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Full length article

Exposure to surrounding greenness and natural-cause and cause-specific mortality in the ELAPSE pooled cohort

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ABSTRACT

Background: The majority of studies have shown higher greenness exposure associated with reduced mortality risks, but few controlled for spatially correlated air pollution and traffic noise exposures. We aim to address this research gap in the ELAPSE pooled cohort.
Methods: Mean Normalized Difference Vegetation Index (NDVI) in a 300-m grid cell and 1-km radius were assigned to participants' baseline home addresses as a measure of surrounding greenness exposure. We used Cox proportional hazards models to estimate the association of NDVI exposure with natural-cause and cause-specific mortality, adjusting for a number of potential confounders including socioeconomic status and lifestyle factors at individual and area-levels. We further assessed the associations between greenness exposure and mortality after adjusting for fine particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2) and road traffic noise.
Results: The pooled study population comprised 327,388 individuals who experienced 47,179 natural-cause deaths during 6,374,370 person-years of follow-up. The mean NDVI in the pooled cohort was 0.33 (SD 0.1) and 0.34 (SD 0.1) in the 300-m grid and 1-km buffer. In the main fully adjusted model, 0.1 unit increment of NDVI inside 300-m grid was associated with 5% lower risk of natural-cause mortality (Hazard Ratio (HR) 0.95 (95% CI: 0.94, 0.96)). The associations attenuated after adjustment for air pollution [HR (95% CI): 0.97 (0.96, 0.98) adjusted for $PM_{2.5}$; 0.98 (0.96, 0.99) adjusted for NO_2]. Additional adjustment for traffic noise hardly affected the associations. Consistent results were observed for NDVI within 1-km buffer. After adjustment for air pollution, NDVI was inversely associated with diabetes, respiratory and lung cancer mortality, yet with wider 95% confidence intervals. No association with cardiovascular mortality was found.
Conclusions: We found a significant inverse association between surrounding greenness and natural-cause mortality, which remained after adjusting for spatially correlated air pollution and traffic noise.

1. Introduction

Green space is defined as areas covered by vegetation, such as trees or grass (Pickard et al., 2015). Greenness surrounding home addresses is often used in research to characterize the general greenness exposure of the study subjects. A number of health benefits of greenness exposure have been reported including reduced obesity (Kondo et al., 2018; Lachowycz & Jones, 2014), improved cardiovascular health (Donovan et al., 2013; Pereira et al., 2012; Seo et al., 2019), improved mental health (Alcock et al., 2014; Gascon et al., 2015; Engemann, et al., 2020a; Engemann, et al., 2020b; Engemann et al., 2021), boosted immune system (Li et al., 2008; Egorov et al., 2017; Rook, 2013) and improved birth outcomes (Hystad et al., 2014). Several ecological and cross-sectional studies have provided evidence on the association of greenness with reduced premature mortality (Hu et al., 2008; Jonker et al., 2014; Lachowycz & Jones, 2014; Mitchell & Popham, 2008; Richardson & Mitchell, 2010). In the last decade, much effort has been made to examine the association between greenness and mortality prospectively in North America, Europe, Asia and Australia (Bauwelinck et al., 2021; Crouse et al., 2017; James et al., 2016; Ji et al., 2019, 2020; Klompmaker et al., 2020, 2021; Nieuwenhuijsen et al., 2018; Orioli et al., 2019; Vienneau et al., 2017; Villeneuve et al., 2012; Wang et al., 2017; Zijlema et al., 2019). Despite some contradictory findings, the majority of studies have shown that higher amounts of greenness were associated with lower natural-cause mortality risks. Much less is known for the associations of surrounding greenness with cause-specific mortality. Evidence for respiratory and cardiovascular mortality seems stronger than for natural causes (Crouse et al., 2017; James et al., 2016; Klompmaker et al., 2021; Orioli et al., 2019; Vienneau et al., 2017; Villeneuve et al., 2012; Wang et al., 2017), but is not fully consistent (Bauwelinck et al., 2021; Klompmaker et al., 2020; Orioli et al., 2019; Wang et al., 2017).

