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Long-Term Mortality Effects Associated with Exposure to Particles and NO_x in the Malmö Diet and Cancer Cohort

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Abstract: In this study, long-term mortality effects associated with exposure to PM_{10}, $PM_{2.5}$, BC (black carbon), and NO_x were analyzed in a cohort in southern Sweden during the period from 1991–2016. Participants (those residing in Malmö, Sweden, born between 1923–1950) were randomly recruited from 1991–1996. At enrollment, 30,438 participants underwent a health screening, which consisted of questionnaires about lifestyle and diet, a clinical examination, and blood sampling. Mortality data were retrieved from the Swedish national cause of death register. The modeled concentrations of PM_{10} (particles with an aerodynamic diameter smaller than or equal to 10 μm), $PM_{2.5}$ (particles with an aerodynamic diameter smaller than or equal to 2.5 μm), BC (black carbon), and NO_x (nitrogen oxides) at the cohort participants' home addresses were used to assess air pollution exposure. Cox proportional hazard models were used to estimate the associations between long-term exposure to PM_{10}, $PM_{2.5}$, BC, and NO_x and the time until death among the participants during the period from 1991–2016. The hazard ratios (HRs) associated with an interquartile range (IQR) increase in each air pollutant were calculated based on the exposure lag windows of the same year (lag0), 1–5 years (lag1–5), and 6–10 years (lag6–10). Three models were used with varying adjustments for possible confounders including both single-pollutant estimates and two-pollutant estimates. With adjustments for all covariates, the HRs for PM_{10}, $PM_{2.5}$, BC, and NO_x in the single-pollutant models at lag1–5 were 1.06 (95% CI: 1.02–1.11), 1.01 (95% CI: 0.95–1.08), 1.07 (95% CI: 1.04–1.11), and 1.11 (95% CI: 1.07–1.16) per IQR increase, respectively. The HRs were in most cases decreased by the inclusion of a larger number of covariates in the models. The most robust associations were shown for NO_x, with statistically significant positive HRs in all models. An overall conclusion is that road traffic-related pollutants had a significant association with mortality in the cohort.

Keywords: air pollution; long-term exposure; particles; nitrogen oxides; Cox regression; proportional hazard; hazard ratio

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1. Introduction

Exposure to air pollution has, in a wide range of studies, been shown to have detrimental long-term health effects. According to the World Health Organization, ambient (outdoor) air pollution is estimated to have caused around 4.2 million premature deaths worldwide in 2019 [1]. The long-term mortality effects associated with exposure to $PM_{2.5}$ and PM_{10} have been analyzed in several previous studies. In a meta-analysis, reporting pooled estimates of the results from different studies around the world, natural-cause mortality was associated with long-term exposure to both $PM_{2.5}$ and PM_{10} [2]. Increases in all-cause mortality associated with exposure to $PM_{2.5}$ were found in other meta-analyzes including studies from a wide range of geographic areas [3,4]. In Europe, associations between mortality and long-term exposure to $PM_{2.5}$ were found in two multi-cohort studies [5,6]. Furthermore, in a systematic review based on cohort studies conducted in Australia, Mainland China, Hong Kong, Taiwan, and South Korea, an association between long-term exposure to $PM_{2.5}$ and mortality was found [7]. Considering Sweden specifically, a multi-cohort study demonstrated a statistically significant increase in natural mortality associated with long-term exposure to PM_{10}, and for $PM_{2.5}$, the effect was positive, but not statistically significant [8].

The long-term effects on mortality associated with exposure to black carbon (BC), colloquially called soot particles, have been analyzed in a few studies. BC refers to the carbonaceous fraction of particles originating from incomplete combustion, and they are usually measured by light absorption. In a large population-based French cohort, with data collected from 1989–2017, long-term exposure to BC was associated with all-cause mortality [9]. Long-term exposure to black smoke (BS), a previously common technique to measure soot particles, has been used in older cohort studies. One such cohort study, spanning seven cities in France, found an association between non-accidental mortality and exposure to BS (assessed in the 1970s) over a 25 year study period [10]. Similarly, a Dutch cohort study on long-term exposure to traffic-related air pollutants, analyzed from 1987–1996, demonstrated an association between natural mortality and exposure to BS [11].

In addition to particulate air pollution, the mortality effects associated with long-term exposure to gaseous pollutants, including nitrogen oxides (NO_x), the sum of nitrogen monoxide (NO) and nitrogen dioxide (NO_2), and NO_2 itself, have been investigated in previous studies. For instance, associations between mortality and long-term exposure to NO_2 have been shown in several meta-analyzes based on pooled estimates from many original studies [3,12–15]. The mortality effects associated with long-term exposure to NO_x were analyzed in a cohort in Gothenburg, Sweden, during the period from 1973–2007, and associations were found for three different time lag windows [16].

The long-term health effects associated with exposure to air pollutants have been explored in previous studies in a cohort in Malmö, Southern Sweden, called "The Malmö Cancer and Diet Cohort (MDC)". In this cohort, air pollution concentrations were assessed at the participants' home addresses. The associations between cardiovascular diseases and exposure to NO_x and particles were analyzed in the MDC cohort during the period from 1991–2016. Several statistically significant hazard ratios between exposure to NO_x or particles and cardiovascular outcomes were found [17]. The long-term associations between a number of biomarkers and exposure to NO_x and particles were also analyzed in the MDC cohort, where several statistically significant associations were found [18]. Statistically significant associations between long-term exposure to NO_x and particles and chronic kidney disease have also been shown in the MDC cohort [19].

In the present study, the aim was to analyze the associations between long-term exposure to PM_{10}, $PM_{2.5}$, BC, and NO_x and mortality in the MDC cohort.

2. Materials and Methods

2.1. Description of the Study Population and the Study period

This study is based on "The Malmö Diet and Cancer Cohort", abbreviated MDC, which included those residing in Malmö, Sweden, born during the period from 1923–1950. Initially, the main purpose of this cohort was to clarify whether a Western diet is associated with specific types of cancer while

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controlling for other relevant lifestyle factors [20]. The MDC cohort has been described in more detail in a number of previous studies [20–23].

At enrollment, during the period from 1991–1996, the participants underwent health screening in terms of questionnaires about lifestyle and diet, clinical examination, and blood sampling where a total number of 30,438 participants were selected. The cohort participants were followed from enrollment until death, or until the end of year 2016 for those who survived the entire study period. Among the total number of 30,438 participants, 17,551 (57.5%) survived the entire study period, 12,663 (41.6%) were deceased during the study period, and 264 (0.9%) moved out of the study area. The cohort participants who survived the entire study period and those who moved out of the study area were censored.

2.2. Air Pollution Exposure Assessment

The modeled concentrations of PM_{10}, $PM_{2.5}$, BC, and NO_x at the cohort participants' home addresses were used to calculate exposure. The air pollution concentrations in Malmö (18 km x 18 km) were modeled by the Environmental Department of the City using EnviMan software package (Opsis AB, Sweden) (Figure 1). Each pollutant was modeled as the sum of local emissions from traffic exhaust, non-exhaust traffic emissions (mechanically generated particles from road wear, tire wear, and brake wear, including resuspension), heating, shipping, industry, households, and long-distance transported emissions. The modeled concentrations were presented as grids with a spatial resolution of 50 x 50 m. The participants` addresses during the period from 1991–2016 were retrieved and geocoded by Statistics Sweden. The mean concentrations of PM_{10}, $PM_{2.5}$, BC, and NO_x for each year during the period from 1991–2016 were assigned to each participant´s home address. In order to capture the lag effects associated with exposure and mortality, the modeled concentrations were based on the exposure lag windows of the same year (lag0), 1–5 years (lag1–5), and 6–10 years (lag6–10) (Table 1).

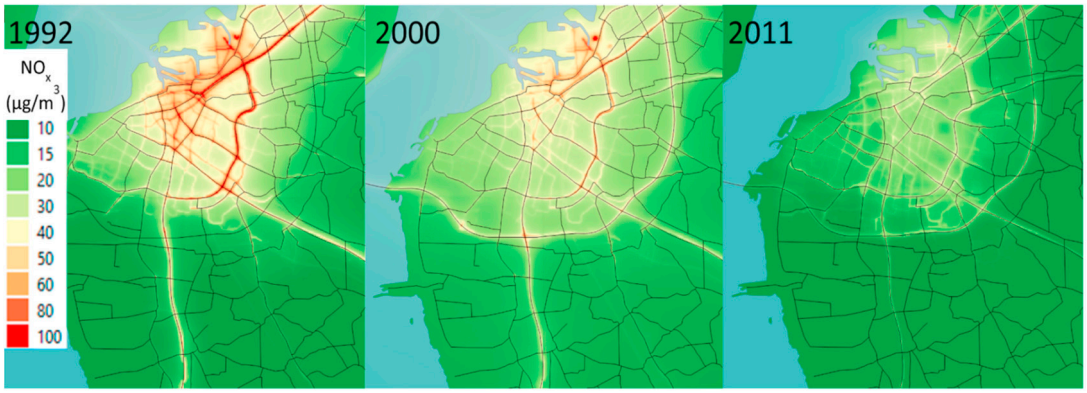

Figure 1. The modeled concentrations (µg m^{-3}) of NO_x in the study area in Malmö during 1992, 2000, and 2011. Source: Carlsen et al. (2022) [17]. .

Table 1. The modeled concentrations (µg m^{-3}) of air pollutants in the study area during the period from 1991–2018.

