Environment International 181 (2023) 108257

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Full length article

Long-term exposure to low-level air pollution and greenness and mortality in Northern Europe. The Life-GAP project

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ARTICLE INFO

Handling Editor: Hanna Boogaard

Keywords:
Green space
Long-term effect
Nitrogen dioxide
Ozone
Particulate matter
Premature mortality

ABSTRACT

Background: Air pollution has been linked to mortality, but there are few studies examining the association with different exposure time windows spanning across several decades. The evidence for the effects of green space and mortality is contradictory.

Objective: We investigated all-cause mortality in relation to exposure to particulate matter ($PM_{2.5}$ and PM_{10}), black carbon (BC), nitrogen dioxide (NO_2), ozone (O_3) and greenness (normalized difference vegetation index - NDVI) across different exposure time windows.

Methods: The exposure assessment was based on a combination of the Danish Eulerian Hemispheric Model and the Urban Background Model for the years 1990, 2000 and 2010. The analysis included a complete case dataset with 9,135 participants from the third Respiratory Health in Northern Europe study (RHINE III), aged 40–65 years in 2010, with mortality follow-up to 2021. We performed Cox proportional hazard models, adjusting for potential confounders.

Results: Altogether, 327 (3.6 %) persons died in the period 2010–2021. Increased exposures in 1990 of $PM_{2.5}$, PM_{10}, BC and NO_2 were associated with increased all-cause mortality hazard ratios of 1.40 (95 % CI1.04–1.87 per 5 μg/m^3), 1.33 (95 % CI: 1.02–1.74 per 10 μg/m^3), 1.16 (95 % CI: 0.98–1.38 per 0.4 μg/m^3) and 1.17 (95 % CI: 0.92–1.50 per 10 μg/m^3), respectively. No statistically significant associations were observed between air pollution and mortality in other time windows. O_3 showed an inverse association with mortality, while no association was observed between greenness and mortality. Adjusting for NDVI increased the hazard ratios for $PM_{2.5}$, PM_{10}, BC and NO_2 exposures in 1990. We did not find significant interactions between greenness and air pollution metrics.

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https://doi.org/10.1016/j.envint.2023.108257
Received 13 April 2023; Received in revised form 28 September 2023; Accepted 9 October 2023
Available online 11 October 2023

Conclusion: Long term exposure to even low levels of air pollution is associated with mortality. Opening up for a long latency period, our findings indicate that air pollution exposures over time may be even more harmful than anticipated.

1. Introduction

Air pollution is one of our major global health threats, and 99 % of the world's population breathes air that exceed the recommended limit values in the World Health Organization (WHO) air quality guidelines 2021 (World Health Organization, 2021). Several epidemiological studies have established associations between long term exposure to air pollution and mortality. However, the exposure assessment time varied among these studies, with some using exposure data at a single time point (Stafoggia et al., 2022), while others applied time-varying exposure assessment (Bentayeb et al., 2015; Huang et al., 2023). A small number of studies have looked at air pollution exposure over different time periods in association with mortality (Hansell et al., 2016; Sommar et al., 2021). Moreover, even fewer studies have compared mortality risk from different time periods representing multiple decades within the same population cohort (Hansell et al., 2016; Laden et al., 2006). However, these studies have reported conflicting results. For instance, the extended follow-up of the Harvard Six Cities Study found slightly higher all-cause mortality risk associated with exposure during 1980–1985 compared to 1990–1998 (Laden et al., 2006), whereas the study by Hansell et al. (2016) observed higher mortality risk linked to more recent exposures. The follow-up of the American Cancer Society Study did not find clear differences in the risk of $PM_{2.5}$ exposure between periods of 1–5, 6–10 and 11–15 years before death (Krewski et al., 2009). The variation in the risk of air pollution over time may be attributed to shifts in pollutants' sources, composition and toxicity, changes in environmental and socioeconomic conditions, modification in behavioral patterns and lifestyles, environmental policies and regulations and public health interventions (Tainio et al., 2021; Valavanidis et al., 2008). Knowledge of particularly important time periods for harmful effects of air pollution exposures with regard to mortality would be valuable from a public health perspective, to improve longevity and ensure healthier lives.

Another important environmental exposure is greenness, which has shown to be potentially health-promoting according to several proposed mechanisms, including increasing physical activity levels and reducing stress and exposure to noise and traffic-related air pollutants (Hartig et al., 2014; Yang et al., 2021a). A growing body of literature has investigated the effects of greenness exposure on mortality. Several studies have suggested an inverse association between greenness exposure and all-cause mortality (Rojas-Rueda et al., 2019; Yuan et al., 2021), but results are inconsistent with cohort studies from China and the Netherlands that did not detect such associations (Ji et al., 2019; Klompmaker et al., 2020). Furthermore, vegetation could potentially mitigate air pollution (Setälä et al., 2013), but evidence for the interplay between air pollution and greenness remains unclear.

Using the Respiratory Health in Northern Europe (RHINE) study, we aimed to investigate the association of exposure to air pollution and greenness with all-cause mortality at different exposure time windows spanning across three decades. Low-level air pollution was defined as the concentrations below the current European Union (EU) limit values or the 2021 WHO air quality guideline. Considering both EU standards and WHO health recommendations allows for a comprehensive assessment of low-level air pollution. The EU has established annual average limit values of 25 $\mu g/m^3$ for $PM_{2.5}$, 40 $\mu g/m^3$ for PM_{10}, and 40 $\mu g/m^3$ for NO_2. The 2021 WHO air quality guideline recommends even lower annual average values of 5 $\mu g/m^3$ for $PM_{2.5}$, 15 $\mu g/m^3$ for PM_{10}, and 10 $\mu g/m^3$ for NO_2.

2. Materials and methods

2.1. Study population

In the present study we used data from RHINE, with its study centers, Reykjavik (Iceland); Umea, Uppsala and Gothenburg (Sweden); Aarhus (Denmark); Bergen (Norway) and Tartu (Estonia) (RHINE Study Homepage 2022). The flowchart of our study with map of the centers is shown in Fig. 1. RHINE is a large prospective cohort study initiated in 1990–1994, with longitudinal assessment of environmental exposures, respiratory symptoms and diseases in 1999–2001 (RHINE II) and 2010–2012 (RHINE III). Information on the cohort has been provided in detail elsewhere (Janson et al., 2018; Johannessen et al., 2014; Toren et al., 2004). Based on availability of covariates, we used data from RHINE III participants in 2010 (then aged between 40 and 65 years), as our target population (n = 13,656) and followed them with regard to mortality until 31st December 2021. In addition, we included retrospective environmental air pollution and greenness exposure assessment for these RHINE III participants in year 1990 and 2000, as well as in year 2010. In this manner, we were able to analyse different time periods in a scope we believe have not previously been undertaken.

Informed consent was obtained from each participant prior to each follow-up. The study was approved by the Regional Committees for Medical and Health Research Ethics according to national legislations (RHINE Study Homepage 2022).

