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## **Long-Term Exposure to Urban Air Pollution and Mortality in a Cohort of More than A Million Adults in Rome**

Giulia Cesaroni<sup>1</sup>, Chiara Badaloni<sup>1</sup>, Claudio Gariazzo<sup>2</sup>, Massimo Stafoggia<sup>1</sup>, Roberto Sozzi<sup>3</sup>, Marina Davoli<sup>1</sup>, and Francesco Forastiere<sup>1</sup>

<sup>1</sup>Department of Epidemiology, Lazio Regional Health Service, Rome, Italy

<sup>2</sup>Italian Workers' Compensation Authority (INAIL), Rome, Italy

<sup>3</sup>Regional Environmental Protection Agency, Rome, Italy

### **Institution where the work was performed:**

Department of Epidemiology of Lazio Regional Health Service,  
Via di S. Costanza 53, 00198 Rome, Italy

### **Corresponding Author:**

Giulia Cesaroni,

Department of Epidemiology of Lazio Regional Health Service

Via di S. Costanza 53,

00198 Rome, Italy

e-mail: [g.cesaroni@deplazio.it](mailto:g.cesaroni@deplazio.it)

tel. +390683060462 fax. +390683060374

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### **Competing financial interests declaration**

The authors declare they do not have competing interests.

### **List of relevant abbreviations and definitions used in the manuscript**

BIC Bayesian information criterion

BMI Body Mass Index

CI Confidence Interval

CMR Crude Mortality Rate

COPD Chronic Obstructive Pulmonary Disease

CVD Cardiovascular Disease

EU European Union

GIS Geographic Information System

HR Hazard Ratio

HTR High Traffic Road: road with >10,000 vehicles per day

ICD International Classification of Diseases

IHD Ischemic Heart Disease

IQR Interquartile Range

LUR Land Use Regression

NO<sub>2</sub> Nitrogen Dioxide

PM<sub>10</sub> Particulate Matter with a diameter  $\leq 10 \mu\text{m}$

PM<sub>2.5</sub> Particulate Matter with a diameter  $\leq 2.5 \mu\text{m}$

RoLS Rome Longitudinal Study

## ABSTRACT

**Background:** Few European studies have investigated the effects of long-term exposure to both fine particulate matter (PM<sub>2.5</sub>) and nitrogen dioxide (NO<sub>2</sub>) on mortality.

**Objectives:** To analyze the association of exposure to NO<sub>2</sub>, PM<sub>2.5</sub> and traffic indicators on cause-specific mortality; to evaluate the form of the concentration-response relationship.

**Methods:** We analyzed a population-based cohort enrolled at 2001 Census with 9 years of follow-up. We selected all 1,265,058 subjects, aged  $\geq 30$  years, who had been living in Rome for at least 5 years at baseline. Residential exposures included annual NO<sub>2</sub> (from a land use regression model), annual PM<sub>2.5</sub> (from a Eulerian dispersion model), traffic intensity and distance to roads with  $>10,000$  vehicles/day. We used Cox regression models to estimate associations with cause-specific mortality adjusted for individual (sex, age, place of birth, residential history, marital status, education, occupation) and area (socioeconomic status, clustering) characteristics.

**Results:** Long-term exposures to both NO<sub>2</sub> and PM<sub>2.5</sub> were associated with an increase in non-accidental mortality (Hazard Ratio, HR=1.03; 95% CI: 1.02, 1.03 per 10  $\mu\text{g}/\text{m}^3$  NO<sub>2</sub>; HR = 1.04; 95% CI: 1.03, 1.05 per 10  $\mu\text{g}/\text{m}^3$  PM<sub>2.5</sub>). The strongest association was found for ischemic heart diseases (IHD, HR = 1.10; 95% CI: 1.06, 1.13 per 10  $\mu\text{g}/\text{m}^3$  PM<sub>2.5</sub>), followed by cardiovascular diseases and lung cancer. The only association showing some deviation from linearity was that between NO<sub>2</sub> and IHD. In a bi-pollutant model, the estimated effect of NO<sub>2</sub> on mortality was independent of PM<sub>2.5</sub>.

**Conclusions:** This large study strongly supports an effect of long-term exposure to NO<sub>2</sub> and PM<sub>2.5</sub> on mortality, especially from cardiovascular causes. The results are relevant for the next European policy decisions regarding air quality.

## INTRODUCTION

Most of the available evidence linking long-term air pollution exposure with mortality comes from North American studies and is based on exposure contrasts between and within various communities (Abbey et al. 1999; Dockery et al. 1993; Gan et al. 2011; Lepeule et al. 2012; Lipsett et al. 2011; Pope et al. 2004; Puett et al. 2008). There are only few European studies on the effects of long-term exposure to both fine particles (diameter  $\leq 2.5 \mu\text{m}$ ;  $\text{PM}_{2.5}$ ) and nitrogen dioxide ( $\text{NO}_2$ ) on all-cause and cause-specific mortality (Beelen et al. 2008; Filleul et al. 2005; Gehring et al. 2006; Hoek et al. 2002; Naess et al. 2007).

The estimated effects of long-term exposure to air pollution seem to be stronger for cardiovascular, respiratory, and lung cancer mortality than other causes of mortality (Beelen et al. 2008; Crouse et al. 2012; Dockery and Stone 2007; Gan et al. 2011; Lepeule et al. 2012; Lipsett et al. 2011; Pope et al. 2002, 2004), but the specific roles of  $\text{PM}_{2.5}$  and  $\text{NO}_2$ , which both originate in urban areas (at least partially) from traffic and chemical transformation processes, have not been elucidated. Therefore, a recent review of the literature conducted by the Health Effect Institute states that the evidence linking traffic air pollution and mortality is suggestive but not yet sufficient (HEI 2010).

In 2013, the European Union (EU) will revise its main air pollution control policies (the EU air pollution directive 2008/50/EC). Hence, the European Commission has recently requested that the World Health Organization respond to several scientific open questions (the REVIHAAP project, Evidence on health aspects of air pollution to review EU policies, [www.euro.who.int](http://www.euro.who.int)). In particular, there is a need to better evaluate the form of the concentration-response functions

of fine particles (PM<sub>2.5</sub>), to assess the independent role of NO<sub>2</sub> on PM<sub>2.5</sub>, and to establish the outcomes to be considered in health impact assessment studies.

The identification of population subgroups that may be particularly vulnerable to air pollution effects is an additional research concern. Some studies have suggested that gender, socioeconomic position, smoking, and health characteristics, which are usually treated as confounders, could modify exposure-mortality associations. For example, Chen and colleagues reported that coronary deaths were associated with increasing levels of fine particulate matter in women but not men (Chen et al. 2005). Therefore, it has been suggested that the next generation of studies should identify the characteristics of subjects who are most susceptible to the effects of air pollution (Puett et al. 2008).

In this study, we analyzed associations of NO<sub>2</sub>, PM<sub>2.5</sub>, and two GIS (Geographic Information System) indicators of traffic exposure (distance to heavy traffic roads with >10,000 vehicles per day, and traffic intensity in a buffer of 150 meters) with cause-specific mortality in adults included in the Rome Longitudinal Study (RoLS) (Cesaroni et al. 2010). We estimated the overall effect of each single pollutant and traffic indicator on mortality and examined the form of the concentration-response relationships. In addition, we investigated effect modification by personal characteristics (i.e. sex, age group, socioeconomic position) to identify potential susceptible subgroups.