Air pollutant	Number of obs.	Mean	SD	Median	25 percentile	75 percentile	Min.	Max.
PM_{10} lag0	552,608	15.9	2.2	15.7	14.5	17.2	9.7	27.6
$PM_{2.5}$ lag0	552,608	10.9	1.8	10.8	9.8	11.4	6.6	18.4
BC lag0	552,608	1.0	0.1	1.0	0.9	1.1	0.7	1.9
NO_x lag0	552,608	26.5	8.8	24.9	20.8	30.5	6.8	130.0
Air pollutant	**Number of obs.**	**Mean**	**SD**	**Median**	**25 percentile**	**75 percentile**	**Min.**	**Max.**
PM_{10} lag1–5	534,059	15.8	1.5	15.9	14.8	16.9	11.2	25.8
$PM_{2.5}$ lag1–5	534,059	10.9	0.9	10.8	10.1	11.8	8.8	14.9

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BC lag1–5	534,059	0.9	0.1	1.0	0.9	1.0	0.7	1.7
NO_x lag1–5	534,059	28.3	10.0	26.3	21.7	33.0	7.8	134.0
Air pollutant	**Number of obs.**	**Mean**	**SD**	**Median**	**25 percentile**	**75 percentile**	**Min.**	**Max.**
PM_{10} lag6–10	417,278	15.6	1.6	15.6	14.5	16.8	11.2	24.6
$PM_{2.5}$ lag6–10	417,278	10.7	0.9	10.6	10.0	11.5	8.8	13.8
BC lag6–10	417,278	0.9	0.1	0.9	0.9	1.0	0.7	1.7
NO_x lag6–10	417,278	30.1	10.6	28.1	22.7	35.4	8.6	134.0

2.3. Outcome Assessment

Natural cause mortality (mortality due to causes other than injuries and trauma) was used as an outcome variable, and data were retrieved from the National Cause of Death Register. Natural cause mortality was defined on the basis of the underlying cause of death according to the International Classification of Diseases, Tenth Revision (ICD-10: A00–R99).

2.4. Covariates

All covariates were collected at enrollment. Adjustments for potential confounders were made with age and gender as two basic covariates. Education level (low < 9 years, medium = 9–12 years, and high > 12 years) and cohabitation (yes or no) were included as adjustments for socio-economic factors. Smoking habits were included as never, former, or current smoker (occasional and regular). Systolic and diastolic blood pressure as well as the use of antihypertensive medications (yes or no) were included as covariates. Alcohol consumption was included as the self-reported quantity in terms of grams per day. Physical activity was categorized into low, medium, or high. Waist/hip ratio was also included as a covariate. Tables 2 and 3 present the different covariates included in the models. Table 2 presents the continuous variables included in the models, and Table 3 presents the categorical variables included in the models.

Table 2. The continuous covariates included in the calculations.

Covariate	Number of obs.	Mean	SD	Min.	Max.
Age at enrollment	30,438	58.0	7.6	44.5	73.6
Systolic blood pressure	30,389	141.1	20.1	61	240
Diastolic blood pressure	30,386	85.6	10.0	40	150
Waist/Hip ratio	30,362	0.85	0.1	0.4	1.9
Alcohol consumption (g day^{-1})	28,228	10.7	12.7	0	194

Table 3. The categorical covariates included in the calculations.

Covariate	Number of obs.	Category 1	Category 2	Category 3
Gender	30,438	Male (39.8%)	Female (60.2%)	–
Smoking status	28,557	Never smoker (37.9%)	Former smoker (33.8%)	Current smoker (28.3%)
Educational level	28,492	Elementary school (42.0%)	High school (35.0%)	College (23.0%)
Cohabitation	28,554	Yes (75.4%)	No (24.6%)	–
Physical activity	30,164	Low (33.1%)	Medium (33.3%)	High (33.5%)

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Antihypertensive drugs	28,446	Yes (17.8%)	No (82.2%)	–

2.5. Statistical Analysis

Cox proportional hazard models with time-varying air pollution exposure adjusting for possible confounders (covariates) were used to calculate the associations between long-term exposure to PM_{10}, $PM_{2.5}$, BC, and NO_x and time until death among the MDC cohort participants. The time since the start of the study for each study participant was used on the time axis.

Three statistical models with varying levels of adjustment were used. Model 1 represented a crude model with air pollutants adjusted only for age at enrollment and gender. Model 2 additionally adjusted for smoking habits, educational level, and cohabitation. In addition to the covariates included in Model 1 and Model 2, Model 3 also adjusted for systolic and diastolic blood pressure, self-reported alcohol consumption, physical activity, waist/hip ratio, and the use of antihypertensive medications.

Two-pollutant models were included in cases where the pairwise air pollutants were not so highly correlated (i.e., with a correlation coefficient smaller than 0.8) that multicollinearity could occur. Multicollinearity was tested by creating a multiple regression based on all variables in each model, and the variance inflation factor (VIF) was then calculated. A VIF value below three was accepted for the inclusion in two-pollutant models. The VIF values of the air pollutants were in some cases above the value of three. Regarding the other covariates, the VIF values were below three in all cases and were, therefore, not considered to pose a multicollinearity problem. Table A8 in Appendix A presents correlation coefficients (Pearson) between the different air pollutants based on the exposure lag windows of the same year (lag0), 1–5 years (lag1–5), and 6–10 years (lag6–10).

All analyzes were performed using STATA 17.0 (StataCorp, Texas, TX, USA).

3. Results

3.1. Hazard Ratios Associated with Exposure

Figures 2–7 present hazard ratios (HRs) with 95% confidence intervals (CIs) for natural-cause mortality associated with exposure to PM_{10}, $PM_{2.5}$, BC, and NO_x for lag0, lag1–5, and lag6–10 in single- and two-pollutant models with adjustments for all covariates (Model 3). The HRs correspond to an interquartile range (IQR) increase in each air pollutant. The complete results from the Cox regressions based on all models (Models 1–3) and all lag windows in both single- and multi-pollutant models are presented in Tables A1–A3.

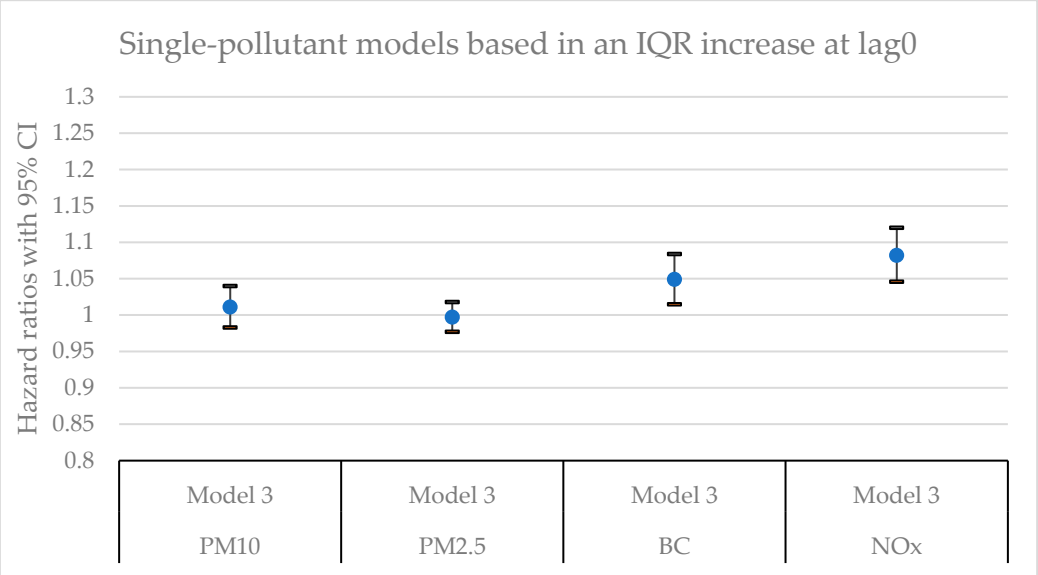

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Figure 2. Hazard ratios with 95% confidence intervals (CI) for the associations between natural-cause mortality and exposure to PM_{10}, $PM_{2.5}$, BC, and NO_x based on lag0 in single-pollutant models with adjustments for all covariates (Model 3).

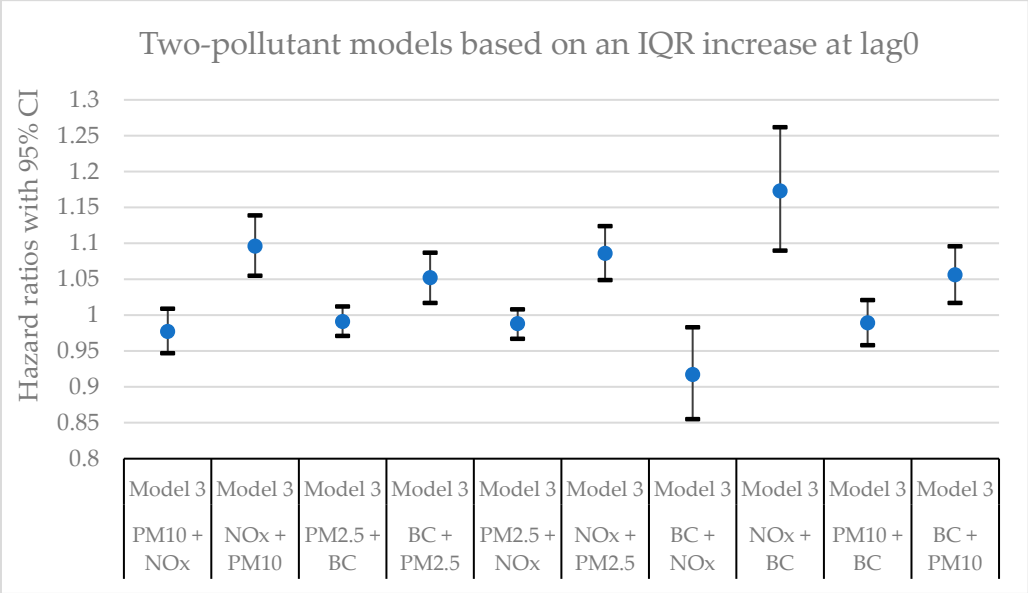

Figure 3. Hazard ratios with 95% confidence intervals (CI) for the associations between natural-cause mortality and exposure to PM_{10}, $PM_{2.5}$, BC, and NO_x based on lag0 in two-pollutant models with adjustments for all covariates (Model 3). The hazard ratios refer to the pollutant listed first.