Multiple pathways have been proposed to explain the potential health benefits of greenness exposure. Greenness exposure may affect health by promoting physical activity, reducing stress, increasing social cohesion, and reducing exposure to air pollution and noise (James et al., 2015; Markevych et al., 2017). However, the potential filtering effect of vegetation on air pollution is small (Nieuwenhuijsen et al., 2017). Air pollution and traffic noise levels are usually lower in greener areas because of the absence of air pollution and noise sources (such as motorized traffic) (Hystad et al., 2014; Markevych et al., 2017; Thiering et al., 2016). Increased mortality risks have been associated with higher exposure to air pollution (Atkinson et al., 2018; Chen & Hoek, 2020; Huangfu & Atkinson, 2020) and traffic noise (Gan et al., 2012; Halonen et al., 2015; Héritier et al., 2017). Therefore, it is of particular interest to

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evaluate the association of mortality with greenness while taking into account the intercorrelation with air pollution and noise. Only few studies have considered air pollution and/or traffic noise as confounding factors (Bauwelinck et al., 2021; Crouse et al., 2017; Ji et al., 2020; Klompmaker et al., 2020, 2021; Nieuwenhuijsen et al., 2018; Vienneau et al., 2017; Villeneuve et al., 2012) or mediators (James et al., 2016; Orioli et al., 2019) when investigating the associations between greenness and mortality. Of these, only four studies have shown that associations of greenness with mortality remained after adjusting for air pollution or traffic noise (James et al., 2016; Ji et al., 2020; Klompmaker et al., 2020; Nieuwenhuijsen et al., 2018). Additionally, previous studies have shown that associations between greenness and mortality may differ by socio-economic status (SES), age or gender (Mitchell and Popham, 2008; Richardson and Mitchell, 2010; Lachowycz and Jones, 2014).

The aim of this study was to investigate the associations of surrounding greenness and natural-cause and cause-specific mortality, adjusting for individual and area-level variables and the additional environmental exposures air pollution and traffic noise. The analyses were performed in a large prospective cohort, created by pooling data of more than 300,000 adults from six European countries within the Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) project (Strak et al., 2021; Chen et al., 2021).

2. Methods

2.1. Study population

The ELAPSE pooled cohort is comprised of 14 sub-cohorts with detailed information on individual- and area-level variables (Chen et al., 2021; Strak et al., 2021). The sub-cohorts included in the analyses were: the *Cardiovascular Effects of Air Pollution and Noise in Stockholm* (CEANS) from Sweden, which includes four sub-cohorts: the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K) (Lagergren et al., 2004); the Stockholm Screening Across the Lifespan Twin study (SALT) (Magnusson et al., 2013); the Stockholm Cohort of 60-year-olds study (SIXTY) (Wändell et al., 2007); and the Stockholm Diabetes Prevention Program (SDPP) (Eriksson et al., 2008); the *Diet, Cancer and Health cohort* (DCH) (Tjønneland et al., 2007) and the *Danish Nurse Cohort* (DNC) (Hundrup et al., 2012) from Denmark; the *Dutch European Investigation into Cancer and Nutrition* (EPIC-NL) from the Netherlands, consisting of EPIC-Monitoring Project on Risk Factors and Chronic Diseases in the Netherlands (EPIC-MORGEN) and (EPIC-Prospect) (Beulens et al., 2010); the *Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale* (E3N) from France (Clavel-Chapelon, 2015); the *Heinz Nixdorf Recall* study (HNR) (Schmermund et al., 2002) and the *Kooperative Gesundheitsforschung in der Region Augsburg* (KORA S3 and KORA S4) (Scheurig et al., 2008) from Germany; and the *Vorarlberg Health Monitoring and Prevention Programme* (VHM&PP) from Austria (Ulmer et al., 2007). The participants were recruited in the period 1985–2005 and were followed-up until 2011–2015 (Table 1). Most of the cohorts consisted of a region including one or multiple large cities and surrounding smaller towns, while the DNC and the E3N cohorts were nationwide cohorts. A more detailed description for each sub-cohort can be found in the Appendix Section 1.