## **METHODS**

### **The study cohort**

Rome is the largest Italian city, with a population of about 2.5 million inhabitants in a 1,290 km<sup>2</sup> area (at the 2001 Census), with the majority living within the large urban area, but also including suburban communities.

The Rome Longitudinal Study is based on the 2001 Census fixed cohort of Rome ascertained from the Municipal Register (Cesaroni et al. 2010). We included all residents age 30 years and older on the census reference day (21st October 2001) who were not living in institutions (prisons, hospitals or nursing homes) and who had resided in Rome for at least five years. Data were available on sex, age, place of birth, residential history, and were obtained for additional variables (marital status, education, occupation) using record-linkage procedures under strict control to protect individual privacy.

We conducted a follow-up to determine vital status using the Rome municipal register during the period October 2001-December 2010. We retrieved information on deceased individuals and considered subjects as lost to follow-up when they moved out of the city. The underlying cause of death (coded according to the International Classification of Diseases revision 9, ICD-9) for deceased subjects was retrieved from the regional health information system (WHO 1977).

The RoLS is part of the National Statistical Program for the years 2011-2013 and was approved by the Italian Data Protection Authority.

### **Air pollution exposure assessment**

We used a land use regression model (LUR) to estimate annual NO<sub>2</sub> concentrations for each residence. The LUR model has been already described (Cesaroni et al. 2012). Briefly, in 2007 we measured NO<sub>2</sub> concentrations using Ogawa passive samplers at 78 sites during three one-week periods in February, May, and October. We assigned to each sampling location a single NO<sub>2</sub> level, the mean of the three measurements. We used several land-use, GIS, and traffic variables to predict log NO<sub>2</sub> levels in multivariable linear regression. The best-fitting regression model had a determination coefficient ( $R^2$ ) of 0.704. The model was validated using leave-one-out cross validation; the  $R^2$ , adjusted- $R^2$ , and root mean square error of the regression analysis between measured and estimated concentrations was 0.61, 0.61, and 5.38, respectively.

Exposure to PM<sub>2.5</sub> at residence was estimated using a one km-grid dispersion model (the flexible air quality regional model, FARM) (Gariazzo et al. 2007), a three-dimensional Eulerian model of the transport and multiphase chemistry of pollutants in the atmosphere (Gariazzo et al. 2007, 2011). Further details on the dispersion model, its validation, and the comparison of the results from the NO<sub>2</sub> and PM<sub>2.5</sub> models with actual measurements are provided in Supplemental Material (see Supplemental Material, pg. 2 – 3).

We applied the estimated annual means from the 2007 NO<sub>2</sub> LUR model and from the 2005 PM<sub>2.5</sub> dispersion model to all addresses from October 1996 to December 2010. For each individual and each year of the follow-up, we calculated the average exposure since October 1996, weighted for the time of residence in each location.

We used two GIS indicators at residential address as proxy measures of exposure to traffic. The first was the distance to high traffic roads (HTR), i.e. roads with >10,000 vehicles per day, which we categorized as <50, 50-100, 100-150, 150-250, and  $\geq 250$  meters. The second was traffic intensity within the 150-metre buffer zone around the home (the sum of the number of vehicles per day multiplied by the length of the roads -in meters- within the buffer) categorized in quintiles of the distribution. The size of the buffer was slightly larger than that used by Beelen and colleagues (2008). For the GIS variables, we used the address of the individuals at the baseline.

### **Outcomes**

We analyzed mortality for non-accidental causes (ICD-9: <800), cardiovascular disease (ICD-9: 390-459), ischemic heart disease (ICD-9: 410-414), cerebrovascular disease (ICD-9: 430-438), respiratory disease (ICD-9: 460-519), and lung cancer (ICD-9: 162).

### **Covariates**

We considered age, sex, and several variables at the baseline as potential confounders: marital status (married, single, separated/divorced, widowed), place of birth (Rome or other), level of education (university, high school, secondary, and primary), and occupation (top qualified non manual employed i.e. managers, university and high school professors, researchers; other non-manual employed; manual labor employed; other employed i.e. armed forces and retail sales; housewife; unemployed; retired; others). Some studies have shown that neighborhood socioeconomic level is associated with smoking, after accounting for individual education and occupation (Diez-Roux et al. 2003). Therefore, we adjusted estimates for a five-level small-area

(census block) socioeconomic position index that is based on 2001 Census data in Rome (5500 census blocks, average population: 500 subjects) and was derived based on a factor analysis including education, occupation, house ownership, family composition, crowding, and immigrant status (Cesaroni et al. 2010).

In addition, since data on lifestyles were not available, we adjusted a subset of models for pre-existing comorbidities related to smoking habits or diet [diabetes (ICD-9: 250), chronic obstructive pulmonary disease (COPD) (ICD-9: 490-492, and 496), and hypertensive heart disease (ICD-9: 401-404)] that were identified based on the principal and up to five secondary diagnoses indicated on hospital discharges from October 1996 to October 2001 (Gan et al. 2011).

### **Statistical analyses**

We investigated the correlation between exposure to  $\text{NO}_2$  and  $\text{PM}_{2.5}$  using Pearson's correlation coefficient. To estimate associations between air pollution exposure and cause-specific mortality we used Cox proportional hazards regression models (hazard ratios, HR) with time-dependent exposures and age as the time-scale. We first calculated hazard ratios adjusted for sex only (Model-1), then adjusted for individual covariates (marital status, place of birth, education, occupation) and the small area socioeconomic position indicator (Model-2), and, finally, we adjusted also for pre-existing comorbidities (diabetes, hypertensive heart disease, and COPD, Model-3). When analyzing respiratory mortality with Model-3, we adjusted for diabetes and hypertensive heart disease only.

We estimated associations with the pollutants using several different scales: quintiles of the distributions, 10- $\mu\text{g}/\text{m}^3$  increases, and inter-quartile range increases (IQR). To estimate the overall effects of  $\text{PM}_{2.5}$  and  $\text{NO}_2$ , we modeled each pollutant in turn (single-pollutant models), and estimated independent effects of each pollutant by including both  $\text{PM}_{2.5}$  and  $\text{NO}_2$  in the same multivariable Cox model (bi-pollutant model). We also adjusted single pollutant models for traffic intensity and distance to HTR.

In addition, we evaluated potential effect modification by including an interaction term between exposure ( $\text{PM}_{2.5}$  or  $\text{NO}_2$ , in turn) and one effect modifier at a time (sex, age group, educational level, small area socioeconomic position, and residential stability, i.e. a binary variable indicating if the subject ever changed the residential address) and used likelihood ratio tests to compare the fit of models with and without interaction terms.

We considered  $p$ -values  $< 0.05$  as indication of statistical significance, and we performed Wald tests to test the trend across quintiles of exposures (treated as ordinal categorical variables coded using integer values 1-5).

Neighborhoods are usually inhabited by residents with similar characteristics (socioeconomic, health, access to services) and similar environmental exposures, which means that confounding and clustering in the association between exposure and mortality should be investigated (Crouse et al. 2012).

In a sensitivity analysis, we performed a frailty model to investigate the role of both neighborhood and district (Rome is divided into 94 neighborhoods and into 19 districts).

We explored the shape of relationships between exposures and outcomes by replacing the linear term in the base model with natural splines with 2, 3 or 4 degrees of freedom (Eisen et al. 2004), which capture potential non-linearity in the data without over-fitting. We used the Bayesian information criterion (BIC) and the likelihood ratio test to compare the relative goodness of fit of the models.