2.2. Mortality data

Mortality data from 1990 to 2021 for the RHINE participants was extracted from the national cause of death registries of each study center. The data included date of death for all-cause mortality in all centers. Because the covariates included in our main analyses were only available in the RHINE III study in 2010, we analyzed mortality data from 2010 to 2021. However, in a sensitivity analysis we also included all deaths from 1990 onwards.

2.3. Exposure assignment

We assigned estimates of exposure to air pollution and greenness based on participants' residential addresses in the years 1990, 2000 and 2010, retrieved from National Population Registries at each study wave. In addition, we assigned exposure estimates of each participant for every year between 1990 and 2010 to make a 20-year averaged exposure. Specifically, we allocated the same exposure of air pollution and greenness in 1990, 2000, 2010 to the adjacent years if the participants lived at the same address during those years, by taking the year of moving between addresses into account. The moving history over the follow-up period was reconstructed based on the question "Year of moving into current home?" from the RHINE II and III questionnaires.

2.4. Air pollution data

Except for Tartu, annual average residential concentrations of fine particulate matter (with diameter $\leq$ 2.5 micrometer (μm), $PM_{2.5}$; and with diameter $\leq$ 10 μm, PM_{10}), nitrogen dioxide (NO_2), near-surface ozone (O_3) and black carbon (BC) were estimated based on a combination of the long-range air pollution model, the Danish Eulerian Hemispheric Model (DEHM) (Brandt et al., 2012) covering the Northern Hemisphere, and the local scale Urban Background Model (UBM) (Brandt et al., 2001a, 2001b, 2003; Frohn et al., 2022) for the years

1990, 2000 and 2010. The DEHM model is a comprehensive Eulerian 3D chemistry-transport model covering the Northern Hemisphere. It effectively captures the crucial atmospheric transport, mixing, and removal (both dry and wet) processes that play a significant role in the transport and transformation of air pollutants on both the hemispheric and regional scales (Brandt et al., 2012). The UBM is a multi-source model with a Gaussian approach for horizontal dispersion and a linear approach for vertical dispersion up to the boundary layer and a horizontal resolution of 1 km × 1 km covering the Nordic countries. The UBM is suitable for modelling local scale air pollution concentrations and is e.g. used for epidemiological studies in the Nordic countries (Frohn et al., 2022). The DEHM/UBM results applied in this study are based on the NordicWelfAir model results covering Denmark, Finland, Iceland, Norway and Sweden for the time period 1979–2018 (Frohn et al., 2022; Paunu et al., 2021). During the NordicWelfAir project, a thorough evaluation was conducted on the DEHM/UBM model. The modelled daily, monthly, and annual averages of $PM_{2.5}$, NO_2, and O_3 were compared with available measurements from the Nordic countries (Denmark, Finland, Norway, and Sweden) for the time periods 1979–2016 and 1990–2016 (Frohn et al., 2022). The evaluation indicated moderate to high model performance of the DEHM/UBM model, showing variations in performance across different pollutants and countries. Specifically, correlation coefficients between the model results and measurements were 0.83, 0.72, and 0.76 for NO_2; 0.70, 0.60, and 0.73 for O_3; and 0.43, 0.56, and 0.96 for $PM_{2.5}$ in Denmark, Norway, and Sweden, respectively (Frohn et al., 2022).

In Tartu center, the data of BC and O_3 were not available during the study period, and annual mean concentrations of $PM_{2.5}$, PM_{10} and NO_2 were modelled using the Eulerian air quality dispersion model with the resolution of 1 km × 1 km across Estonia that is part of the Airviro Air Quality Management System (AirViro, 2011). Airviro is a widely used web-based air pollution data management tool that uses data on air emission, level of air pollution and meteorological variables, and has been implemented in several epidemiological studies (Orru et al., 2011; Orru et al., 2018).

2.5. Greenness data

The exposure to vegetation was measured by the Normalized Difference Vegetation Index (NDVI), a satellite-image-based vegetation index from the cloud-free Landsat 4–5, Thematic Mapper (TM) and Landsat 8 Operational Land Imager (OLI). NDVI ranges from −1 to 1, with higher positive value indicating denser vegetation. We recoded negative NDVI values to zero in the statistical analysis, in accordance with other studies within this field (Bereziartua et al., 2022; Crouse et al., 2017). Satellite images of the area of interest were retrieved every 5 years from 1984 to 2014 in the months with the most abundant vegetation (May, June, July) (Supplementary Material Table S1 and S2), and the years closest to the RHINE data collection time points were chosen as greenness exposure years. In this way, we defined the greenness as the yearly mean NDVI value from May, June and July. We used pixels within 300 m circular buffer zone around each participant's home addresses in the analysis, in accordance with recommendations by the WHO (WHO, 2016).

2.6. Exposure time windows

Individuals were assigned annual mean levels of air pollution and mean exposure to greenness at four different time windows: 1) exposure in 1990, 2) exposure in 2000, 3) exposure in 2010 and 4) average levels of exposures between 1990 and 2010. However, due to missing moving year information for some individuals, fewer subjects had average exposure estimates for the 1990–2010 period than those with individual year-specific assessments. To ensure a direct comparison of estimates,