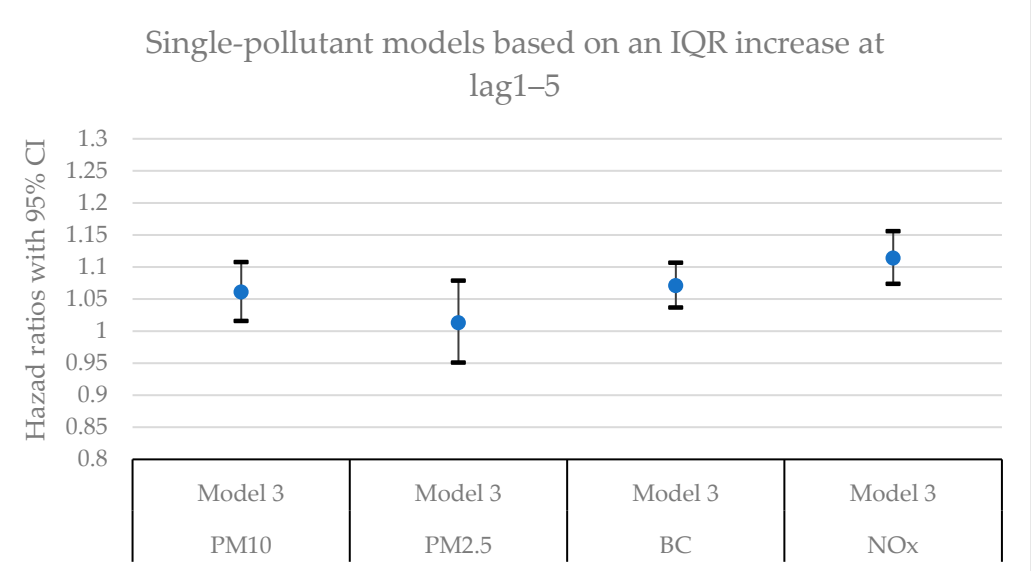

Figure 4. Hazard ratios with 95% confidence intervals (CI) for the associations between natural-cause mortality and exposure to PM_{10}, $PM_{2.5}$, BC, and NO_x based on lag1–5 in single-pollutant models with adjustments for all covariates (Model 3).

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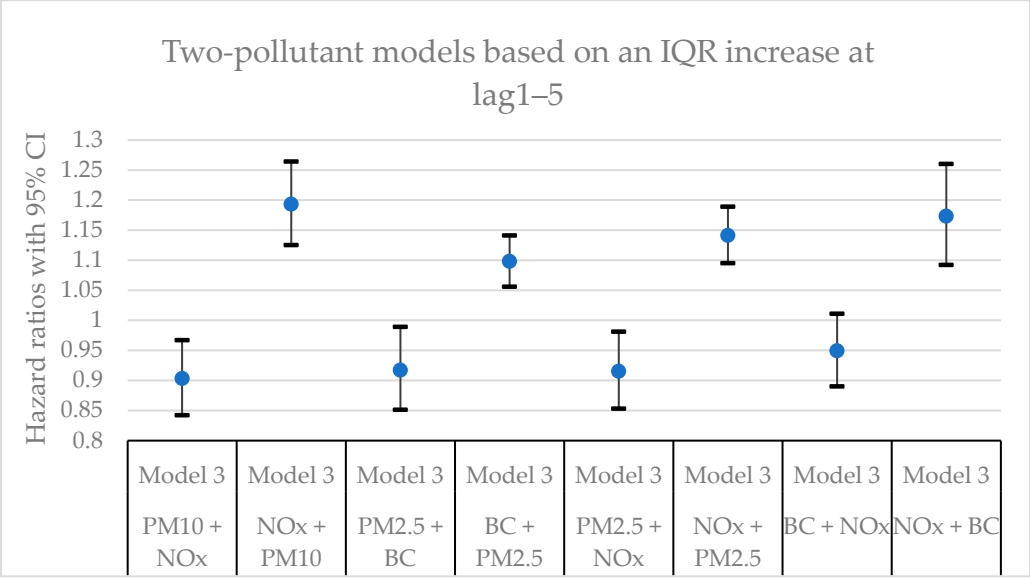

Figure 5. Hazard ratios with 95% confidence intervals (CI) for the associations between natural-cause mortality and exposure to PM_{10}, $PM_{2.5}$, BC, and NO_x based on lag1–5 in two-pollutant models with adjustments for all covariates (Model 3). The hazard ratios refer to the pollutant listed first.

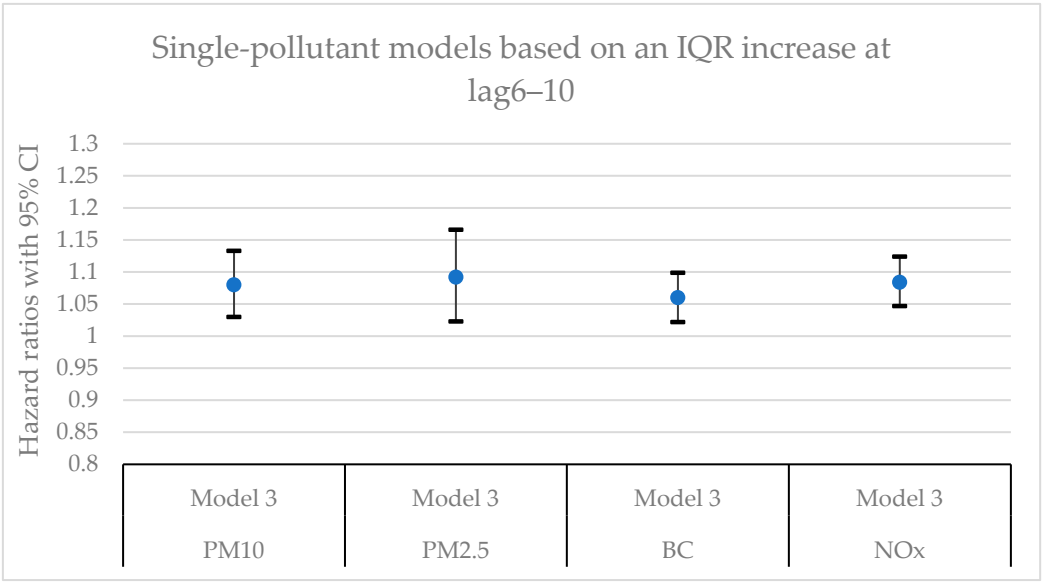

Figure 6. Hazard ratios with 95% confidence intervals (CI) for the associations between natural-cause mortality and exposure to PM_{10}, $PM_{2.5}$, BC, and NO_x based on lag6–10 in single-pollutant models with adjustments for all covariates (Model 3).

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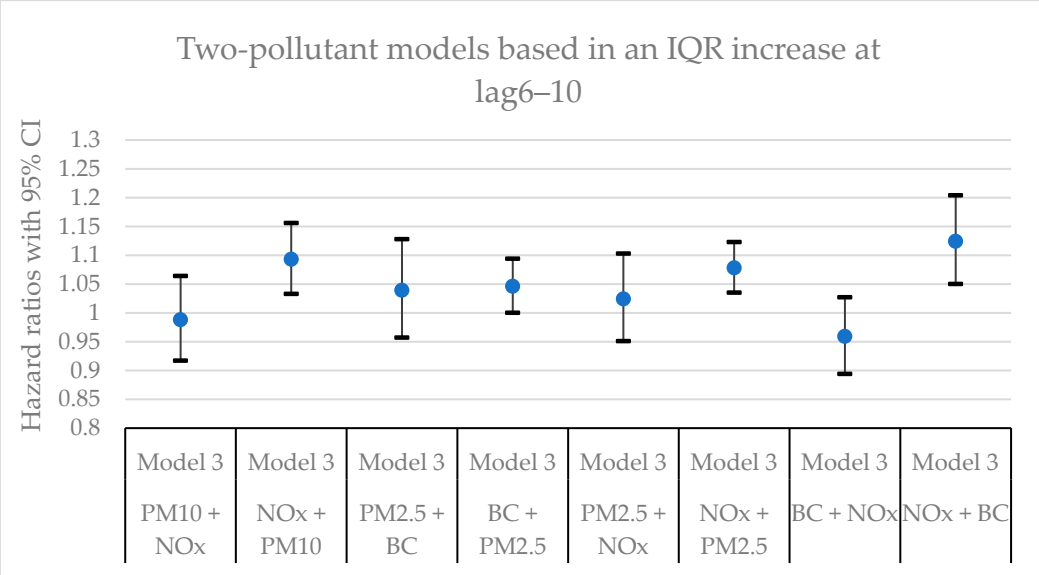

Figure 7. Hazard ratios with 95% confidence intervals (CI) for the associations between natural-cause mortality and exposure to PM_{10}, $PM_{2.5}$, BC, and NO_x based on lag6–10 in two-pollutant models with adjustments for all covariates (Model 3). The hazard ratios refer to the pollutant listed first.

3.2. Sensitivity analysis

In order to determine if there were any differences in the calculated HRs with respect to age, an age stratified analysis was performed. Six different age groups at enrollment were generated: Group 1 ≤ 50 years; 50 years < Group 2 ≤ 55 years; 55 years < Group 3 ≤ 60 years; 60 years < Group 4 ≤ 65 years; 65 years < Group 5 ≤ 70 years; and Group 6 > 70 years. The Cox regression model with adjustments for all covariates (Model 3) was applied for each age group based on lag1–5 in both single- and two-pollutant models (see Tables A4 and A5 in Appendix A). The HRs were in general largest and most robust in age groups 4 and 5.