We used STATA10 for all statistical analyses with the exception of the frailty models and spline plots, for which we used R. Since R was not able to deal with a large number of records for the amount of computer memory available, for the spline and frailty analyses we studied a 20% random sample of the study population, and used fixed time-weighted exposures between October 1996 and October 2001. We applied the appropriate weights to natural spline models to plot effects for the entire population.

## RESULTS

A total of 1,265,058 residents were included in the study. The average exposure levels of the population at baseline were  $43.6 \mu\text{g}/\text{m}^3$  (sd=8.4, min=13.0, max=75.2, p25=38.5, p50=44.5, p75=49.2) for  $\text{NO}_2$ , and  $23.0 \mu\text{g}/\text{m}^3$  (sd=4.4, min=7.2, max=32.1, p25=20.3, p50=23.9, p75=26.0) for  $\text{PM}_{2.5}$ . The average distance to a HTR was 232 meters (sd=224, min=2, max=946, p25=80, p50=165, p75=308), and the average traffic intensity within a 150-m buffer zone was

$4.1 \times 10^6$  vehicles\*m (sd= $5.3 \times 10^6$ , min=0, max= $88.9 \times 10^6$ , p25= $0.6 \times 10^6$ , p50= $5.4 \times 10^6$ , p75= $5.5 \times 10^6$ ).

There was a high correlation between NO<sub>2</sub> and PM<sub>2.5</sub> exposures (0.79). Figure 1 maps the concentrations of the two pollutants in Rome. The highest levels of air pollution are in the city center and in the eastern part of Rome. The resolution of the exposure model for NO<sub>2</sub> is clearly higher than for PM<sub>2.5</sub>.

From October 2001 to December 2010 (average length of follow-up: 8.3 years), 9.5% of the study population emigrated, and 12% died. There were 144,441 non-accidental deaths (95.8% of all deaths) and the crude mortality rate (CMR) was 13.8 per 10,000 person-years. Cardiovascular causes were responsible for 40% of all deaths (CMR=5.8), including ischemic heart diseases (15% of deaths, CMR=2.2) and cerebrovascular diseases (9% of deaths, CMR=1.3), and respiratory diseases and lung cancer accounted for 6% (CMR=0.8) and 8% of all deaths (CMR=1.2), respectively. The majority of the cohort (75.3%) did not change address from October 1996 to the end of follow-up, whereas a change in address within the city was registered for 311,728 residents.

Residents with higher levels of NO<sub>2</sub> exposure were older, better educated, more likely to live alone, closer to high traffic roads, and more exposed to traffic compared with residents who had lower levels of exposure (see Supplemental Material, Table S1).

### **Air pollution and mortality**

While there was little or no evidence of an association between any of the indices of exposure and non-accidental, cardiovascular disease, or ischemic heart disease mortality based on the crude model (Model-1, adjusted for sex only), there was strong evidence of an association between all exposure indicators and these outcomes when we adjusted for personal characteristics and area-based socioeconomic position (Model-2) (Table 1). The variables most responsible for the differences between the two models were education, occupation and area-based socioeconomic position index (data not shown). The magnitude of the estimated effects on non-accidental mortality was similar for NO<sub>2</sub> and PM<sub>2.5</sub>, with a gradual increase in mortality across the quintiles of NO<sub>2</sub> and PM<sub>2.5</sub>, as well as categories of traffic intensity and distance to high traffic roads. Although the trend p-value was <0.05 in the association between proximity to high traffic roads and mortality, only those living <50 meters to a high traffic road had a statistically significant higher mortality risk compared to those living ≥250 meters. Associations with the different exposure indexes followed similar patterns for cardiovascular disease and IHD mortality, and the estimated effects were stronger for IHD mortality than all other causes.

Table 2 shows the results of cerebrovascular, respiratory, and lung cancer mortality. There was evidence of an association between PM<sub>2.5</sub> exposure and cerebrovascular mortality, with an 8% higher risk per 10 µg/m<sup>3</sup> PM<sub>2.5</sub> (Model-2; 95% CI: 1.04, 1.13), but associations with NO<sub>2</sub> and proxy measures of traffic exposure were weaker and not statistically significant. There was some evidence of an effect of NO<sub>2</sub> and traffic intensity on respiratory disease mortality. There was strong evidence of an association between lung cancer mortality and both NO<sub>2</sub> and PM<sub>2.5</sub>, but not with proxy measures of traffic exposure.

Estimated associations with NO<sub>2</sub> and PM<sub>2.5</sub> were similar or slightly stronger for all outcomes when we also adjusted for pre-existing comorbidity (see Supplemental Material, Table S2).

Associations with 10- $\mu\text{g}/\text{m}^3$  increases in NO<sub>2</sub> and PM<sub>2.5</sub> (run on a 20% random sample) were similar when estimated using the standard Cox model (Model-2), the frailty model with districts, and frailty model with neighborhoods (see Supplemental Material, Table S3). Note that the effect estimates in the 20% sample were very similar to those obtained for the entire data set, with the only exception of the PM<sub>2.5</sub>- lung cancer association that was clearly underestimated.

Figure 2 shows estimated concentration-response curves (natural splines, 2 degrees of freedom) for non-accidental mortality, cardiovascular, IHD, and lung cancer mortality for NO<sub>2</sub> (upper panel) and PM<sub>2.5</sub> (lower panel) based on a 20% random sample of the study population. In general, the results showed no evidence of deviation from linearity (based on BIC), with the only exception being the association between NO<sub>2</sub> exposure and IHD mortality (likelihood ratio test comparing the linear and the spline model with two degrees of freedom gave a p-value=0.028, although with very similar BIC). Results were similar for natural splines with 3 or 4 degrees of freedom (data not shown).

Despite the high correlation between the two pollutants, the estimated effect of a 10 $\mu\text{g}/\text{m}^3$  increase in NO<sub>2</sub> on non-accidental mortality was still statistically significant when adjusted for PM<sub>2.5</sub> in a bi-pollutant model (Model-2 HR = 1.02; 95% CI: 1.01, 1.03). In contrast, the estimated effect of PM<sub>2.5</sub> decreased when adjusted for NO<sub>2</sub> (HR = 1.01; 95% CI: 0.99, 1.02 for a

10 $\mu\text{g}/\text{m}^3$  increase in  $\text{PM}_{2.5}$  compared with HR = 1.04; 95% CI: 1.03, 1.05 based on the single pollutant model). Adjusting for proximity to HTR or traffic intensity in separate models of  $\text{NO}_2$  and  $\text{PM}_{2.5}$  did not change estimates for either pollutant (data not shown).

Figure 3 presents the adjusted HRs, 95% CIs, and p-values for interaction (likelihood ratio test) for non-accidental, cardiovascular, IHD, and lung cancer mortality per 10 $\mu\text{g}/\text{m}^3$   $\text{NO}_2$  and  $\text{PM}_{2.5}$ , by sex, level of education (high=university, middle=high school, low=secondary and primary school), age group, area-based socioeconomic position, and residential stability (movers: those who changed residence during the study). There was some suggestion of effect modification by age (with <60 year olds at higher risk than  $\geq 75$  year olds), by residential stability (with non-movers at higher risk than movers), and by sex (with men at higher risk than women) for non-accidental mortality and cardiovascular mortality (for  $\text{PM}_{2.5}$  only).