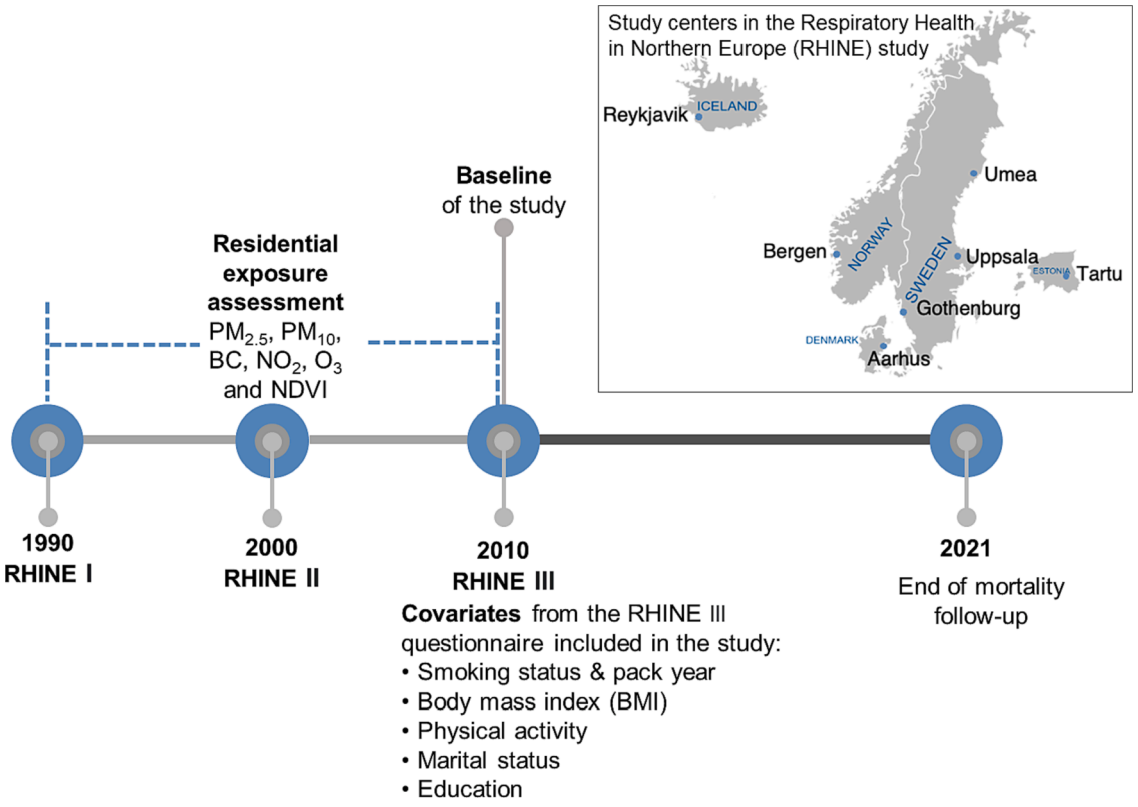

Fig. 1. Map of study center in the Respiratory Health in Northern Europe (RHINE) Study. Illustration of study population, data source and linkage for modeling. Abbreviation: $PM_{2.5}$ = particulate matter with an aerodynamic diameter less than 2.5 μm; PM_{10} = particulate matter with an aerodynamic diameter less than 10 μm; BC = black carbon; NO_2 = nitrogen dioxide; O_3 = ozone; NDVI = normalized difference vegetation index; RHINE = Respiratory Health in Norther Europe.

we incorporated only the exposure time windows of 1990, 2000, and 2010 into the main analysis. The outcomes of average exposure time windows, alongside other exposure time windows using the same study population, were included in the sensitivity analysis.

2.7. Statistical analysis

Spearman's coefficients between environmental exposures across different exposure time periods were estimated to assess degree of correlation. We also examined the correlation of air pollutants and greenness among non-movers during 1990–2010 to assess the exposure dynamic and potential trends. We applied Cox proportional hazards regression with study center and sex as strata variables to assess the associations between air pollution and greenness and mortality, with age as the underlying time scale (Strak et al., 2021). Study center was included as a strata to account for regional heterogeneity (Samoli et al., 2021). The Cox regression model included a left truncation adjustment for age at the RHINE III follow-up. Right-censoring occurred at the time of event, or end of follow-up, whichever came first. Schoenfeld residuals were used to test the proportional hazards (PH) assumption.

Associations were estimated for the various exposure time windows (Fig. 1) using different adjustment sets. Model 1 included only time scale (age) and strata variables (sex and study center). Model 2 further adjusted for covariates from RHINE III: body mass index (BMI, as BMI $<$ 25, 25–30, $\geq$30), smoking (never smokers, former light smokers with pack years $\leq$ 10, former moderate to heavy smokers with pack years $>$ 10, current light smokers with pack years $\leq$ 10, current moderate to heavy smokers with pack years $>$ 10), education level (primary school, secondary school, college/university), marital status (married or cohabiting, single or widowed, divorced or separated), and physical activity level (never, less than once a week, once a week, 2–3 times a week, almost everyday). Model 3 further included mutual adjustment for individual air pollutant and NDVI in the same model. The associations were expressed as hazard ratios (HR) with 95 % confidence intervals for the following increments: 5 $\mu g/m^3$ for $PM_{2.5}$, 10 $\mu g/m^3$ for PM_{10}, NO_2 and O_3, 0.4 $\mu g/m^3$ for BC, and 0.1 unit for NDVI.

We evaluated the assumption of linearity of the associations between air pollution and mortality through the likelihood-ratio test, comparing the linear model and the restricted cubic spline model with 3 or 4 degrees of freedom. Additionally, we employed the Bayesian information criterion (BIC) to compare the relative goodness-of-fit of linear and spline models. We chose to use the BIC because BIC is often considered more appropriate than the Akaike information criterion (AIC) when the goal of modeling is explanation rather than prediction (Shmueli, 2010). We further assessed the shape of concentration–response association air pollution and greenness with mortality using restricted cubic spline with three degrees of freedom.

We investigated the interaction between NDVI and each air pollutant by introducing the corresponding interaction term. Sensitivity analyses were conducted to test the robustness of our findings. First, given that a different air pollution assessment model was used for Tartu study center, we excluded the participants from Tartu. Second, recognizing that physical activity and BMI may act as mediators in the association between greenness exposure and mortality, we ran the models without adjustment for physical activity and BMI in the NDVI-mortality association. Third, we analyzed subjects with available moving year information to compare estimates for average exposure time windows with other time windows using the same study population. Fourth, since the main analyses only included deaths after 2010 to ensure availability of covariate information from RHINE III, we also analyzed unadjusted associations between air pollutants and greenness exposure in 1990 in relation to all-cause mortality in the larger time period of 1990–2010.

We performed a complete case dataset analysis, excluding participants with missing exposure exposure data for 1990, 2000 and 2010, as well as missing covariate data. Data analyses were performed using Stata statistical software (version 17.0, Stata Corporation, College Station, Texas, USA) and R software (version 4.2.1; R Project for Statistical Computing).

3. Results

The RHINE III survey involved a total of 13,656 subjects aged 40–65 years in 2010. Of these, only 10,914 participants had exposure assessments available for the three time points: years 1990, 2000 and 2010. Due to missing covariate data for some additional participants, 9,135 participants were included in the main analysis. Among them, we observed 327 deaths occurring from 2010 to 2021. Table 1 presents the general characteristics of RHINE III participants who were included in the analysis. The concentrations of $PM_{2.5}$, PM_{10}, BC and NO_2 in 1990 were on average higher than the concentrations in 2000 and 2010, and the standard deviation in regard to the mean were also higher in 1990 compared to other exposure windows, indicating a higher variation of exposure concentrations in 1990 (Table 2). Mean levels of air pollution during 1990 and 2010 were far below the EU standards, but about 75 % of the participants were exposed to $PM_{2.5}$ and NO_2 levels above the WHO 2021 air quality guideline (AQG), and over half of participants were exposed to PM_{10} lower than the WHO 2021 AQG value (Fig. 2). The NDVI variability was highest in Aarhus center (Fig. 2). Supplementary Material Table S3 presents the correlation coefficients between the

Table 1
Characteristics of the RHINE III participants (n = 9,135).