The regression models were also divided into two different periods in terms of survival time; one period for those who passed away within ten years from when the study started, and one period for those who survived more than ten years. The Cox regression model with adjustments for all covariates (Model 3) was applied for each survival time period based on lag1–5 in both single- and two-pollutant models (see Tables A6 and A7 in Appendix A). Similar to the main models (Tables A1–A3), the HRs for PM_{10}, $PM_{2.5}$, and BC did not remain statistically significant in the two-pollutant models together with NO_x. The HRs for NO_x were more stable and robust for those who survived more than ten years.

4. Discussion

4.1. Key Results

In this cohort study from southern Sweden with > 30,000 participants from the general population and up to 25 years of follow-up, clear associations were observed between mortality and long-term residential exposure to NO_x. NO_x was the only air pollutant that exhibited statistically significant associations in all models and for all lags in the main models. The associations for the other air pollutants (PM_{10}, $PM_{2.5}$, and BC) did not remain statistically significant in the two-pollutant models with NO_x. Adjustments for lifestyle factors and other possible confounding factors had some impact on the size of the effect estimates, but, in general, the associations remained.

4.2. The Calculated Hazard Ratios and Possible Explanations

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Among the analyzed air pollutants, the HRs associated with NO_x were the most clear and robust. NO_x is an indicator of traffic emissions, and traffic is typically the major source of NO_x in urban areas [24]. The HRs associated with PM_{10}, $PM_{2.5}$, and BC were in most cases statistically significant in the single-pollutant models. However, in the two-pollutant models with NO_x, no statistically significant positive were shown neither for PM_{10}, $PM_{2.5}$, or BC. Both NO_x and BC originate from combustion processes. However, the correlation coefficients between NO_x and BC, presented in Table A8, were in the range of 0.4 and 0.5, indicating that they largely originate from different sources. Besides traffic, there are several sources that generate combustion-related emissions. BC can also originate from heating, shipping, industry, households, and long-distance transported emissions, and may therefore be modestly correlated with NO_x which mainly originates from traffic. The HRs associated with BC were also statistically significant in all single-pollutant models and all two-pollutant models except for those including NO_x.

In the age stratified analyzes presented in Tables A4 and A5, no consistent patterns were shown. However, a certain pattern in terms of clearer and more robust HRs for group 4 and 5 were shown in several analyzes. Group 4 and 5 represent those in the age groups 60–65 years and 65–70 years at enrollment, respectively. The HRs in the younger age groups and those in the oldest group (> 70 years) were somewhat less clear and robust. Smaller effects in the younger age groups can be expected. Smaller effects in the oldest age group are somewhat unexpected. However, the oldest age group (> 70 years at enrollment) were in some cases older than 90 years old at the end of the cohort time period, and it is possible that air pollution exposure could have a relatively smaller impact on survival time when other age-related causes of death become more apparent.

Considering the different lags, the HRs for particles (PM_{10}, $PM_{2.5}$, and BC) in the single-pollutant models were in general more robust and stable at lag1–5 and lag6–10 compared to lag0. However, the HRs for NO_x in the single-pollutant models were in the same order of magnitude for all lag windows. The larger effects at lag1–5 and lag6–10 compared to lag0 for particles indicate that there could be a noticeable delay effect between exposure and mortality. Another possible explanation is that the particles were more toxic further back in time. When comparing the HRs between two survival time periods (0–10 years and >10 years) shown in Tables A6 and A7, the HRs for particles were in general larger at the survival time period of 0–10 years, while the HRs for NO_x were larger for the survival time period of >10 years. This could possible mean that the PM_{10} and $PM_{2.5}$ were more toxic during the first ten years of the cohort period. However, when considering all analyzes in this study, the HRs for PM_{10} and $PM_{2.5}$ were in most cases statistically significant in the single-pollutant models, but they were non-significant, or in some cases negatively statistically significant, in the two-pollutant models. Unspecified particulate matter (PM_{10} and $PM_{2.5}$) does not constitute a uniform measure of particles with respect to their chemical composition and physical properties. They originate from a variety of sources that may have large spatial and temporal variations within a city. Given that this study has analyzed the exposure effect over a period of up to 25 years, the chemical composition and physical properties of the particles, and likewise their toxic potential, to which the cohort participants have been exposed, most likely varied greatly during this time. Seasonal variations in the above-mentioned factors can also be assumed to have occurred. Road dust, which is most common during springtime, has been found to be particularly harmful to the human health [25]. Indeed, exposure to $PM_{2.5\text{-}10}$ and PM_{10} were associated with increased mortality during springtime, but not during the rest of the year, as has been shown in time-series studies performed in Stockholm [26,27]. The low correlations between NO_x and PM (both PM_{10} and $PM_{2.5}$) in this study (Table A8) indicate that PM_{10} and $PM_{2.5}$ did not to any great extent originate from traffic. The toxic fractions of PM including road dust could be more highly correlated with NO_x, and may therefore not contribute much to the HRs when unspecified PM are used as exposure metrics.

4.3. NO_x as an Indicator for Other Harmful Exposures

The largest and most robust hazard ratios in this study were shown for NO_x; however, some uncertainty remains regarding the toxicity of NO_x itself. Experimental studies with humans have demonstrated noticeable health effects after short-term exposure to NO_2 at concentrations at or above

400 μg m^{-3}, and health effects among patients with mild asthma could not be detected at concentrations below 200 μg m^{-3} [28]. Based on a review of several long-term studies on NO_2 exposure, increased mortality was suggested above a threshold value of 20 μg m^{-3} [29]. The modeled mean concentrations of NO_x ($NO + NO_2$) during the study period in this study were in the range of 25–30 μg m^{-3}, and a large number of study participants may therefore have been exposed to concentrations of NO_2 that have exceeded 20 μg m^{-3} during a long period of time. However, the toxicity of NO_2 itself, and its impact on mortality, has been addressed in two literature reviews. One study indicates that there is an independent effect on long-term mortality associated with exposure to NO_2 [13]. Contrary, the other study indicates that the greater the demands placed on the studies, the less support there is for an independent effect on long-term mortality associated with exposure to NO_2 [15]. It is thus uncertain to what extent NO_x itself would have caused the robust and statistically significant associations with mortality observed in the present study. Indeed, some other component(s) of vehicle exhaust, with similar dispersion pattern, may have been driving the negative health effects.

As previously discussed, NO_x is an established proxy for road traffic exhaust emissions. Vehicle exhaust is not a homogeneous substance, however, it is comprised of harmful components other than NO_x. For example, high correlations between NO_x and particle number count (PNC) have been shown in Gothenburg, Sweden [30], and between NO_2 and PNC in Stockholm, Sweden [31]. NO_x can, therefore, be considered a marker for PNC. PNC, in turn, is a marker for ultrafine particles (particles with an aerodynamic diameter smaller than or equal to 100 nm in all dimensions). Due to their small size and large surface area in relation to volume, ultrafine particles are believed to be more toxic than larger particles [32]. From a health perspective, particles smaller than 300 nm are especially important since they are capable of diffusing rapidly in the airway mucus through the mucus pores [33]. Ultrafine particles may, thus, be a contributing factor to the negative health effects of exposure to traffic exhaust emissions. However, fine and ultrafine particles from traffic are not only emitted from combustion processes, but can also be derived from brake and tire wear [34].

Traffic noise is another health risk that can be correlated with exposure to NO_x. The correlation between NO_x and noise in urban areas is determined by several factors. The short-term correlations between NO_x or NO_2 and noise were analyzed in a study based on 103 urban sites with varying traffic, environment, and infrastructure characteristics. Factors that largely determined the degree of correlation were the number of lanes on the closest road, number of cars and trucks during noise sampling, and the presence of major intersections [35]. Based on a systematic review and meta-analysis [36], the associations between long-term exposure to traffic noise and mortality were weak, except for mortality related to ischemic heart disease. With this, authors suggested a possible threshold of 53 decibel for cardiovascular mortality from road traffic noise [35]. In a cohort study from Gothenburg, Sweden, positive but non-significant associations were found for cardiovascular mortality and morbidity and long-term residential exposure to noise above 60 decibel, compared to 50 decibel, after adjusting for air pollution exposure [37]. As traffic noise has not been included as a covariate in this study, it is not possible to draw conclusions regarding its impact on mortality among the MDC cohort participants.

In summary, the association between NO_x and mortality in this study is clear and robust. However, NO_x itself is not likely to be the main driver of this association. Traffic noise is also not expected to be responsible for the observed association, and there is a great need for studies that disentangle the effects of traffic-related noise and traffic-related air pollution on ill health. The ultrafine particles originating from both exhaust and from abrasion of tires, road surfaces, and brakes are probably an important factor, but more research is needed to confirm this. As road traffic is the main source of anthropogenic NO_x emissions in Europe [38], NO_x as well as its components and correlates will continue to be important.

4.4. Strengths and Limitations of This Study

A strength of this study is that it includes more than 30,000 participants and 25 years of follow-up, which provides a robust statistical basis both in terms of measurement data and number of

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participants. Exposure misclassification, a possible limitation, must be considered in all epidemiological studies on long-term exposure to air pollution. In this study, exposure was modeled at the participants' home addresses, and other sources of air pollution, such as occupational and/or indoor exposure, were not considered. This is regarded as standard practice in epidemiological studies of air pollution's health effects. Consequently, residential mobility among the study participants and its impact on exposure to air pollutants could not be taken into account. However, a previous study in another part of Sweden has shown that residential mobility does not seem to cause major exposure misclassification [39]. Also, exposure misclassification would have to depend on mortality to cause bias in the present study. Exposure misclassification (assumed to be non-differential) may have reduced the precision of the estimates, but low precision is not considered to be a plausible explanation for the results in the present study.