## DISCUSSION

We found statistically significant positive associations between long-term exposure to  $\text{NO}_2$  and  $\text{PM}_{2.5}$  and non-accidental, cardiovascular, ischemic heart disease, and lung-cancer mortality in the adult population of Rome. In addition, exposure to  $\text{PM}_{2.5}$  was associated with cerebrovascular mortality, while  $\text{NO}_2$  exposure was associated with respiratory mortality. Proximity to HTR and traffic intensity were associated with non-accidental, cardiovascular, and IHD mortality. Despite the high correlation of the pollutants,  $\text{NO}_2$  was significantly associated with mortality when adjusted for  $\text{PM}_{2.5}$ , though the estimated effect of  $\text{PM}_{2.5}$  was no longer significant. There was no evidence of deviation from linearity of the effects of either  $\text{NO}_2$  or  $\text{PM}_{2.5}$  on non-accidental, cardiovascular and lung cancer mortality. The estimated effects on non-

accidental mortality tended to be stronger in males, younger subjects (<60 years), and non-movers.

Average exposure of the cohort was slightly higher than in other study populations from Europe or North America, but near the values being discussed as potential European standards ( $40\mu\text{g}/\text{m}^3$  for  $\text{NO}_2$  and  $20\mu\text{g}/\text{m}^3$  for  $\text{PM}_{2.5}$ ). The mean concentrations of  $\text{NO}_2$  and  $\text{PM}_{2.5}$  (in Rome:  $44\mu\text{g}/\text{m}^3$  and  $23\mu\text{g}/\text{m}^3$ , respectively) ranged from 32.1 and  $4.1\mu\text{g}/\text{m}^3$  in Canada (Gan et al. 2011) to  $39\mu\text{g}/\text{m}^3$   $\text{NO}_2$  in Germany (Gehring et al. 2006), and  $28.3\mu\text{g}/\text{m}^3$   $\text{PM}_{2.5}$  in the Netherlands (Beelen et al. 2008).

The associations we found for the selected causes of mortality were comparable with, but slightly lower than, those reported in other European and North American settings (Crouse et al. 2012). The 4% (95% CI: 3, 5%) higher risk of non-accidental mortality per  $10\mu\text{g}/\text{m}^3$   $\text{PM}_{2.5}$  in Rome was comparable to the 6% higher risk (95% CI: 3, 9%) reported based on a meta-analysis of five studies (Abbey et al. 1999; Beelen et al. 2008; Gehring et al. 2006; Laden et al. 2006; Pope et al. 2002), while the 3% (95% CI: 2, 3%) estimated increase in risk per  $10\mu\text{g}/\text{m}^3$   $\text{NO}_2$  was lower than the meta-analytic estimate of 6% (95% CI: 4, 8%) based on four (Beelen et al. 2008; Gehring et al. 2006; Filleul et al. 2005; Nafstad et al. 2004) European studies (data reported in Cesaroni et al. 2012b).

As expected, associations with IHD and cardiovascular mortality were stronger than with other causes of death (Crouse et al. 2012; Lepeule et al. 2012; Jerrett et al. 2009). Linear association between the pollutant exposures and cause-specific mortality were reported in some previous

studies (Crouse et al. 2012; Gan et al. 2011). The shapes of the NO<sub>2</sub> curves were similar to estimates reported for a study population in Oslo, Norway (Naess et al. 2007).

Although stronger estimated effects for non-movers may simply reflect improved exposure estimation, evidence of higher risks in men compared to women deserve additional attention. Evidence of gender differences in susceptibility to air pollution is controversial. In the US, an association between exposure to PM<sub>10</sub> and mortality was reported for women in the Nurses' Health Study (Puett et al. 2008) but not men in the Health Professionals Follow-Up Study (Puett et al. 2011). However, Gan and colleagues reported strong evidence of an effect of black carbon on coronary heart disease mortality (after adjusting for NO<sub>2</sub> and PM<sub>2.5</sub>) in men but not women (Gan et al. 2011). We estimated the strongest effects in the youngest age group of our population (<60 years), consistent with a previous study (Naess et al. 2007).

Our study has several strengths. It is the largest European cohort study of the effects of both NO<sub>2</sub> and PM<sub>2.5</sub> and provides the statistical power to detect the effects of different indices of exposure on mortality. Residential history and several individual characteristics were available, and we had estimates of both NO<sub>2</sub> and PM<sub>2.5</sub> at the residences of all participants.

This study has some limitations. The RoLS is a cohort built on administrative data and information on individual risk factors such as smoking habits, diet, alcohol consumption, and obesity were not available. As previously done in the literature, we adjusted the models for pre-existing diabetes, COPD and hypertensive heart disease, conditions which share the lifestyle risk factors cited (Gan et al. 2011); we adjusted also for small-area socioeconomic position, which

could be a predictor of smoking habits independent of personal characteristics (Diex-Roux et al. 2003). The adjustment for pre-existing conditions might have led to an underestimation of the effect, because the comorbidities might act as intermediate variables (Gan et al. 2011). To further investigate the role of smoking, we selected 7,845 adult subjects from the study population for whom information on smoking habits was available from another investigation (SIDRIA, Cesaroni et al. 2008). Once we adjusted for all covariates used in Model-2 in a logistic regression model predicting ever smoking, there was no evidence of an association between exposure to  $\text{NO}_2$  or  $\text{PM}_{2.5}$  and ever smoking (all ORs close to 1.0), indicating that smoking is unrelated to the exposures and thus an unlikely confounder. Moreover, when we added smoking status in a survival analysis (Model-2) restricted only to SIDRIA participants, the association between the air pollution exposures and non-accidental mortality did not change (data not shown).

To analyze frailty and concentration-response curves we had to use a 20% random sample of the population, but these alternate models provided only slightly different estimates of the effects for non-accidental, cardiovascular and ischemic heart disease mortality. Therefore, we expect that frailty analyses of the entire population would be comparable. On the other hand,  $\text{PM}_{2.5}$  effect estimates for lung cancer based the 20% sample were quite different (close to unity) from estimates based on the entire population, and for this reason the relative spline plot should be interpreted cautiously.

To estimate  $\text{NO}_2$  and  $\text{PM}_{2.5}$  exposure we used both a land use regression model based on measurements carried out on 2007 and a dispersion model based on simulation for the year 2005, respectively. Both models were independently validated (see Supplemental Material).  $\text{PM}_{2.5}$  and

NO<sub>2</sub> were highly correlated, but PM<sub>2.5</sub> estimates had a lower resolution than estimates for NO<sub>2</sub>. We are fairly confident that the spatial gradient of pollutants within the city remained stable over time. Rome is a city which changes very slowly, as two NO<sub>2</sub> LUR models developed using measures taken 12 years apart showed very similar results both in terms of estimates of exposure of the population (the correlation was 0.96) and in their associations with natural mortality (Cesaroni et al. 2012a). We took into account the changes of address (and exposure) during the follow-up in the main time-dependent analyses. Conversely, we used time-weighted exposure for the five years before enrolment, without taking account of changes of address, for frailty models and spline curves. We have evaluated that the bias introduced in this way is negligible, because the results on the entire population based on 1996-2001 average exposure were similar to those obtained with time-dependent exposure (data not shown).

## CONCLUSIONS

Long-term exposure to NO<sub>2</sub> and PM<sub>2.5</sub> was associated with increased mortality in this large population-based cohort. We found the strongest associations with IHD, followed by cardiovascular and lung cancer mortality. The estimated effect of NO<sub>2</sub> persisted after adjustment for PM<sub>2.5</sub>, and the shapes of the concentration response for both pollutants showed no evidence of deviation from linearity for all causes except IHD. European policy decisions regarding environment and public health should be made considering the specific scientific research results on the health effects of air pollution, such as those provided here.

