somewhat over-estimated compared to more relaxed circumstances (Wilhelmsen et al., 2004). In addition, many cardiovascular risk factors were more prevalent at the time (Wilhelmsen et al., 2008). Only a minority regularly took hypertensive medication.

2.2. Exposure assessment

Yearly mean levels of NO_x for the Gothenburg area were modeled in 75,000 (250*300) 50 meter squares for the years 1975, 1983, 1991, 1997, 2004, and 2009 by the Gothenburg Environment Department in a Gaussian dispersion model using the EnviMan AQPlanner (OPSIS, Furulund, Sweden). NO_x levels for the intervening years were interpolated linearly and, thus, each individual was given an exposure value at the residential address for each year. When there was no address information for the participant's last year (due to death or emigration before addresses were collected for that year), we used the NO_x exposure of that year at the preceding year's address. For the years 1973 and 1974, the NO_x values for 1975 were used. For more detailed information, see (Molnár et al., 2015).

A small number of participants ($n=46$) died before the start of the study period and were excluded from the analysis, as were the