Characteristics	Number of participants (%)	Number of deaths 2010–2021 (%)
Study center		
Aarhus	1,831 (20.0 %)	76 (4.2 %)
Bergen	1,445 (15.8 %)	41 (2.8 %)
Gothenburg	1,349 (14.8 %)	57 (4.2 %)
Umea	1,343 (14.7 %)	52 (3.9 %)
Uppsala	1,536 (16.8 %)	36 (2.3 %)
Reykjavik	1,154 (12.6 %)	44 (3.8 %)
Tartu	477 (5.2 %)	21 (4.4 %)
Sex		
Male	4,255 (46.6 %)	184 (4.3 %)
Female	4,880 (53.4 %)	143 (2.9 %)
Age		
40–44 years	1,612 (17.7 %)	20 (1.2 %)
45–49 years	1,871 (20.5 %)	30 (1.6 %)
50–54 years	1,937 (21.2 %)	62 (3.2 %)
55–54 years	1,835 (20.1 %)	82 (4.5 %)
60–65 years	1,880 (20.6 %)	133 (7.1 %)
Smoking status		
Never smoker	4,743 (51.9 %)	108 (2.3 %)
Former smoker with pack years $\leq$ 10	1,574 (17.2 %)	40 (2.5 %)
Former smoker with pack years $>$ 10	1,433(15.7 %)	74 (5.2 %)
Current smoker with pack years $\leq$ 10	371 (4.1 %)	16 (4.3 %)
Current smoker with pack years $>$ 10	1,014 (11.1 %)	89 (8.8 %)
Body mass index (kg/m^2)		
$<$25.0	4,154 (45.5 %)	129 (3.1 %)
25.0–30.0	3,630 (39.7 %)	128 (3.5 %)
$\geq$30.0	1,351 (14.8 %)	70 (5.2 %)
Marital status		
Married or cohabiting	7,205 (75.5 %)	207 (2.9 %)
Single or widowed	1,091 (11.6 %)	76 (7.0 %)
Divorced or separated	839 (8.9 %)	44 (5.2 %)
Education		
Primary school	1,032 (11.3 %)	67 (6.5 %)
Secondary school	3,885 (42.5 %)	150 (3.9 %)
College or university	4,218 (46.2 %)	110 (2.6 %)
Physical activity		
Never	735 (8.1 %)	59 (8.0 %)
Less than once a week	1,273 (13.9 %)	45 (3.5 %)
Once a week	1,697 (18.6 %)	52 (3.1 %)
2–3 times a week	3,481 (38.1 %)	99 (2.8 %)
Almost every day	1,949 (21.3 %)	72 (3.7 %)

Table 2
Annual mean level of air pollution and greenness at different time points and 20-year annual mean level.

Time Point	Exposure in 1990		Exposure in 2000		Exposure in 2010		Mean exposure in 1990–2010[b]	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
$PM_{2.5}$ (μg/m^3)	9,135	9.98 (4.61)	9,135	7.40 (2.86)	9,135	6.91 (2.63)	7,954	8.16 (3.19)
PM_{10} (μg/m^3)	9,135	17.24 (7.19)	9,135	13.69 (4.67)	9,135	12.80 (5.54)	7,954	14.65 (5.18)
BC (μg/m^3)[a]	8,658	0.47 (0.29)	8,658	0.43 (0.24)	8,658	0.44 (0.26)	7,491	0.44 (0.24)
NO_2 (μg/m^3)	9,135	15.67 (7.90)	9,135	13.98 (7.17)	9,135	13.39 (7.58)	7,954	14.31 (7.01)
O_3 (μg/m^3)[a]	8,658	54.84 (6.69)	8,658	56.69 (6.62)	8,658	55.35 (5.38)	7.491	55.34 (5.95)
NDVI	9,135	0.27 (0.16)	9,135	0.32 (0.15)	9,135	0.38 (0.13)	7,954	0.31 (0.13)

Abbreviation: $PM_{2.5}$ = particulate matter with an aerodynamic diameter less than 2.5 μm; PM_{10} = particulate matter with an aerodynamic diameter less than 10 μm; BC = black carbon; NO_2 = nitrogen dioxide; O_3 = ozone; NDVI = normalized difference vegetation index; SD = standard deviation.

[a] The BC and O_3 data were not available at Tartu center, resulting in fewer observation for BC and O_3 compared to other exposure variables.

[b] The annual mean exposure for the period of 1990–2010 was estimated based on the year of moving between addresses during the follow-up period. However, some respondents did not provide responses to the questionnaire questions regarding the year of moving into their current home. As a result, the number of subjects included in the analysis with mean exposure estimates was lower than those with individual year-specific assessments.