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Table 1. Adjusted Hazard Ratios (HRs, 95%CI) of Mortality According to Different Air Pollution Exposure Indices. Rome 2001-2010

Exposure	Non-accidental Causes (N=144,441)			Cardiovascular Disease (N=60,318)			Ischemic Heart Disease (N=22,562)		
	Cases	HR <sup>a</sup>	HR <sup>b</sup> (95% CI)	Cases	HR <sup>a</sup>	HR <sup>b</sup> (95% CI)	Cases	HR <sup>a</sup>	HR <sup>b</sup> (95% CI)
<b>Quintiles of NO<sub>2</sub><sup>c</sup></b>									
Q1	21,496	1.00	1.00	8,400	1.00	1.00	3,181	1.00	1.00
Q2	23,521	1.00 (0.98, 1.02)	1.04 (1.02, 1.06)	9,443	1.00 (0.97, 1.03)	1.04 (1.01, 1.08)	3,651	1.04 (0.99, 1.09)	1.09 (1.04, 1.14)
Q3	30,272	1.00 (0.98, 1.01)	1.05 (1.03, 1.07)	12,647	0.99 (0.96, 1.02)	1.06 (1.03, 1.09)	4,678	1.01 (0.96, 1.04)	1.08 (1.03, 1.13)
Q4	32,820	1.00 (0.98, 1.01)	1.06 (1.04, 1.07)	14,090	0.99 (0.96, 1.01)	1.06 (1.03, 1.09)	5,183	1.02 (0.98, 1.07)	1.10 (1.05, 1.15)
Q5	36,332	1.01 (0.99, 1.03)	1.07 (1.05, 1.09)	15,738	1.00 (0.98, 1.03)	1.07 (1.04, 1.10)	5,869	1.06 (1.01, 1.10)	1.13 (1.08, 1.19)
p-trend		0.184	<0.001		0.994	<0.001		0.041	<0.001
10µg/m <sup>3</sup> NO <sub>2</sub>		1.01 (1.00, 1.01)	1.03 (1.02, 1.03)		1.00 (0.99, 1.01)	1.03 (1.02, 1.04)		1.02 (1.00, 1.03)	1.05 (1.03, 1.06)
IQR NO <sub>2</sub> (10.7µg/m <sup>3</sup> )		1.01 (1.00, 1.01)	1.03 (1.02, 1.04)		1.00 (0.99, 1.01)	1.03 (1.02, 1.04)		1.02 (1.00, 1.04)	1.05 (1.03, 1.07)
<b>Quintiles of PM<sub>2.5</sub><sup>d</sup></b>									
Q1	22,432	1.00	1.00	8,878	1.00	1.00	3,339	1.00	1.00
Q2	25,657	0.98 (0.97, 1.00)	1.03 (1.01, 1.05)	10,238	0.95 (0.93, 0.98)	1.01 (0.98, 1.04)	3,925	0.99 (0.95, 1.04)	1.06 (1.01, 1.11)
Q3	28,109	0.98 (0.96, 1.00)	1.05 (1.03, 1.06)	11,560	0.95 (0.92, 0.98)	1.02 (1.00, 1.05)	4,346	0.99 (0.94, 1.03)	1.08 (1.03, 1.13)
Q4	32,194	1.01 (0.99, 1.03)	1.04 (1.03, 1.06)	13,823	1.01 (0.98, 1.04)	1.05 (1.02, 1.08)	5,085	1.04 (0.99, 1.08)	1.08 (1.03, 1.13)
Q5	36,049	1.00 (0.98, 1.01)	1.05 (1.03, 1.07)	15,819	1.00 (0.98, 1.03)	1.07 (1.04, 1.10)	5,867	1.05 (1.00, 1.09)	1.13 (1.08, 1.18)
p-trend		0.153	<0.001		0.006	<0.001		<0.001	<0.001
10µg/m <sup>3</sup> PM <sub>2.5</sub>		1.01 (1.00, 1.02)	1.04 (1.03, 1.05)		1.03 (1.01, 1.05)	1.06 (1.04, 1.08)		1.06 (1.02, 1.09)	1.10 (1.06, 1.13)
IQR PM <sub>2.5</sub> (5.8µg/m <sup>3</sup> )		1.01 (1.00, 1.01)	1.02 (1.02, 1.03)		1.02 (1.00, 1.03)	1.04 (1.03, 1.05)		1.03 (1.01, 1.05)	1.06 (1.04, 1.07)
<b>Distance to High Traffic Road</b>									
≥250 m	41,274	1.00	1.00	16,668	1.00	1.00	6,316	1.00	1.00
[150-250 m)	30,537	0.98 (0.97, 0.99)	0.99 (0.98, 1.01)	12,824	0.98 (0.95, 1.00)	0.99 (0.97, 1.02)	4,810	0.99 (0.95, 1.03)	1.01 (0.97, 1.05)
[100-150 m)	22,683	0.99 (0.97, 1.01)	1.01 (0.99, 1.02)	9,520	0.98 (0.96, 1.00)	1.00 (0.97, 1.02)	3,491	0.98 (0.94, 1.02)	0.99 (0.95, 1.04)
[50-100 m)	22,078	0.99 (0.97, 1.01)	1.01 (0.99, 1.03)	9,255	0.97 (0.94, 0.99)	0.99 (0.97, 1.02)	3,479	0.99 (0.95, 1.04)	1.02 (0.98, 1.06)
<50 m	27,869	1.00 (0.99, 1.02)	1.02 (1.00, 1.01)	12,051	1.01 (0.98, 1.03)	1.03 (1.01, 1.05)	4,466	1.02 (0.98, 1.06)	1.05 (1.01, 1.09)
p-trend		0.688	0.004		0.953	0.043		0.385	0.034
<b>Quintiles of traffic intensity within 150m<sup>e</sup></b>									
Q1	23,038	1.00	1.00	9,149	1.00	1.00	3,551	1.00	1.00
Q2	27,857	1.00 (0.98, 1.02)	1.02 (1.00, 1.04)	11,461	0.99 (0.96, 1.02)	1.02 (0.99, 1.04)	4,275	0.97 (0.93, 1.02)	1.00 (0.95, 1.04)
Q3	29,034	1.01 (0.99, 1.02)	1.03 (1.01, 1.05)	12,076	1.00 (0.97, 1.02)	1.03 (1.00, 1.05)	4,469	0.98 (0.94, 1.03)	1.01 (0.97, 1.04)
Q4	31,447	1.00 (0.98, 1.02)	1.03 (1.01, 1.05)	13,400	0.99 (0.97, 1.02)	1.03 (1.00, 1.06)	5,029	1.00 (0.96, 1.05)	1.04 (1.00, 1.09)
Q5	33,065	1.01 (0.99, 1.02)	1.04 (1.03, 1.06)	14,232	1.01 (0.98, 1.03)	1.05 (1.02, 1.07)	5,238	1.00 (0.96, 1.05)	1.04 (1.00, 1.09)
p-trend		0.218	<0.001		0.570	0.001		0.421	0.009

<sup>a</sup>HR Hazard Ratios adjusted for sex<sup>b</sup>HR Hazard Ratios adjusted for sex, marital status, place of birth, education, occupation, and area-based socioeconomic position<sup>c</sup>Quintiles of NO<sub>2</sub>: Q1 ≤36.5, Q2 36.5-42.7, Q3 42.7-46.2, Q4 46.2-50.4, Q5 >50.4 µg/m<sup>3</sup><sup>d</sup>Quintiles of PM<sub>2.5</sub>: Q1 ≤19.4, Q2 19.4-22.5, Q3 22.5-24.8, Q4 24.8-26.8, Q5 >26.8 µg/m<sup>3</sup><sup>e</sup>Quintiles of traffic intensity (x10<sup>6</sup>): Q1: <0.25, Q2: 0.25-1.63, Q3: 1.63-3.23, Q4: 3.23-6.66, Q5: ≥ 6.66