4.5. Future Research Needs and Policy Implications

The results of this study support traffic-related air pollution as an important environmental exposure with respect to premature mortality. While the number of epidemiological studies linking traffic emissions to adverse health effects continues to grow, the relative impact of specific components of pollutant mixtures generated by combustion engines have largely been overlooked. For instance, the health effects associated with exposure to specific exhaust components, e.g., particle bound or free volatile organic compounds (VOCs) and polycyclic aromatic hydrocarbons (PAHs), remain to be clarified. The role of metals that originate from engine abrasion, lubrication oils, and from the fuels themselves [40] and bind to exhaust particles also needs to be further explored.

Additionally, the characteristics and effects of non-exhaust emissions are becoming increasingly important. Mechanically generated particles from road abrasion and brakes are present in the coarse fraction (2.5–10 μm), the fine fraction (≤ 2.5 μm), and the ultrafine fraction (≤ 100 nm) [34]. Epidemiological studies analyzing the health effects associated with different chemical components of particles are not abundant. However, a time-series study conducted in the U.S., focusing on the relative risks for cardiovascular and respiratory hospital admissions associated with different chemical compositions of $PM_{2.5}$, showed that elemental carbon, vanadium, and nickel contents were associated with increased risk of hospital admissions [41]. Moreover, a literature review on exposure to road dust particles demonstrated serious health effects, especially for the respiratory system [25]. The components of road dust that were most frequently referenced in the reviewed studies were platinum, rhodium, bohrium, aluminum, zinc, vanadium, and polycyclic aromatic hydrocarbons [25]. Regarding brake wear particles, a toxicological study based on cell models has shown that brake abrasion particles and diesel exhaust particles are equally capable of damaging pulmonary cells [42].

With this, future epidemiological studies on the health effects of road traffic-related emissions should aim to include ultrafine particles and carefully adjust for different components using high-quality air pollution data.

From a policy point of view, reducing emissions from traffic has not always given rise to improved air quality in Europe and the U.S. despite long-established and progressively stringent tailpipe emission limitations. Thus, the health effects associated with different components of traffic-related emissions from combustion engines, including fuel qualities like aromatic content and metal content, still need to be addressed. These aspects influence the harmfulness of PM emissions not only from diesel, but also from gasoline- and ethanol-powered vehicles, and non-road machinery. Air pollution's chemical components and physical composition are further modified by atmospheric processes, making their regulation more difficult. Future studies need to address the above mentioned uncertainties.

5. Conclusions

In this cohort study, with roughly 30,000 participants from the general population and almost 25 years of follow-up, clear associations were observed between natural-cause mortality and long-term exposure to modeled concentrations of NO_x at the residential addresses. The robust hazard ratios for NO_x indicate that traffic-related air pollution had a significant association with mortality in

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the MDC cohort. However, it is uncertain to what extent NO_x exposure in itself is the main driver of these clear and robust hazard ratios, or if it rather is an indicator of combustion-related air pollutants including ultrafine particles and their toxic components, or road traffic noise. Hence, further research is needed to clarify the importance of specific exposures related to road traffic, air pollutants and noise, especially ultrafine particles, their chemical components, and their toxic potential.

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Institutional Review Board Statement: The study was approved by the Regional Ethics Committee at the University of Lund (dnr 2016/4).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data that support the findings of this study are available from the Lund University Medical Faculty – Malmo Diet and Cancer Cohort, but restrictions apply to the availability of these data, which were used under license for the current study, and are not publicly available. Data are however available from the authors upon reasonable request and with permission of Lund University Medical Faculty – Malmo Diet and Cancer Cohort. Ethical approval from The Swedish Ethical Review Authority is needed to access the data.

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Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

Table A1. Hazard ratios (HR) with 95% confidence intervals (CI) for the associations between natural-cause mortality and an IQR increase of the investigated air pollutants in single- and two-pollutant models with an exposure lag window of the same year (lag0). In the two-pollutant models, the HRs refer to the pollutant listed first.

Air pollutant*	Model†	IQR (μg m^{-3})	HR	95% CI	p-value
PM_{10}	M1	2.7	1.05	1.02–1.07	<0.001
	M2	–	1.02	0.99–1.05	0.14
	M3	–	1.01	0.98–1.04	0.43
$PM_{2.5}$	M1	1.6	1.01	0.99–1.03	0.43
	M2	–	1.00	0.98–1.02	0.99
	M3	–	1.00	0.98–1.02	0.77
BC	M1	0.15	1.13	1.09–1.16	<0.001
	M2	–	1.06	1.03–1.09	<0.001
	M3	–	1.05	1.02–1.08	0.004
NO_x	M1	9.7	1.15	1.12–1.19	<0.001
	M2	–	1.08	1.05–1.12	<0.001
	M3	–	1.08	1.05–1.12	<0.001
PM_{10} + BC	M1	–	1.00	0.97–1.03	0.76
	M2	–	1.00	0.97–1.03	0.82
	M3	–	0.99	0.96–1.02	0.49
BC + PM_{10}	M1	–	1.13	1.09–1.17	<0.001
	M2	–	1.06	1.02–1.10	0.001
	M3	–	1.06	1.02–1.10	0.004

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PM_{10} + NO_x	M1	–	0.99	0.96–1.02	0.49
	M2	–	0.99	0.96–1.02	0.42
	M3	–	0.98	0.95–1.01	0.16
NO_x + PM_{10}	M1	–	1.16	1.12–1.20	<0.001
	M2	–	1.09	1.05–1.13	<0.001
	M3	–	1.10	1.06–1.14	<0.001
$PM_{2.5}$ + BC	M1	–	0.99	0.98–1.01	0.52
	M2	–	0.99	0.97–1.01	0.53
	M3	–	0.99	0.97–1.01	0.41
BC + $PM_{2.5}$	M1	–	1.13	1.09–1.16	<0.001
	M2	–	1.06	1.03–1.09	<0.001
	M3	–	1.05	1.02–1.09	0.003
$PM_{2.5}$ + NO_x	M1	–	0.99	0.97–1.01	0.32
	M2	–	0.99	0.97–1.01	0.34
	M3	–	0.99	0.97–1.01	0.24
NO_x + $PM_{2.5}$	M1	–	1.16	1.12–1.19	<0.001
	M2	–	1.09	1.05–1.13	<0.001
	M3	–	1.09	1.05–1.12	<0.001
BC + NO_x	M1	–	0.99	0.93–1.05	0.67
	M2	–	0.94	0.88–1.01	0.08
	M3	–	0.92	0.86–0.98	0.02
NO_x + BC	M1	–	1.17	1.09–1.25	<0.001
	M2	–	1.15	1.07–1.23	<0.001
	M3	–	1.17	1.09–1.26	<0.001

* Exposure based on concentrations according to each pollutant's IQR value. † Model 1 (M1) is adjusted only for age and gender. Model 2 (M2) also adjusts for smoking habits, educational level, and cohabitation. Model 3 (M3) adjusts in addition for systolic and diastolic blood pressure, self-reported alcohol consumption, physical activity, waist/hip ratio, and the use of antihypertensive medications.

Table A2. Hazard ratios (HR) with 95% confidence intervals (CI) for the associations between natural-cause mortality and an IQR increase of the investigated air pollutants in single- and two-pollutant models with an exposure lag window of 1–5 years (lag1–5). In the two-pollutant models, the HRs refer to the pollutant listed first.

Air pollutant*	Model†	IQR (μg m^{-3})	HR	95% CI	p-value
PM_{10}	M1	2.1	1.16	1.12–1.21	<0.001
	M2	–	1.08	1.03–1.12	<0.001
	M3	–	1.06	1.02–1.11	0.007
$PM_{2.5}$	M1	1.7	1.11	1.05–1.17	<0.001
	M2	–	1.04	0.98–1.10	0.24
	M3	–	1.01	0.95–1.08	0.69
BC	M1	0.14	1.15	1.11–1.18	<0.001
	M2	–	1.08	1.04–1.11	<0.001
	M3	–	1.07	1.04–1.11	<0.001
NO_x	M1	11.4	1.19	1.15–1.22	<0.001
	M2	–	1.11	1.07–1.15	<0.001
	M3	–	1.11	1.07–1.16	<0.001
PM_{10} + NO_x	M1	–	0.98	0.92–1.04	0.49
	M2	–	0.95	0.89–1.01	0.10
	M3	–	0.90	0.84–0.97	0.004
NO_x + PM_{10}	M1	–	1.20	1.14–1.27	<0.001
	M2	–	1.15	1.09–1.22	<0.001
	M3	–	1.19	1.13–1.26	<0.001

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$PM_{2.5}$ + BC	M1	–	0.94	0.88–1.00	0.07
	M2	–	0.94	0.87–1.01	0.09
	M3	–	0.92	0.85–0.99	0.02
BC + $PM_{2.5}$	M1	–	1.17	1.13–1.21	<0.001
	M2	–	1.10	1.06–1.14	<0.001
	M3	–	1.10	1.06–1.14	<0.001
$PM_{2.5}$ + NO_x	M1	–	0.96	0.90–1.02	0.22
	M2	–	0.95	0.88–1.01	0.11
	M3	–	0.92	0.85–0.98	0.01
NO_x + $PM_{2.5}$	M1	–	1.20	1.15–1.24	<0.001
	M2	–	1.13	1.08–1.17	<0.001
	M3	–	1.14	1.10–1.19	<0.001
BC + NO_x	M1	–	1.02	0.97–1.09	0.41
	M2	–	0.98	0.93–1.05	0.61
	M3	–	0.95	0.89–1.01	0.10
NO_x + BC	M1	–	1.16	1.09–1.23	<0.001
	M2	–	1.13	1.05–1.21	<0.001
	M3	–	1.17	1.09–1.26	<0.001

* Exposure based on concentrations according to each pollutant's IQR value. † Model 1 (M1) is adjusted only for age and gender. Model 2 (M2) also adjusts for smoking habits, educational level, and cohabitation. Model 3 (M3) adjusts in addition for systolic and diastolic blood pressure, self-reported alcohol consumption, physical activity, waist/hip ratio, and the use of antihypertensive medications.