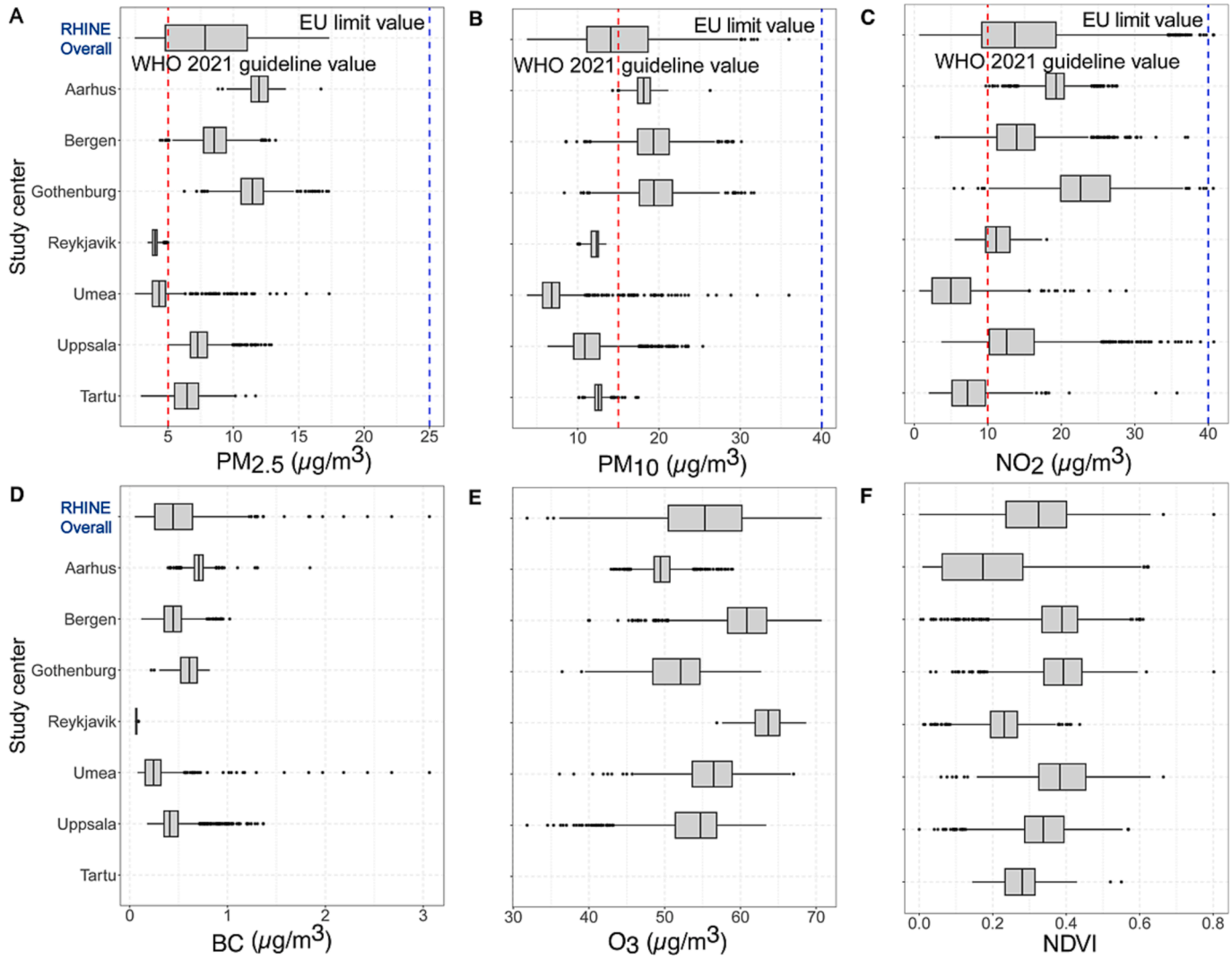

Fig. 2. Distribution of $PM_{2.5}$, PM_{10}, NO_2, BC, O_3 and NDVI at different study centers using 20 year annual average exposure between 1990 and 2010. Comparison of 20 year annual average exposure with the current EU limit values and 2021 World Health Organization (WHO) air guildeline values. In each box plot, the median value is indicated by a vertical line in the box. The whiskers stop at minimum and maximum. Abbreviation: $PM_{2.5}$ = particulate matter with an aerodynamic diameter less than 2.5 μm; PM_{10} = particulate matter with an aerodynamic diameter less than 10 μm; BC = black carbon; NO_2 = nitrogen dioxide; O_3 = ozone; NDVI = normalized difference vegetation index; RHINE = Respiratory Health in Norther Europe.

different environmental variables in the four exposure time windows. $PM_{2.5}$, PM_{10}, NO_2 and BC were highly correlated with each other within exposure time windows. O_3 had a moderate to high negative correlation with $PM_{2.5}$, PM_{10}, NO_2 and BC. In general, NDVI was negatively correlated with $PM_{2.5}$, PM_{10}, BC and NO_2 in all exposure windows. Supplementary Material Table S4 displays the correlation coefficients of the

same exposure variables from different exposure time periods among all participants, ranging from −0.08 (NDVI in 1990 and NDVI in 2010) to 0.87 (BC in 2000 and BC in 2010). Approximately 64% of participants indicated they had relocated their residence between the RHINE I and RHINE III study follow-up. Furthermore, the correlation coefficients of the environmental variables among non-movers during study period across different exposure time windows were higher than the correlation among the overall participants (Supplementary Material Table S5).

Overall, the models showed that $PM_{2.5}$, PM_{10}, BC and NO_2 at different exposure time windows had adverse effects on all-cause mortality. However, none of these increased risks reached statistical significance, except for the association between particulate matter exposure in 1990 and mortality (Fig. 3). The adjusted hazard ratio per increment in exposures assessed in 1990 were 1.40 (95 % CI: 1.04–1.87) per 5.00 μg/m^3 for $PM_{2.5}$, 1.33 (95 % CI: 1.02–1.74) per 10 μg/m^3 in PM_{10}, 1.16 (95 % CI: 0.98–1.38) per 0.4 μg/m^3 in BC and 1.17 (95 % CI: 0.92–1.50) per 10 μg/m^3 in NO_2. We observed a small change in the association estimates after the adjustment (Fig. 3. **Model 1** versus **Model 2**). The adjusted association estimates of $PM_{2.5}$ and PM_{10} were slightly lower than the unadjusted estimates for exposure in 1990, 2000 and 2010. In the single exposure model, we did not observe any statistically significant associations between O_3 and greenness exposure and mortality in any of the exposure time windows. When assessing the linearity assumption, we found that the p-value of the likelihood-ratio test was consistently above 0.05, indicating that our data is not better described with a restricted cubic spline model than with a linear model (Supplementary Material Table S6). Additionally, BIC values were smaller in the linear model compared to the spline model, suggesting that the linear model provided a better fit than the spline model (Supplementary Material Table S7). Supplementary Material Figure S1 shows the shape of the concentration–response association between air pollution and greenness with mortality using restricted cubic splines with three degrees of freedom.

In the two-exposure model, the adjustment for NDVI resulted in increased HRs for $PM_{2.5}$, PM_{10}, BC and NO_2 in exposure in 1990, O_3 exposure in 1990 was found to be inversely associated with mortality after adjusting for NDVI (Table 3). In addition, it is worth noting that in the 2000 exposure, NDVI was positively associated with mortality after adjusting for air pollutants, as shown in Table 3. There was no interaction between NDVI and air pollution on mortality (Supplementary Material Table S8). After excluding Tartu center in the sensitivity analysis the results were in general consistent with the main findings (Supplementary Material Table S9). The model examining the association between NDVI and mortality without adjustment for physical activity and BMI yielded consistent results with those obtained from the main analysis (Supplementary Material Table S10). The results from averaged exposure time windows and other exposure time windows remained consistent with those of the main analysis (Supplementary Material Table S11). The unadjusted associations between exposure in 1990 and mortality from 1990 to 2021 were consistent with the main findings, but with a higher precision (Supplementary Material Table S12).

4. Discussion

This study investigated air pollution and greenness exposure with all-cause mortality in 9,135 participants in the third survey of RHINE study, followed from 2010 to 2021, with additional retrospective environmental exposure assessment in year 1990 and 2000. We observed a significant association between higher exposure to $PM_{2.5}$ and PM_{10} in 1990, when age was 20–45 years, and an increased risk of all-cause mortality 20–30 years later. Indications of increased mortality risk were also observed with higher BC and NO_2, but none of these increased risks reached statistical significance in adjusted models. In the single exposure model, no associations were found between the O_3 and greenness exposure at any of the investigated time points and mortality. However, in the two-exposure model, after adjusting for NDVI, an inverse relationship was observed between O_3 exposure in 1990 and mortality, and increased HRs for $PM_{2.5}$, PM_{10}, BC and NO_2 were observed for the 1990 exposure after adjustment for NDVI. Furthermore, NDVI exposure in 2000 was found to be positively associated with mortality after controlling for air pollutants.

The observed concentrations of air pollutants in the RHINE study centers are relatively homogeneous, but with certain differences; the differences may reflect the regional dissimilarities in historical and current emissions through industry, traffic and agriculture. Reykjavik and Umea centers with high latitude had relatively lower levels of air pollutants than other centers; this is in line with the finding from the ELAPSE study, where Strak et al. (2021) reported a north-to-south upward gradient of air pollution exposure in Europe. In general, our study participants had lower air pollution exposure than those in other cohort studies (Shi et al., 2022; So et al., 2022; Strak et al., 2021; Zhang et al., 2021).

Associations with mortality were only observed with particulate matter exposure using the exposures in 1990. Additionally, the association between $PM_{2.5}$ and NO_2 with mortality using the exposure in 1990 was stronger compared to 2000 and 2010, but the association did not reach significant level for the exposure in 2000 and 2010. Air pollution levels in the RHINE study area was higher in 1990 than in 2000 and 2010, which aligns with time trends in air pollution in Europe during that period. Despite this, the underlying mechanism for why 1990 exposures appear more harmful than more recent exposures probably lies elsewhere.