**Table 2. Adjusted Hazard Ratios (HRs, 95%CI) of Mortality According to Different Air Pollution Exposure Indices. Rome 2001-2010**

Exposure	Cerebrovascular Disease (N=13,576)			Respiratory Disease (N=8,825)			Lung Cancer (N=12,208)		
	Cases	HR <sup>a</sup>	HR <sup>b</sup> (95% CI)	Cases	HR <sup>a</sup>	HR <sup>b</sup> (95% CI)	Cases	HR <sup>a</sup>	HR <sup>b</sup> (95% CI)
<b>Quintiles of NO<sub>2</sub><sup>c</sup></b>									
Q1	1,935	1.00	1.00	1,242	1.00	1.00	2,008	1.00	1.00
Q2	2,141	0.97 (0.91, 1.03)	1.02 (0.96, 1.09)	1,412	1.01 (0.94, 1.09)	1.07 (0.99, 1.15)	2,187	1.04 (0.98, 1.11)	1.07 (1.01, 1.14)
Q3	2,830	0.94 (0.89, 1.00)	1.01 (0.96, 1.08)	1,798	0.95 (0.88, 1.02)	1.02 (0.95, 1.10)	2,568	1.05 (0.99, 1.11)	1.09 (1.03, 1.16)
Q4	3,151	0.94 (0.88, 0.99)	1.01 (0.96, 1.08)	2,043	0.97 (0.90, 1.04)	1.05 (0.97, 1.13)	2,610	1.05 (0.99, 1.11)	1.09 (1.03, 1.16)
Q5	3,519	0.95 (0.90, 1.00)	1.03 (0.97, 1.09)	2,330	1.01 (0.94, 1.08)	1.08 (1.00, 1.16)	2,835	1.07 (1.01, 1.13)	1.11 (1.05, 1.18)
p-trend		0.040	0.459		0.967	0.097		0.054	0.002
10µg/m <sup>3</sup> NO <sub>2</sub>		0.98 (0.96, 1.00)	1.01 (0.99, 1.03)		1.00 (0.98, 1.03)	1.03 (1.00, 1.06)		1.03 (1.00, 1.05)	1.04 (1.02, 1.07)
IQR NO <sub>2</sub> (10.7µg/m <sup>3</sup> )		0.98 (0.95, 1.00)	1.01 (0.99, 1.03)		1.01 (0.98, 1.03)	1.03 (1.00, 1.06)		1.03 (1.01, 1.06)	1.05 (1.02, 1.08)
<b>Quintiles of PM<sub>2.5</sub><sup>d</sup></b>									
Q1	2,018	1.00	1.00	1,319	1.00	1.00	2,090	1.00	1.00
Q2	2,228	0.91 (0.85, 0.96)	0.97 (0.91, 1.03)	1,542	0.96 (0.90, 1.04)	1.03 (0.96, 1.11)	2,268	1.01 (0.95, 1.07)	1.04 (0.98, 1.10)
Q3	2,577	0.92 (0.86, 0.97)	1.00 (0.94, 1.06)	1,744	0.96 (0.90, 1.03)	1.05 (0.98, 1.13)	2,397	1.03 (0.97, 1.10)	1.09 (1.02, 1.15)
Q4	3,114	0.98 (0.93, 1.04)	1.03 (0.97, 1.09)	1,953	0.96 (0.89, 1.03)	1.00 (0.93, 1.07)	2,611	1.05 (0.99, 1.11)	1.07 (1.01, 1.13)
Q5	3,639	0.99 (0.94, 1.05)	1.08 (1.02, 1.14)	2,267	0.97 (0.91, 1.04)	1.05 (0.97, 1.12)	2,842	1.03 (0.98, 1.10)	1.08 (1.02, 1.15)
p-trend		0.076	<0.001		0.507	0.536		0.105	0.006
10µg/m <sup>3</sup> PM <sub>2.5</sub>		1.03 (0.99, 1.08)	1.08 (1.04, 1.13)		0.99 (0.94, 1.04)	1.03 (0.97, 1.08)		1.02 (0.98, 1.07)	1.05 (1.01, 1.10)
IQR PM <sub>2.5</sub> (5.8µg/m <sup>3</sup> )		1.02 (0.99, 1.04)	1.05 (1.02, 1.07)		0.99 (0.96, 1.02)	1.01 (0.99, 1.05)		1.01 (0.99, 1.04)	1.03 (1.01, 1.06)
<b>Distance to High Traffic Road</b>									
>=250 m	3,721	1.00	1.00	2,458	1.00	1.00	3,782	1.00	1.00
[150-250 m)	2,908	0.98 (0.94, 1.03)	1.00 (0.96, 1.05)	1,848	0.95 (0.89, 1.01)	0.97 (0.91, 1.03)	2,552	0.98 (0.93, 1.03)	0.98 (0.93, 1.03)
[100-150 m)	2,131	0.97 (0.92, 1.02)	1.00 (0.94, 1.05)	1,356	0.95 (0.88, 1.01)	0.96 (0.90, 1.03)	1,894	1.00 (0.95, 1.06)	1.01 (0.96, 1.07)
[50-100 m)	2,111	0.98 (0.93, 1.03)	1.01 (0.95, 1.06)	1,413	1.00 (0.94, 1.07)	1.02 (0.96, 1.09)	1,790	0.99 (0.94, 1.05)	1.01 (0.95, 1.07)
<50 m	2,705	1.00 (0.95, 1.05)	1.03 (0.98, 1.08)	1,750	0.99 (0.93, 1.05)	1.01 (0.95, 1.08)	2,190	0.98 (0.93, 1.03)	0.99 (0.94, 1.05)
p-trend		0.848	0.305		0.863	0.390		0.670	0.907
<b>Quintiles of traffic intensity within 150m</b>									
Q1	2,067	1.00	1.00	1,320	1.00	1.00	2,179	1.00	1.00
Q2	2,632	1.00 (0.94, 1.05)	1.02 (0.97, 1.09)	1,673	1.00 (0.93, 1.07)	1.02 (0.95, 1.10)	2,437	1.01 (0.95, 1.07)	1.02 (0.96, 1.08)
Q3	2,686	0.97 (0.91, 1.02)	1.00 (0.95, 1.06)	1,796	1.03 (0.95, 1.10)	1.06 (0.99, 1.14)	2,433	1.00 (0.94, 1.06)	1.02 (0.96, 1.08)
Q4	3,015	0.97 (0.92, 1.03)	1.02 (0.96, 1.08)	1,917	0.98 (0.92, 1.05)	1.02 (0.95, 1.10)	2,567	1.01 (0.95, 1.07)	1.04 (0.98, 1.10)
Q5	3,176	0.97 (0.92, 1.03)	1.02 (0.97, 1.08)	2,119	1.04 (0.97, 1.11)	1.08 (1.00, 1.15)	2,592	1.00 (0.95, 1.06)	1.03 (0.97, 1.09)
p-trend		0.231	0.584		0.439	0.065		0.865	0.300

<sup>a</sup>HR Hazard Ratios adjusted for sex

<sup>b</sup>HR Hazard Ratios adjusted for sex, marital status, place of birth, education, occupation, and area-based socioeconomic position

<sup>c</sup>Quintiles of NO<sub>2</sub>: Q1 ≤36.5, Q2 36.5-42.7, Q3 42.7-46.2, Q4 46.2-50.4, Q5 >50.4 µg/m<sup>3</sup>

<sup>d</sup>Quintiles of PM<sub>2.5</sub>: Q1 ≤19.4, Q2 19.4-22.5, Q3 22.5-24.8, Q4 24.8-26.8, Q5 >26.8 µg/m<sup>3</sup>

<sup>e</sup>Quintiles of traffic intensity (x10<sup>6</sup>): Q1: <0.25, Q2: 0.25-1.63, Q3: 1.63-3.23, Q4: 3.23-6.66, Q5: ≥ 6.66

## Figure Legends

Figure 1. Maps of the concentrations of fine particulate matter (PM<sub>2.5</sub>) and nitrogen dioxide (NO<sub>2</sub>) in Rome.