2.2. Exposure assessment

2.2.1. Surrounding greenness

We defined greenness using mean-Normalised Difference Vegetation Index (NDVI) composite of the year 2010. We considered greenness in a radius of 1-km as surrounding greenness that is easily accessible, and thus assign NDVI values inside a 300-m grid cell (NDVI 300-m) and a radius of 1-km (NDVI 1-km) to the participants' baseline residential addresses. The selection of year 2010 is in agreement with previous ELAPSE analyses, which used air pollution concentrations estimated for year 2010 (Chen et al., 2021; Strak et al., 2021). We assumed that the spatial contrast of greenness has been stable over time. Our assumption was supported by high correlations between NDVI estimates extracted from 1 × 1 km grids covering study areas in years 2005, 2010, 2015 and 2020. The medians of cohort-specific correlations between years were above 0.93 (details provided in the Appendix Section 3). NDVI values were extracted from the Terra Moderate-resolution Imaging Spectroradiometer (MODIS) Vegetation Indices (MOD13Q1), which are generated every 16 days at a 250-m resolution. The MODIS NDVI product is computed from atmospherically corrected bi-directional surface reflectances that have been masked for water, clouds, heavy aerosols, and cloud shadows (Didan et al., 2015). Mean-NDVI composite was calculated as a mean of the summer and winter values derived from the most available scenes in the middle of each season. Although the original resolution was approximated 250-m, after re-projecting to European Terrestrial Reference System 1989 Lambert Azimuthal Equal-Area projection coordinate reference system (ETRS_1989_LAEA) this was changed to approximated 300-m, thus the NDVI value within 300-m resolution grids was created. Next, the Focal Statistics in ArcGIS was used to create the 1-km buffer, based on the 300-m resolution grids. The NDVI metric ranges between −1.0 to 1.0, with negative NDVI values representing blue space or water and higher positive values indicating higher levels of vegetation density. As our study focused on exposure to greenness, we recoded negative NDVI values as zero. The negative values only accounted for 0.3% and 0.007% of the total values for NDVI 300-m and NDVI 1-km, respectively.

2.2.2. Air pollution

Individual exposure to 2010 annual average concentrations of $PM_{2.5}$ and NO_2 were assessed at participants' baseline residential addresses based on Europe-wide hybrid land use regression (LUR) models (de Hoogh et al., 2018). The LUR models were built on the European Environmental Agency AirBase routine monitoring data with satellite-derived estimates, chemical transport model estimates, land-use, road and population density data as predictors. The $PM_{2.5}$ and NO_2 models explained 66% and 58% of the measured concentration variation at the European scale, respectively. We focused on $PM_{2.5}$ and NO_2 as these pollutants showed consistent associations with mortality (Strak et al., 2021).

2.2.3. Road traffic noise

Information on road traffic noise levels at participants' baseline residential addresses was only available for a subset of the pooled cohort, including Swedish CEANS, Danish DCH and DNC and German HNR and KORA cohorts (Strak et al., 2021). Traffic noise exposure was expressed as the annual mean of a weighted 24 h average noise levels. This was assessed locally by calculating the day-evening-night equivalent noise level for the most exposed facade of dwellings. More specifically, road traffic noise levels were estimated implementing national calculation methods: Nordic Prediction Method (Nord2000) in the Swedish and Danish cohorts and RLS-90 and LLIS methods in German HNR and KORA cohorts, respectively. Noise barriers and actual or estimated building heights and terrain effects from absorption and reflection in the ground were included in the modelling. Noise exposure was reported with a resolution of 0.1 dB obtained from grids (Stockholm city 5x5m, Stockholm County 25x25m, HNR 10x10 m) or by using an assessment point directly at the residential address (DCH, DNC, KORA). The noise data refer to the year 2009 for KORA, 2006 for HNR, 1992 for CEANS, 1995 for DCH and 1993 or 1999 for DNC, the latter three matched to the recruitment year (Wolf et al., 2021).

2.3. Outcomes

Identification of outcomes was based on linkage to mortality registries. Mortality outcomes were defined based on the underlying cause of death recorded on the death certificates. Cause of death was coded with

Table 1
Description of the ELAPSE (Effects of Low-Level Air Pollution: A Study in Europe) pooled study population including information on the studied outcomes.