One plausible explanation for why the 1990 exposure and not more recent exposures increased mortality risk in our study is that the most distant exposure time window was closer to childhood exposures. A study from California showed that air pollution is negatively associated with pre-adolescent airway growth, which could be of importance for mortality risk when individuals are aging (Gauderman et al., 2015). The higher association estimates in the 1990 exposure in our study may be because the exposure levels in 1990 were correlated with such earlier life exposure (Hansell et al., 2016). We observed greater variability in the 1990 exposure, suggesting that these exposures may have more power to capture potential effects of air pollution. Notably, the air pollution levels were higher in 1990 compared to the more recent exposures. However, it is essential to acknowledge that the measurements and data availability might have been limited in 1990, potentially leading to an underestimation of the true air pollution levels during that time. Additionally, we observed varying correlation coefficients of the same air pollutants across the exposure time windows of 1990, 2000, and 2010 among non-movers and overall participants, indicating potential spatial variation in their relationships. The weaker correlation between pollutants in 2010 and 1990 renders it likely that also associations in the main analyses will be different using 2010 exposures and 1990 exposures. It is also possible that changes in emission source and composition of particulate matter over time may contribute to the observed spatial variation in air pollutant levels over time. The composition of particulate matter in 1990 might have been more toxic than in 2010, further contributing to potential differences in mortality risks observed between the three exposure periods. Prolonged exposure during this critical period may lead to a higher cumulative dose of pollutants, resulting in potential long-lasting effects on health. Furthermore, it is probable that air pollution exposure of relatively low levels (as we have in the study area) must accumulate over time in order to harm health, which renders it likely that exposure far back in time is more important than exposure in recent times - in the same manner as cigarette exposure has a long latency period before disease develops, it is normally not acutely harmful in lower doses but definitely harmful when accumulated over a longer period of time (LaCroix et al., 1991). These complexities highlight the importance of considering temporal and spatial factors when studying the impact of air pollutants on mortality.

Our findings on particulate matter exposure align with previous

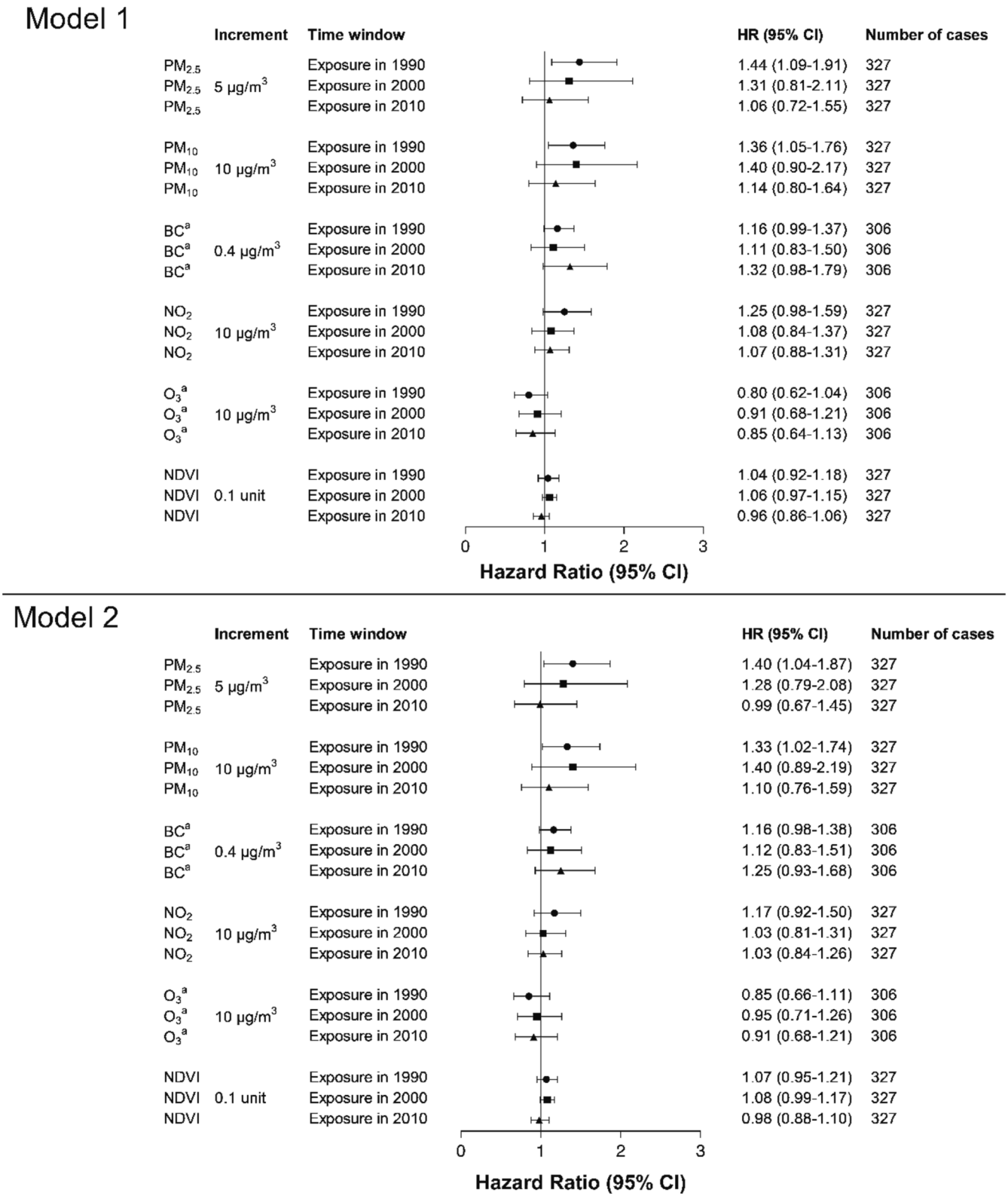

Fig. 3. Hazard ratio and 95 % confidence interval (CI) for all-cause mortality associated with per fixed increment increase in air pollution and greenness. The increment of the exposure is as follows: 5 μg/m^3 for $PM_{2.5}$, 10 μg/m^3 for PM_{10}, NO_2 and O_3, 0.4 μg/m^3 for BC, and 0.1 unit for NDVI. Model 1 included age (as timescale), sex (strata) and study center (strata). Model 2: model 1 further adjusted for smoking status, pack-years of smoking, body mass index, education, physical activity and marital status. Abbreviation: $PM_{2.5}$ = particulate matter with an aerodynamic diameter less than 2.5 μm; PM_{10} = particulate matter with an aerodynamic diameter less than 10 μm; BC = black carbon; NO_2 = nitrogen dioxide; O_3 = ozone; NDVI = normalized difference vegetation index; IQR = interquartile range. [a] The BC and O_3 data were not available at Tartu center, resulting in fewer observations for BC and O_3 compared to other exposure variables.