Figure 2. Nitrogen dioxide (NO<sub>2</sub>) and fine particles (PM<sub>2.5</sub>) concentration-response curves (solid lines) and 95% CIs (dashed lines) for non-accidental causes, cardiovascular diseases, ischemic heart diseases, and lung cancer. Cox models adjusted for sex, marital status, place of birth, education, occupation, and area-based socioeconomic position on a 20% sample of the cohort.

Figure 3. Adjusted HRs, 95% CIs, and p-values for interaction for cause-specific mortality per 10µg/m<sup>3</sup> elevation in NO<sub>2</sub> and PM<sub>2.5</sub> concentrations, by population characteristics and cause of death.

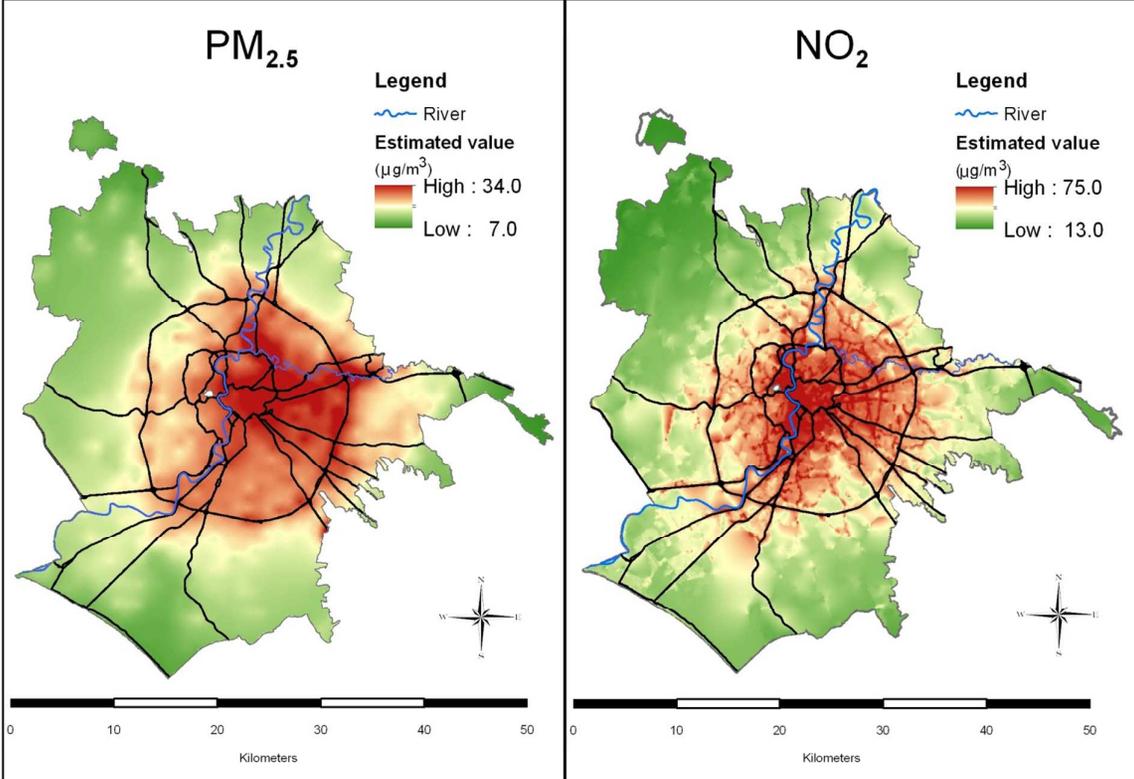


Figure 1. Maps of the concentrations of fine particulate matter (PM<sub>2.5</sub>) and nitrogen dioxide (NO<sub>2</sub>) in Rome.

NO<sub>2</sub> map (adapted from Cesaroni et al. 2012) was obtained using natural neighbor interpolation method of all the estimated values at study population's residential addresses.