Table A3. Hazard ratios (HR) with 95% confidence intervals (CI) for the associations between natural-cause mortality and an IQR increase of the investigated air pollutants in single- and two-pollutant models with an exposure lag window of 6–10 years (lag6–10). In the two-pollutant models, the HRs refer to the pollutant listed first.

Air pollutant*	Model†	IQR (μg m^{-3})	HR	95% CI	p-value
PM_{10}	M1	2.3	1.17	1.12–1.23	<0.001
	M2	–	1.09	1.04–1.14	<0.001
	M3	–	1.08	1.03–1.13	0.002
$PM_{2.5}$	M1	1.5	1.18	1.11–1.26	<0.001
	M2	–	1.10	1.03–1.17	0.002
	M3	–	1.09	1.02–1.17	0.009
BC	M1	0.15	1.14	1.11–1.18	<0.001
	M2	–	1.07	1.03–1.10	<0.001
	M3	–	1.06	1.02–1.10	0.002
NO_x	M1	12.7	1.16	1.12–1.19	<0.001
	M2	–	1.08	1.05–1.12	<0.001
	M3	–	1.08	1.05–1.12	<0.001
PM_{10} + NO_x	M1	–	1.03	0.96–1.10	0.42
	M2	–	1.00	0.93–1.08	0.94
	M3	–	0.99	0.92–1.06	0.74
NO_x + PM_{10}	M1	–	1.14	1.08–1.20	<0.001
	M2	–	1.08	1.03–1.14	0.004
	M3	–	1.09	1.03–1.16	0.002
$PM_{2.5}$ + BC	M1	–	1.03	0.96–1.11	0.41
	M2	–	1.04	0.96–1.13	0.30
	M3	–	1.04	0.96–1.13	0.36
BC + $PM_{2.5}$	M1	–	1.13	1.08–1.18	<0.001
	M2	–	1.05	1.01–1.10	0.02
	M3	–	1.05	1.00–1.09	0.05

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$PM_{2.5}$ + NO_x	M1	–	1.05	0.98–1.13	0.13
	M2	–	1.04	0.97–1.11	0.31
	M3	–	1.02	0.95–1.10	0.53
NO_x + $PM_{2.5}$	M1	–	1.14	1.10–1.18	<0.001
	M2	–	1.07	1.03–1.12	<0.001
	M3	–	1.08	1.04–1.12	<0.001
BC + NO_x	M1	–	1.03	0.97–1.10	0.38
	M2	–	0.99	0.92–1.05	0.67
	M3	–	0.96	0.89–1.03	0.23
NO_x + BC	M1	–	1.13	1.06–1.20	<0.001
	M2	–	1.10	1.03–1.17	0.006
	M3	–	1.12	1.05–1.20	0.001

* Exposure based on concentrations according to each pollutant's IQR value. † Model 1 (M1) is adjusted only for age and gender. Model 2 (M2) also adjusts for smoking habits, educational level, and cohabitation. Model 3 (M3) adjusts in addition for systolic and diastolic blood pressure, self-reported alcohol consumption, physical activity, waist/hip ratio, and the use of antihypertensive medications.

Table A4. Hazard ratios (HR) with 95% confidence intervals (CI) for the associations between natural-cause mortality and an IQR increase of the investigated air pollutants in single-pollutant models divided into different age groups. All HRs are based on lag1–5, and with adjustments for all covariates according to Model 3. .

Air pollutant	Age group	HR	95% CI	p-value
PM_{10}	Group 1 ≤ 50 years	1.00	0.84–1.19	0.99
	50 years < Group 2 ≤ 55 years	1.08	0.95–1.23	0.23
	55 years < Group 3 ≤ 60 years	1.02	0.91–1.14	0.72
	60 years < Group 4 ≤ 65 years	1.10	1.02–1.20	0.02
	65 years < Group 5 ≤ 70 years	1.12	1.01–1.23	0.03
	Group 6 > 70 years	1.02	0.91–1.15	0.73
$PM_{2.5}$	Group 1 ≤ 50 years	1.06	0.82–1.37	0.65
	50 years < Group 2 ≤ 55 years	1.05	0.86–1.28	0.61
	55 years < Group 3 ≤ 60 years	0.92	0.78–1.08	0.31
	60 years < Group 4 ≤ 65 years	1.06	0.94–1.20	0.37
	65 years < Group 5 ≤ 70 years	1.16	1.00–1.34	0.05
	Group 6 > 70 years	0.94	0.77–1.15	0.56
BC	Group 1 ≤ 50 years	1.04	0.92–1.18	0.54
	50 years < Group 2 ≤ 55 years	1.07	0.98–1.18	0.14
	55 years < Group 3 ≤ 60 years	1.05	0.96–1.14	0.28
	60 years < Group 4 ≤ 65 years	1.10	1.03–1.17	0.004
	65 years < Group 5 ≤ 70 years	1.09	1.01–1.17	0.02
	Group 6 > 70 years	1.01	0.93–1.10	0.80
NO_x	Group 1 ≤ 50 years	1.05	0.90–1.23	0.52
	50 years < Group 2 ≤ 55 years	1.11	1.01–1.23	0.04
	55 years < Group 3 ≤ 60 years	1.07	0.97–1.17	0.16
	60 years < Group 4 ≤ 65 years	1.12	1.05–1.20	0.001
	65 years < Group 5 ≤ 70 years	1.11	1.03–1.20	0.006
	Group 6 > 70 years	1.05	0.95–1.15	0.35

Table A5. Hazard ratios (HR) with 95% confidence intervals (CI) for the associations between natural-cause mortality and an IQR increase of the investigated air pollutants in two-pollutant models divided into different age groups. All HRs are based on lag1–5, and with adjustments for all covariates according to Model 3. In these two-pollutant models, the HRs refer to the pollutant listed first.

Air pollutant	Age group	HR	95% CI	p-value

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PM_{10} + NO_x	Group 1 ≤ 50 years	0.89	0.67–1.17	0.41
	50 years < Group 2 ≤ 55 years	0.91	0.73–1.14	0.43
	55 years < Group 3 ≤ 60 years	0.88	0.73–1.07	0.20
	60 years < Group 4 ≤ 65 years	0.97	0.84–1.12	0.69
	65 years < Group 5 ≤ 70 years	1.00	0.84–1.18	0.99
	Group 6 > 70 years	0.88	0.69–1.13	0.32
NO_x + PM_{10}	Group 1 ≤ 50 years	1.14	0.89–1.45	0.29
	50 years < Group 2 ≤ 55 years	1.18	0.99–1.40	0.06
	55 years < Group 3 ≤ 60 years	1.16	0.99–1.36	0.06
	60 years < Group 4 ≤ 65 years	1.14	1.02–1.29	0.03
	65 years < Group 5 ≤ 70 years	1.12	0.98–1.28	0.11
	Group 6 > 70 years	1.14	0.94–1.39	0.18
$PM_{2.5}$ + BC	Group 1 ≤ 50 years	1.02	0.74–1.40	0.91
	50 years < Group 2 ≤ 55 years	0.94	0.74–1.20	0.63
	55 years < Group 3 ≤ 60 years	0.81	0.67–1.00	0.05
	60 years < Group 4 ≤ 65 years	0.94	0.81–1.09	0.40
	65 years < Group 5 ≤ 70 years	1.08	0.90–1.29	0.40
	Group 6 > 70 years	0.86	0.65–1.14	0.29
BC + $PM_{2.5}$	Group 1 ≤ 50 years	1.04	0.88–1.21	0.67
	50 years < Group 2 ≤ 55 years	1.09	0.97–1.23	0.15
	55 years < Group 3 ≤ 60 years	1.11	1.00–1.23	0.04
	60 years < Group 4 ≤ 65 years	1.12	1.03–1.20	0.004
	65 years < Group 5 ≤ 70 years	1.06	0.98–1.16	0.16
	Group 6 > 70 years	1.05	0.94–1.18	0.36
$PM_{2.5}$ + NO_x	Group 1 ≤ 50 years	1.02	0.76–1.37	0.87
	50 years < Group 2 ≤ 55 years	0.93	0.74–1.17	0.54
	55 years < Group 3 ≤ 60 years	0.83	0.69–1.00	0.06
	60 years < Group 4 ≤ 65 years	0.95	0.83–1.10	0.51
	65 years < Group 5 ≤ 70 years	1.07	0.90–1.26	0.44
	Group 6 > 70 years	0.82	0.63–1.06	0.13
NO_x + $PM_{2.5}$	Group 1 ≤ 50 years	1.04	0.88–1.24	0.63
	50 years < Group 2 ≤ 55 years	1.13	1.01–1.27	0.04
	55 years < Group 3 ≤ 60 years	1.12	1.01–1.25	0.03
	60 years < Group 4 ≤ 65 years	1.14	1.05–1.23	0.002
	65 years < Group 5 ≤ 70 years	1.10	1.00–1.20	0.04
	Group 6 > 70 years	1.11	0.98–1.25	0.09
BC + NO_x	Group 1 ≤ 50 years	1.01	0.78–1.32	0.92
	50 years < Group 2 ≤ 55 years	0.95	0.79–1.14	0.56
	55 years < Group 3 ≤ 60 years	0.98	0.84–1.15	0.84
	60 years < Group 4 ≤ 65 years	1.02	0.90–1.15	0.80
	65 years < Group 5 ≤ 70 years	0.99	0.86–1.14	0.88
	Group 6 > 70 years	0.87	0.72–1.05	0.15
NO_x + BC	Group 1 ≤ 50 years	1.04	0.76–1.42	0.82
	50 years < Group 2 ≤ 55 years	1.17	0.96–1.43	0.12
	55 years < Group 3 ≤ 60 years	1.09	0.91–1.30	0.37
	60 years < Group 4 ≤ 65 years	1.10	0.96–1.27	0.16
	65 years < Group 5 ≤ 70 years	1.13	0.96–1.32	0.13
	Group 6 > 70 years	1.21	0.97–1.50	0.09

Table A6. Hazard ratios (HR) with 95% confidence intervals (CI) for the associations between natural-cause mortality and an IQR increase of the investigated air pollutants in single-pollutant models divided into two survival time periods. All HRs are based on lag1–5, and with adjustments for all covariates according to Model 3.