Table 3
Hazard ratio (HR) (95 % confidence interval (CI)) for the associations of air pollution and greenness with all-cause mortality from two exposure model.

Exposure		Exposure in 1990	Exposure in 2000	Exposure in 2010
		HR (95 % CI)	HR (95 % CI)	HR (95 % CI)
$PM_{2.5}$	+NDVI	1.48 (1.11–1.97)	1.42 (0.88–2.31)	0.97 (0.65–1.44)
PM_{10}	+NDVI	1.40 (1.07–1.82)	1.54 (0.98–2.41)	1.09 (0.74–1.60)
BC	+NDVI	1.19 (1.01–1.40)	1.21 (0.91–1.60)	1.26 (0.91–1.73)
NO_2	+NDVI	1.32 (1.00–1.72)	1.12 (0.87–1.45)	1.02 (0.81–1.27)
O_3	+NDVI	0.75 (0.56–1.00)	0.85 (0.62–1.15)	0.91 (0.66–1.25)
NDVI	+$PM_{2.5}$	1.11 (0.98–1.26)	1.09 (1.00–1.18)	0.98 (0.88–1.09)
NDVI	+PM_{10}	1.11 (0.98–1.25)	1.09 (1.01–1.19)	0.99 (0.89–1.11)
NDVI	+BC	1.09 (0.96–1.24)	1.09 (1.00–1.19)	1.01 (0.90–1.13)
NDVI	+NO_2	1.13 (0.99–1.30)	1.09 (1.00–1.19)	0.99 (0.88–1.11)
NDVI	+O_3	1.14 (0.99–1.31)	1.09 (1.00–1.20)	0.99 (0.88–1.12)

Models include each pollutant + NDVI and are adjusted for smoking status, pack-years of smoking, body mass index, education, physical activity and marital status. Abbreviation: PM2.5 = particulate matter with an aerodynamic diameter less than 2.5 μm; PM10 = particulate matter with an aerodynamic diameter less than 10 μm; BC = black carbon; NO2 = nitrogen dioxide; O3 = ozone; NDVI = normalized difference vegetation index.

cohort studies, demonstrating that long-term exposure to low-level $PM_{2.5}$ and PM_{10} is associated with an increased risk of all-cause mortality (Shi et al., 2022; So et al., 2022; Stafoggia et al., 2022). Similarly to our study, the Danish Nurse cohort study employed comparable exposure assessment methods. So et al. (2022) reported a lower effects estimates for the association between $PM_{2.5}$ (1.06, 95 % 1.01–1.10 per 4.39 μg/m^3) and PM_{10} (1.06, 95 % CI 1.01–1.11 per 5.20 μg/m^3) with total mortality. However, slight differences in exposure increments existed between their study and ours. Furthermore, the mean $PM_{2.5}$ (20.5 μg/m3) and PM_{10} (24.4 μg/m3) levels in 1993 or 1999 in the Danish study were higher compared to the levels in our 1990 exposure. In contrast, we did not find an association between $PM_{2.5}$ exposure using the 2010 exposure, while ELAPSE study reported a natural cause mortality of 1.13 (95 % CI 1.11–1.16) per 5 μg/m^3 increase in $PM_{2.5}$ using the exposure in 2010. Notably, the concentration of $PM_{2.5}$ in our study's 2010 exposure was much lower (6.91 μg/m^3) compared to the ELAPSE study (15.02 μg/m^3) (Strak et al., 2021). This reduction in pollution levels might have attenuated the observed effects, which could lead to the weaker effects we observed with the 2010 exposure. Additionally, it is noteworthy that a study conducted in Northern Sweden by Sommar et al. (2021) aligns with our findings. They did not find a statistically significant association between exposure to $PM_{2.5}$, NO_2, BC, and O_3 and natural cause mortality using annual average exposure data spanning from 1990 to 2014. Interestingly, the air pollution levels in their study were slightly lower than those in our study. Furthermore, when comparingour study area in Northern Europe with regions such as Sweden, Denmark, France, the Netherlands, Germany, and Austria, as examined in the ELAPSE study during the same period, we found that our study area had notably lower pollution levels in 2010. While our study consistently aligns with previous research in showing associations between long-term PM exposure and all-cause mortality, the variations in pollutant concentrations and methodological differences across studies emphasize the need for region-specific analyses and considerations.

We did not detect statistically significant associations between BC and NO_2 with mortality, although indications of increased mortality was observed in relation to levels of BC and NO_2. Previous epidemiological evidence has well-documented the mortality risk associated with NO_2 and BC exposure (Shi et al., 2022; So et al., 2022; Yang et al., 2021b). The discrepancies in effects estimates may be explained by various factors, such as differences in study populations' characterictics, exposure assessment methods, exposure levels, pollution mixture, time window, and confounders (Hoek et al., 2013; Yang et al., 2021b). Different geographic areas between studies also yield differences in study populations and socioeconomic contexts which could play a role in the varying associations. The impacts of air pollution on mortality can be influenced by numerous intricate variables that interact differently in diverse settings. For example, comparing our study in a low-pollution region with those in high-pollution urban or industrial areas reveals significant differences in exposure profiles. Urban areas with elevated pollution levels expose residents to a mix of pollutants from vehicles and industry, influencing mortality. Socioeconomic factors, healthcare access, and behaviors may also differ, modifying air pollution's health effects (Geng et al., 2021). The mean age of people who died in our study was 62 years old. Since the average life expectancy in all RHINE study centers is over 75 years, the majority of the deaths in our study can be categorized as premature. In that regard, our findings suggest that exposure to particulate matter yields an increased risk of dying prematurely. The tendencies observed in the unadjusted and adjusted model were similar, with estimates slightly lower in the adjusted model. This observation is in line with previous studies, which have suggested that the magnitude and strength of the association between air pollution and mortality is reduced as additional covariates are adjusted for in the model (Hanigan et al., 2019; Hvidtfeldt et al., 2019). Considering these complexities is crucial when interpreting and comparing findings with other studies, enhancing the understanding of the impact of air pollution on mortality.

Findings from past epidemiological studies on long term exposure to O_3 and mortality have been heterogeneous. Similar to previous studies (Hvidtfeldt et al., 2019; Strak et al., 2021), we observed an indication of inverse relationship between O_3 and mortality. However, several studies have reported a positive association between O_3 and mortality (Lim et al., 2019; Turner et al., 2016). A meta-analysis reported that the effects of O_3 differ by age and employment status, sex and race/ethnicity (Bell et al., 2014), thus, the difference in the target population might be one explanation for the variations in the effect estimates. In addition, there is often a distinct pattern with lower O_3 concentrations in urban areas due to the higher NO_2 emissions from traffic in these areas, which is a causal effect of the chemistry in the atmosphere. However, the inverse correlations between O_3 and the particulate components may also be due to O_3 being high in summer (due to photochemical effects) where particulate matter is low because the residential wood combustion is low. The association between O_3 and adverse health outcomes might therefore be masked by other pollutants.