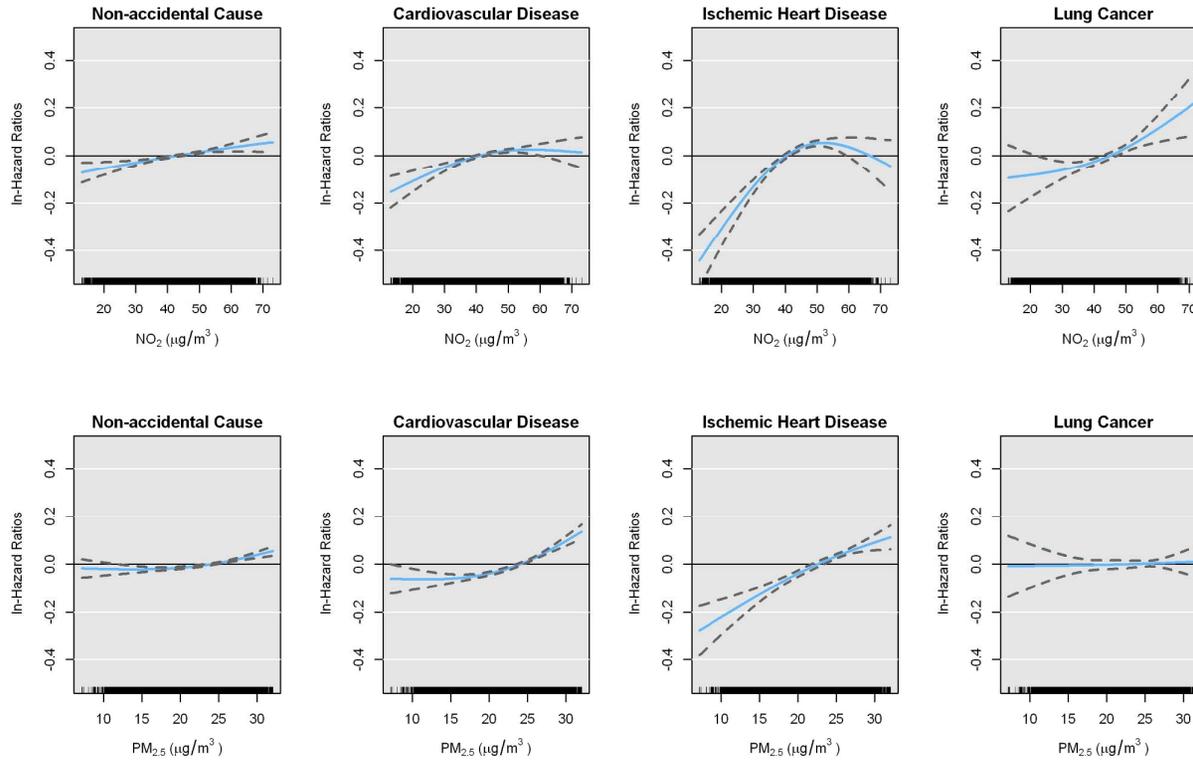
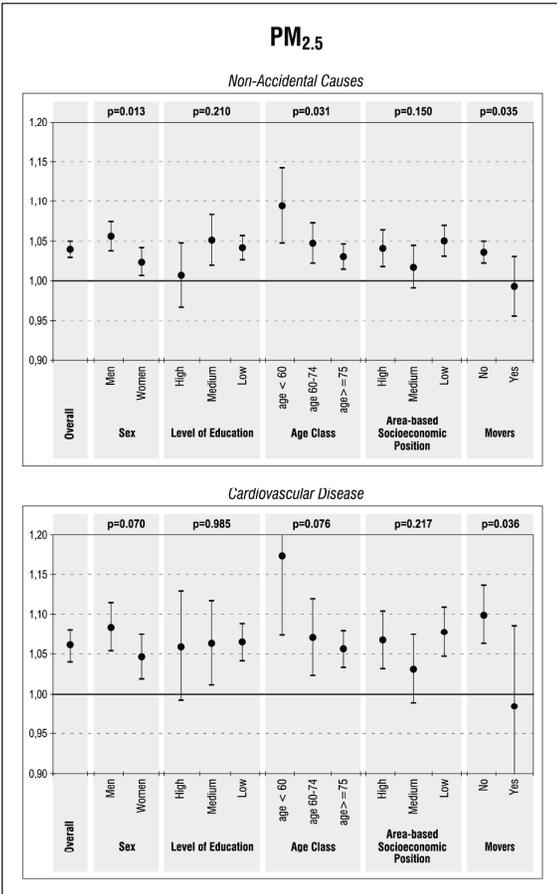
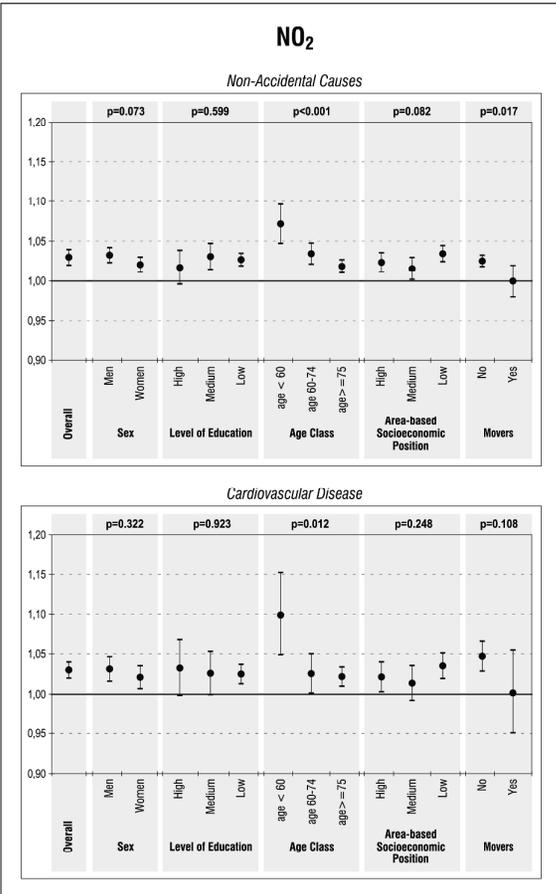


Figure 2. Nitrogen dioxide (NO<sub>2</sub>) and fine particles (PM<sub>2.5</sub>) concentration-response curves (solid lines) and 95% CIs (dashed lines) for non-accidental causes, cardiovascular diseases, ischemic heart diseases, and lung cancer. Natural splines with two degrees of freedom. Cox models adjusted for sex, marital status, place of birth, education, occupation, and area-based socioeconomic position on a 20% sample of the cohort.



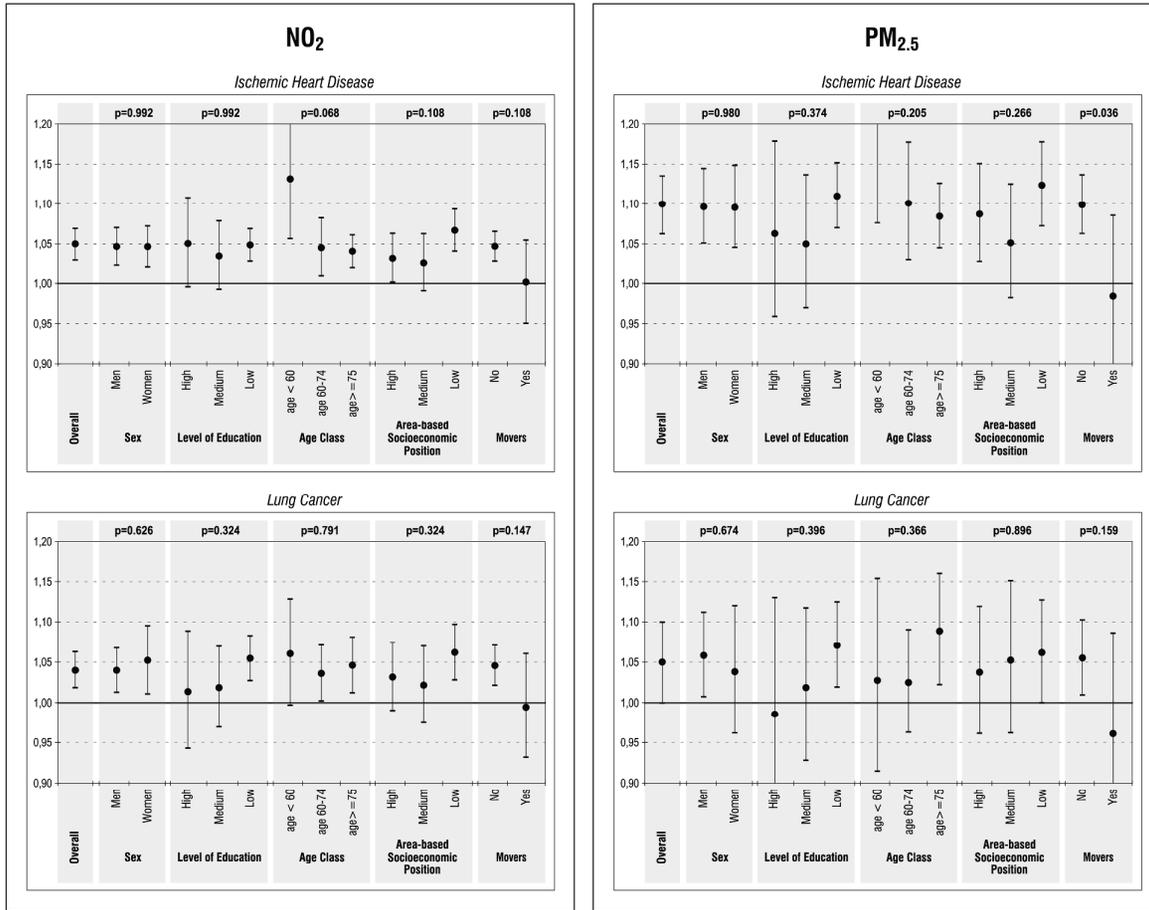


Figure 3. Adjusted HRs, 95% CIs, and p-values for interaction for cause-specific mortality per 10µg/m<sup>3</sup> elevation in NO<sub>2</sub> and PM<sub>2.5</sub> concentrations, by population characteristics and cause of death.