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Air pollutant	Survival time	HR	95% CI	p-value
PM_{10}	0–10 years	1.11	1.02–1.20	0.01
	> 10 years	1.06	1.01–1.12	0.02
$PM_{2.5}$	0–10 years	1.16	1.00–1.35	0.05
	> 10 years	1.01	0.94–1.08	0.76
BC	0–10 years	1.10	1.03–1.18	0.003
	> 10 years	1.06	1.02–1.10	0.001
NO_x	0–10 years	1.09	1.03–1.14	0.001
	> 10 years	1.12	1.06–1.18	<0.001

Table A7. Hazard ratios (HR) with 95% confidence intervals (CI) for the associations between natural-cause mortality and an IQR increase of the investigated air pollutants in two-pollutant models divided into two survival time periods. All HRs are based on lag1–5, and with adjustments for all covariates according to Model 3. In these two-pollutant models, the HRs refer to the pollutant listed first.

Air pollutant	Model*	HR	95% CI	p-value
PM_{10} + NO_x	0–10 years	1.00	0.88–1.14	0.95
	> 10 years	0.92	0.83–1.01	0.07
NO_x + PM_{10}	0–10 years	1.08	1.00–1.17	0.05
	> 10 years	1.20	1.09–1.33	<0.001
$PM_{2.5}$ + BC	0–10 years	1.02	0.85–1.23	0.82
	> 10 years	0.93	0.86–1.01	0.10
BC + $PM_{2.5}$	0–10 years	1.10	1.01–1.19	0.03
	> 10 years	1.08	1.04–1.13	<0.001
$PM_{2.5}$ + NO_x	0–10 years	1.05	0.89–1.24	0.54
	> 10 years	0.92	0.85–1.00	0.04
NO_x + $PM_{2.5}$	0–10 years	1.08	1.02–1.14	0.01
	> 10 years	1.15	1.08–1.23	<0.001
BC + NO_x	0–10 years	1.03	0.91–1.16	0.62
	> 10 years	0.91	0.81–1.01	0.09
NO_x + BC	0–10 years	1.07	0.97–1.17	0.18
	> 10 years	1.27	1.08–1.49	0.003

Table A8. Correlation matrix with correlation coefficients (Pearson) between the modeled air pollutants based on lag0 (upper part), lag1–5 (middle part), and lag6–10 (lower part).

	PM_{10} lag0	**$PM_{2.5}$ lag0**	**BC lag0**	**NO_x lag0**
PM_{10} lag0	1			
$PM_{2.5}$ lag0	0.81	1		
BC lag0	0.55	0.25	1	
NO_x lag0	0.24	0.03	0.50	1
	PM_{10} lag1–5	**$PM_{2.5}$ lag1–5**	**BC lag1–5**	**NO_x lag1–5**
PM_{10} lag1–5	1			
$PM_{2.5}$ lag1–5	0.81	1		
BC lag1–5	0.85	0.64	1	
NO_x lag1–5	0.19	-0.18	0.41	1
	PM_{10} lag6–10	**$PM_{2.5}$ lag6–10**	**BC lag6–10**	**NO_x lag6–10**
PM_{10} lag6–10	1			
$PM_{2.5}$ lag6–10	0.90	1		
BC lag6–10	0.84	0.66	1	
NO_x lag6–10	0.22	-0.09	0.47	1

References

1. WHO, 2022. Ambient (outdoor) air pollution. https://www.who.int/news-room/fact-sheets/detail/ambient-(outdoor)-air-quality-and-health Last access 2023-08-22
2. Chen, J.; Hoek, G. Long-term exposure to PM and all-cause and cause-specific mortality: A systematic review and meta-analysis. *Environ. Int*. **2020**, *143*, 105974.
3. Faustini, A; Rapp, R; Forastiere, F. Nitrogen dioxide and mortality: review and meta-analysis of long-term studies. *Eur. Respir. J.* **2014**, *44*, 744–753.
4. Hoek, G.; Krishnan, R.M.; Beelen, R.; Peters, A.; Ostro, B.; Brunekreef, B.; Kaufman, J.D. Long-term air pollution exposure and cardio- respiratory mortality: a review. *Environ. Health*. **2013**, *12*, 43.
5. Beelen, R.; Raaschou-Nielsen, O.; Stafoggia, M.; Andersen, Z.J.; Weinmayr, G.; Hoffmann, B.; Wolf, K.; Samoli, E.; Fischer, P.; Nieuwenhuijsen, M.; Vineis, P.; Xun, W.W.; Katsouyanni, K.; Dimakopoulou, K.; Oudin, A.; Forsberg, B.; Modig, L.; Havulinna, A.S.; Lanki, T.; Turunen, A.; Oftedal, B.; Nystad, W.; Nafstad, P.; De Faire, U.; Pedersen, N.L.; Östenson, C.G.; Fratiglioni, L.; Penell, J.; Korek, M.; Pershagen, G.; Eriksen, K.T.; Overvad, K.; Ellermann, T.; Eeftens, M.; Peeters, P.H.; Meliefste, K.; Wang, M.; Bueno-de-Mesquita, B.; Sugiri, D.; Krämer, U.; Heinrich, J.; de Hoogh, K.; Key, T.; Peters, A.; Hampel, R.; Concin, H.; Nagel, G.; Ineichen, A.; Schaffner, E.; Probst-Hensch, N.; Künzli, N.; Schindler, C.; Schikowski, T.; Adam, M.; Phuleria, H.; Vilier, A.; Clavel-Chapelon, F.; Declercq, C.; Grioni, S.; Krogh, V.; Tsai, M.Y.; Ricceri, F.; Sacerdote, C.; Galassi, C.; Migliore, E.; Ranzi, A.; Cesaroni, G.; Badaloni, C.; Forastiere, F.; Tamayo, I.; Amiano, P.; Dorronsoro, M.; Katsoulis, M.; Trichopoulou, A.; Brunekreef, B.; Hoek, G. Effects of long-term exposure to air pollution on natural-cause mortality: an analysis of 22 European cohorts within the multicentre ESCAPE project. *Lancet* **2014**, *383*, 785–795.
6. Stafoggia, M.; Oftedal, B.; Chen, J.; Rodopoulou, S.; Renzi, M.; Atkinson, R.W.; Bauwelinck, M.; Klompmaker, J.O.; Mehta, A.; Vienneau, D.; Andersen, Z.J.; Bellander, T.; Brandt, J.; Cesaroni, G.; de Hoogh, K.; Fecht, D.; Gulliver, J.; Hertel, O.; Hoffmann, B.; Hvidtfeldt, U.A.; Jöckel, K.H.; Jørgensen, J.T.; Katsouyanni, K.; Ketzel, M.; Kristoffersen, D.T.; Lager, A.; Leander, K.; Liu, S.; Ljungman, P.L.S.; Nagel, G.; Pershagen, G.; Peters, A.; Raaschou-Nielsen, O.; Rizzuto, D.; Schramm, S.; Schwarze, P.E.; Severi, G.; Sigsgaard, T.; Strak, M.; van der Schouw, Y.T.; Verschuren, M.; Weinmayr, G.; Wolf, K.; Zitt, E.; Samoli, E.; Forastiere, F.; Brunekreef, B.; Hoek, G.; Janssen, N.A.H. Long-term exposure to low ambient air pollution concentrations and mortality among 28 million people: results from seven large European cohorts within the ELAPSE project. *Lancet Planet Health* **2022**, *6*, e9–e18.
7. Yang, Z.; Mahendran, R.; Yu, P.; Xu, R.; Yu, W.; Godellawattage, S.; Li, S.; Guo, Y. Health Effects of Long-Term Exposure to Ambient $PM_{2.5}$ in Asia-Pacific: a Systematic Review of Cohort Studies. *Curr. Environ. Health. Rep*. **2022**, *9*, 130–151.
8. Nilsson Sommar, J.; Andersson, E.M.; Andersson, N.; Sallsten, G.; Stockfelt, L.; Ljungman, P.L.; Segersson, D.; Eneroth, K.; Gidhagen, L.; Molnar, P.; Wennberg, P.; Rosengren, A.; Rizzuto, D.; Leander, K.; Lager, A.; Magnusson, P.K.; Johansson, C.; Barregard, L.; Bellander, T.; Pershagen, G.; Forsberg, B. Long-term exposure to particulate air pollution and black carbon in relation to natural and cause-specific mortality: a multicohort study in Sweden. *BMJ Open* **2021**, *11*, e046040.
9. Yang, J.; Sakhvidi, M.J.Z.; de Hoogh, K.; Vienneau, D.; Siemiatyck, J.; Zins, M.; Goldberg, M.; Chen, J.; Lequy, E.; Jacquemin, B. Long-term exposure to black carbon and mortality: A 28-year follow-up of the GAZEL cohort. *Environ Int*. **2021**, *157*, 106805.
10. Filleul, L.; Rondeau, V.; Vandentorren, S.; Le Moual, N.; Cantagrel, A.; Annesi-Maesano, I.; Charpin, D.; Declercq, C.; Neukirch, F.; Paris, C.; Vervloet, D.; Brochard, P.; Tessier, J.F.; Kauffmann, F.; Baldi, I. Twenty five year mortality and air pollution: results from the French PAARC survey. *Occup. Environ. Med*. **2005**, *62*, 453–460.
11. Beelen, R.; Hoek, G.; van den Brandt, P.A.; Goldbohm, R.A.; Fischer, P.; Schouten, L.J.; Jerrett, M.; Hughes, E.; Armstrong, B.; Brunekreef, B. Long-term effects of traffic-related air pollution on mortality in a Dutch cohort (NLCS-AIR study). *Environ. Health Perspect*. **2008**, *116*, 196–202.
12. Huangfu, P.; Atkinson, R. Long-term exposure to NO_2 and O_3 and all-cause and respiratory mortality: A systematic review and meta-analysis. *Environ. Int*. **2020**, *144*, 105998.
13. Huang, S.; Li, H.; Wang, M.; Qian, Y.; Steenland, K.; Caudle, W.M.; Liu, Y.; Sarnat, J.; Papatheodorou, S.; Shi, L. Long-term exposure to nitrogen dioxide and mortality: A systematic review and meta-analysis. *Sci. Total Environ*. **2021**, *776*, 145968.
14. Atkinson, R.W.; Butland, B.K.; Anderson, H.R.; Maynard, R.L. Long-term Concentrations of Nitrogen Dioxide and Mortality: A Meta-analysis of Cohort Studies. *Epidemiology* **2018**, *29*, 460–472.
15. Stieb, D.M.; Berjawi, R.; Emode, M.; Zheng, C.; Salama, D.; Hocking, R.; Lyrette, N.; Matz, C.; Lavigne, E.; Shin, H.H. Systematic review and meta-analysis of cohort studies of long term outdoor nitrogen dioxide exposure and mortality. *PLoS One* **2021**, *16*, e0246451.
16. Stockfelt, L.; Andersson, E.M.; Molnár, P.; Rosengren, A.; Wilhelmsen, L.; Sallsten, G.; Barregard, L. Long term effects of residential NO(x) exposure on total and cause-specific mortality and incidence of myocardial infarction in a Swedish cohort. *Environ. Res.* **2015**, *142*, 197–206.