For greenness, the mean NDVI between 1990 and 2010 in our study was 0.31 (mean value ranges 0.27–0.38 across the three time points), which was lower than the mean NDVI of 0.58 in the Canadian cohort (Crouse et al., 2017) and 0.33 of ELAPSE pooled cohort (Bereziartua et al., 2022). Similar to the Canadian study, we calculated greenness value from the most abundant vegetation months during the year, while the ELAPSE study used the mean value from summer and winter seasons. Both the Canadian and ELAPSE cohorts found protective effects of greenness exposure on mortality (Bereziartua et al., 2022; Crouse et al., 2017). By contrast, we did not observe significant associations between greenness exposure and mortality. Potential pathways linking greenness to health can be summarized in three domains, including reducing harm (e.g. mitigating exposure to air pollution), restoring capacities (e.g. recovery from stress) and building capacities (e.g. facilitating social cohesion) (Markevych et al., 2017). Greenness affects air quality because green space are less likely to have sources of air pollution emissions and also the concentration of air pollutants is likely to be reduced through deposition and dispersion (Janhäll 2015). In our study, we did not find a significant interaction between greenness and air pollution. Similarly, Kasdagli et al. (2021) reported no synergistic effects of greenness and air pollution on natural-cause mortality. By contrast, Crouse et al. (2019) suggested that decreasing risks of mortality associated with exposure to $PM_{2.5}$ among individuals in each successive quintile of increased greenness. Kim et al. (2019) also found interaction between PM_{10} and greenness on all-cause mortality, while the relationships differed in cause-specific mortality. Contrary to our expectations, we observed higher risk of $PM_{2.5}$, PM_{10}, BC and NO_2 exposure in

1990 on mortality after adjustment for greenness compared to before adjustment. Comparatively, the association between air pollution and mortality was suggested to be attenuated after adjusting for greenness (Crouse et al., 2019; James et al., 2016). Furthermore, in constrast to previous studies (Bereziartua et al., 2022; Crouse et al., 2019), we found positive association between the NDVI exposure in 2000 and mortality after adjustment for for air pollutants. This may reflect a potentially complex relationship between air pollution and greenness (NDVI) with mortality. One possible explnantion is that in 2000, certain areas with higher NDVI might have experienced elevated air pollution due to various factor such as urbanization, air pollution entrapment under tall trees, or traffic congestion. Consequently, people living in those areas might have been exposed to both higher air pollution and increased NDVI. Another plausible explanation is the potential for confounding or effect modification. Factors like socioeconomic status, lifestyle behaviors, or health conditions might differ between regions with varying levels of greenness, influencing the observed association between NDVI with mortality. To better understand the underlying mechanisms, further investigations of the mortality effects of exposure to greenness are warranted.

The strengths of our study are first that we investigate associations of air pollution and greenness exposure with mortality at different exposure time windows, with the most distant time window being as far back in time as three decades. Secondly, this is a multi-center prospective cohort study with individual information on various potential confounders, which allowed for more comprehensive analysis minimising the risk that the results were caused by confounding. Thirdly, we used state-of-the-art atmospheric chemical transport models, which enabled an assessment exposure covering many years. Also, the possibility in Northern Europe to link the research data with national registry data, as well as to follow up the same participants over decades, are important strengths.

Nevertheless, the present study has several limitations. First, the participants were relatively young, resulting in a relatively small number of deaths, and as a consequence limited statistical power. Cause-specific mortality data was only available in Bergen and Reykjavik centers during the study period, thus we did not have enough statistical power to analyze the association with cause-specific mortality. Previous studies have comprehensively adjusted for individual covariates, such as income, employment status, alcohol consumption, dietary intake, etc (Hanigan et al., 2019; Hvidtfeldt et al., 2019; Strak et al., 2021). However, these variables were unavailable in the current study and could potentially account for the differences in estimates compared to previous research. Additionally, the absence of area-level socioeconomic status (SES) data in our study hampers a complete understanding of health disparities and inequities related to environmental exposures, and may underestimate the impact of urban planning and policy interventions in addressing health inequalities and improving public health outcomes (Bereziartua et al., 2022; Josey et al., 2023; Roscoe et al., 2022). Furthermore, information of potential confounders were only available in RHINE III. Ideally, information on covariates should be collected at the same time as the most distant exposure time window for a more robust analysis. However, we have treated RHINE III as our study baseline, with the inclusion of pollution and greenness exposure time windows also before baseline. The sensitivity analysis where we included all mortality cases from 1990 onwards, however, showed that our results were robust, as the exposure effect estimates for mortality in 2010–2021 in the main model were very similar to the crude model with mortality from 1990 onwards. Two different methodologies of air pollution exposure assessment were used in this study, the sensitivity analyses show that results remained the same when only focusing on the DEHM/UBM-derived exposures, this limitation did not affect our findings. Another limitation is that we did not have full residential histories from an objective source, and model's performance might have been poorer in the early stages of the calculation period (in this case, the 1980s) due to less accurate emission data sets compiled then as compared to the more refined emission data available now. In addition, exposure misclassification cannot be excluded. Personal exposure does not only include the exposure in the residential area, but also exposures indoors, at work, and during the commute to and from work. We only included residential ambient air pollution exposure for the analysis. However, as the exposure status was determined independently from the outcome, misclassification is likely to be nondifferential and would - if anything - result in bias towards the null.

5. Conclusion

This study of a general population in Northern Europe supports that long-term exposure to $PM_{2.5}$, PM_{10}, BC and NO_2 is associated with increased all-cause mortality even at low air pollution levels and in a relatively young population. Given the fact that associations estimated for exposures assessed when subjects were aged 20–45 years were stronger compared to association estimated at older ages, our findings suggest that exposures during early adult life may be more harmful than previously reported.

CRediT authorship contribution statement

Shanshan Xu: Conceptualization, Methodology, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Alessandro Marcon:** Conceptualization, Methodology, Validation, Writing – review & editing, Supervision. **Randi Jacobsen Bertelsen:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Bryndis Benediktsdottir:** Writing – review & editing. **Jørgen Brandt:** Investigation, Writing – review & editing. **Kristine Engemann:** Investigation, Writing – review & editing. **Lise Marie Frohn:** Investigation, Writing – review & editing. **Camilla Geels:** Investigation, Writing – review & editing. **Thorarinn Gislason:** Writing – review & editing. **Joachim Heinrich:** Writing – review & editing. **Mathias Holm:** Writing – review & editing. **Christer Janson:** Writing – review & editing. **Iana Markevych:** Investigation, Writing – review & editing. **Lars Modig:** . **Hans Orru:** Writing – review & editing. **Vivi Schlünssen:** Writing – review & editing. **Torben Sigsgaard:** Writing – review & editing. **Ane Johannessen:** Conceptualization, Methodology, Project administration, Funding acquisition, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data presented in this paper are not readily available due to potential privacy violations, but can be obtained with justifiable request and with the consent of the national ethics committee.

Acknowledgement

This work was funded by a grant from the Research Council of Norway (No. 300765).

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2023.108257.

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