17. Carlsen, H.K.; Andersson, E.M.; Molnár, P.; Oudin, A.; Xu, Y.; Wichmann, J.; Spanne, M.; Stroh, E.; Engström, G.; Stockfelt, L. Incident cardiovascular disease and long-term exposure to source-specific air pollutants in a Swedish cohort. *Environ. Res*. **2022**, *209*, 112698.
18. Azzouz, M.; Xu, Y.; Barregard, L.; Fagerberg, B.; Zöller, B.; Molnár, P.; Oudin, A.; Spanne, M.; Engström, G.; Stockfelt, L. Air pollution and biomarkers of cardiovascular disease and inflammation in the Malmö Diet and Cancer cohort. *Environ. Health*. **2022**, *21*, 39.
19. Xu, Y.; Andersson, E.M.; Krage Carlsen, H.; Molnár, P.; Gustafsson, S.; Johannesson, S.; Oudin, A.; Engström, G.; Christensson, A.; Stockfelt, L. Associations between long-term exposure to low-level air pollution and risk of chronic kidney disease-findings from the Malmö Diet and Cancer cohort. *Environ. Int*. **2022**, *160*, 107085.
20. Berglund, G.; Elmståhl, S.; Janzon, L.; Larsson, S.A. The Malmo Diet and Cancer Study. Design and feasibility. *J. Intern Med*. **1993**, *233*, 45–51.
21. Manjer, J.; Carlsson, S.; Elmståhl, S.; Gullberg, B.; Janzon, L.; Lindström, M.; Mattisson, I.; Berglund, G. The Malmö Diet and Cancer Study: representativity, cancer incidence and mortality in participants and non-participants. *Eur. J. Cancer Prev*. **2001**, *10*, 489–499.
22. Rosvall, M.; Ostergren, P.O.; Hedblad, B.; Isacsson, S.O.; Janzon, L.; Berglund, G. Occupational status, educational level, and the prevalence of carotid atherosclerosis in a general population sample of middle-aged Swedish men and women: results from the Malmö Diet and Cancer Study. *Am. J. Epidemiol*. **2000**, *152*, 334–346.
23. Drake, I.; Dias, J.A.; Teleka, S.; Stocks, T.; Orho-Melander, M. Lifestyle and cancer incidence and mortality risk depending on family history of cancer in two prospective cohorts. *Int. J. Cancer* **2020**, *146*, 1198–1207.
24. Kuik, F.; Kerschbaumer, A.; Lauer, A.; Lupascu, A.; von Schneidemesser, E.; Butler, T.M. Top–down quantification of NO_x emissions from traffic in an urban area using a high-resolution regional atmospheric chemistry model. *Atmos. Chem. Phys*. **2018**, *18*, 8203–8225.
25. Khan, R.K.; Strand, M.A. Road dust and its effect on human health: A literature review. *Epidemiol. Health* **2018**, *40*, e2018013.
26. Olstrup, H.; Johansson, C.; Forsberg, B.; Åström, C.; Orru, H. Seasonal Variations in the Daily Mortality Associated with Exposure to Particles, Nitrogen Dioxide, and Ozone in Stockholm, Sweden, from 2000 to 2016. *Atmosphere* **2021**, *12*, 1481.
27. Meister, K.; Johansson, C.; Forsberg, J. Estimated short-term effects of coarse particles on daily mortality in Stockholm, Sweden. *Environ. Health Perspect*. **2012**, *120*, 431–436.
28. Kraft, M.; Eikmann, T.; Kappos, A.; Künzli, N.; Rapp, R.; Schneider, K.; Seitz, H.; Voss, J.U.; Wichmann, H.E. The German view: Effects of nitrogen dioxide on human health–derivation of health-related short-term and long-term values. *Int. J. Hyg. Environ. Health* **2005**, *208*, 305–318.
29. Ritz, B.; Hoffmann, B.; Peters, A. The Effects of Fine Dust, Ozone, and Nitrogen Dioxide on Health. *Dtsch. Arztebl. Int*. **2019**, *116*, 881–886.
30. Grundström, M.; Hak, C.; Chen, D.; Hallquist, M.; Pleijel, H. Variation and Co-variation of PM10, Particle Number Concentration, NOx and NO2 in the Urban Air – Relationships With Wind Speed, Vertical Temperature Gradient and Weather Type. *Atmospheric Environment* **2015**, *120*, 317–327
31. Olstrup, H.; Johansson, C.; Forsberg, B.; Åström, C. Association between Mortality and Short-Term Exposure to Particles, Ozone and Nitrogen Dioxide in Stockholm, Sweden. *Int. J. Environ. Res. Public Health* **2019**, *16*, 1028.
32. Yang, Y.; Qin, Z.; Zeng, W.; Yang, T.; Cao, Y.; Mei, C.; Kuang, Y. Toxicity assessment of nanoparticles in various systems and organs. *Nanotechnol. Rev*. **2017**, *6*, 279–289.
33. Schuster, B.S.; Suk, J.S.; Woodworth, G.F.; Hanes, J. Nanoparticle diffusion in respiratory mucus from humans without lung disease. *Biomaterials* **2013**, *34*, 3439–3446.
34. Fussell, J.C.; Franklin, M.; Green, D.C.; Gustafsson, M.; Harrison, R.M.; Hicks, W.; Kelly, F.J.; Kishta, F.; Miller, M.R.; Mudway, I.S.; Oroumiyeh, F.; Selley, L.; Wang, M.; Zhu, Y. A Review of Road Traffic-Derived Non-Exhaust Particles: Emissions, Physicochemical Characteristics, Health Risks, and Mitigation Measures. Environ. Sci. Technol. 2022, 56, 6813–6835.
35. Davies, H.W.; Vlaanderen, J.J.; Henderson, S.B.; Brauer, M. Correlation between co-exposures to noise and air pollution from traffic sources. *Occup. Environ. Med*. **2009**, 66, 347–350
36. Cai, Y.; Ramakrishnan, R.; Rahimi, K. Long-term exposure to traffic noise and mortality: A systematic review and meta-analysis of epidemiological evidence between 2000 and 2020. *Environ. Pollut*. **2021**, *269*, 116222.
37. Andersson, E.M.; Ögren, M.; Molnár, P.; Segersson, D.; Rosengren, A.; Stockfelt, L. Road traffic noise, air pollution and cardiovascular events in a Swedish cohort. *Environ. Res*. **2020**, *185*, 109446.
38. Krecl, P.; Harrison, R.M.; Johansson, C.; Targino, A.C.; Beddows, D.C.; Ellermann, T.; Lara, C.; Ketzel, M. Long-term trends in nitrogen oxides concentrations and on-road vehicle emission factors in Copenhagen, London and Stockholm. *Environ. Pollut*. **2021**, *290*, 118105.

39. Oudin, A.; Forsberg, B.; Strömgren, M.; Beelen, R.; Modig, L. Impact of residential mobility on exposure assessment in longitudinal air pollution studies: a sensitivity analysis within the ESCAPE project. *Sci. World J.* **2012**, *2012*, 125818.
40. Ulrich, A.; Wichser, A.; Hess, A.; Heeb, N.; Emmenegger, L.; Czerwinski, J.; Kasper, M.; Mooney, J.; Mayer, A. *Particle and Metal Emissions of Diesel and Gasoline Engines—Are Particle Filters Appropriate Measures?* Swiss Federal Laboratories for Material Testing and Research: Dübendorf, Switzerland, 2012.
41. Bell, M.L.; Ebisu, K.; Peng, R.D.; Samet, J.M.; Dominici, F. Hospital admissions and chemical composition of fine particle air pollution. *Am. J. Respir. Crit. Care. Med.* **2009**, *179*, 1115–1120.
42. Selley, L.; Schuster, L.; Marbach, H.; Forsthuber, T.; Forbes, B.; Gant, T.W.; Sandström, T.; Camiña, N.; Athersuch, T.J.; Mudway, I.; Kumar, A. Brake dust exposure exacerbates inflammation and transiently compromises phagocytosis in macrophages. *Metallomics* **2020**, *12*, 371–386.