Study	Total population[a]	Population in the main model (Model 3)	Baseline period	End of follow-up	Person-years of follow-up	Underlying cause of death, rate per 1000 person-years							
						Natural-cause	Cardio-vascular	Respi-ratory	Lung cancer	Cerebro-vascular	Ischemic heart disease	Diabetes	COPD
CEANS Stockholm, Sweden	21,987	21,008	1992–2004	2014	271,372	10.8	3.9	0.7	0.6	0.9	1.7	0.1	0.4
SDPP	7,835	7,750	1992–1998	2011	122,968	2.7	0.6	0.1	0.3	0.1	0.4	0.0	0.1
SIXTY	4,180	3,969	1997–1999	2014	61,328	9.7	2.7	0.6	0.8	0.7	1.5	0.1	0.4
SALT	6,724	6,275	1998–2003	2011	65,104	14.3	5.3	0.9	0.9	1.4	2.4	0.1	0.6
SNAC-K	3,248	3,014	2001–2004	2011	21,972	48.9	21.1	3.1	1.3	4.9	8.0	0.4	1.5
DCH Copenhagen/ Aarhus, Denmark	56,308	53,685	1993–1997	2015	975,433	10.9	2.2	0.9	1.3	0.6	0.9	0.2	0.6
DNC Denmark	28,433	25,323	1993/1999	2013	438,127	10.0	2.3	0.9	0.9	0.7	0.8	0.1	0.5
DNC-1993	19,664	17,161	1993	2013	320,258	12.7	3.0	1.1	1.1	0.9	1.1	0.1	0.7
DNC-1999	8,769	8,162	1999	2013	117,869	2.7	0.4	0.1	0.3	0.2	0.1	0.1	0.1
EPIC-NL Netherlands	36,905	32,891	1993–1997	2013	547,902	5.8	1.3	0.3	0.6	0.4	0.5	0.1	0.2
MORGEN	20,711	18,307	1993–1997	2013	308,309	3.8	0.8	0.2	0.5	0.2	0.4	0.1	0.1
PROSPECT	16,194	14,584	1993–1997	2013	239,592	8.4	1.9	0.5	0.7	0.6	0.5	0.2	0.3
HNR Ruhr area, Germany	4,809	4,756	2000–2003	2015	57,115	12.3	3.4	0.8	1.1	0.7	1.5	0.3	0.5
E3N, France	53,521	40,610	1989–1991	2011	681,339	3.0	0.4	0.1	0.2	0.1	0.1	0.0	0.0
VHM&PP Vorarlberg, Austria	170,250	144,209	1985–2005	2014	3,332,838	6.8	3.0	0.3	0.4	0.7	1.5	0.2	0.2
KORA	8,823	4,906	1994–2001	2014	70,244	8.9	3.4	0.8	0.6	0.7	1.7	0.1	0.3
S3	4,566	2,603	1994–1995	2011	40,432	10.0	4.2	0.9	0.6	1.0	1.9	0.1	0.3
S4	4,257	2,303	1999–2001	2014	29,812	7.3	2.4	0.7	0.6	0.2	1.5	0.0	0.2
Pooled cohort	381,036	327,388	1985–2005	2011–2015	6,374,370	7.4	2.5	0.5	0.6	0.6	1.1	0.2	0.3

Abbreviations: CEANS, Cardiovascular Effects of Air Pollution and Noise in Stockholm; SDPP, The Stockholm Diabetes Preventive Program; SIXTY, The Stockholm cohort of 60-year-olds; SALT, Screening Across the Lifespan Twin Study; SNAC-K, The Swedish National Study of Aging and Care in Kungsholmen; DCH, Diet, Cancer and Health; DNC, Danish Nurses Cohort; EPIC-NL, European Prospective Investigation into Cancer and Nutrition, the Netherlands; MORGEN, Monitoring Project on Risk Factors and chronic diseases in the Netherlands; HNR, Heinz Nixdorf Recall study; E3N, Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale; VHM&PP, Vorarlberg Health Monitoring and Prevention Programme; COPD, Chronic Obstructive Pulmonary Disease.

[a] Number of subjects for which information was transferred to Utrecht University for construction of the pooled cohort.

the International Classification of Disease, Ninth Revision (ICD-9; WHO 1997) and the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (ICD-10; WHO 2016). Our primary outcomes were natural-cause mortality (ICD-9: 001–779; ICD-10: A00-R99), cardiovascular mortality (ICD-9: 400–440; ICD-10: I10-I70), respiratory mortality (ICD-9: 460–519; ICD-10: J00-J99) and lung cancer mortality (ICD-9: 162; ICD-10: C34). Secondary outcomes were cerebrovascular disease mortality (ICD-9: 430–438; ICD-10: I60-I69), ischemic heart disease mortality (ICD-9: 410–414; ICD-10: I20-I25), diabetes mortality (ICD-9: 249–250; ICD-10: E10-E14) and chronic obstructive pulmonary disease (COPD) mortality (ICD-9: 490–492, 494, 496; ICD-10: J40-J44, J47).

2.4. Statistical method

We generally followed the ELAPSE analytical framework (Chen et al., 2021; Strak et al., 2021). In single exposure models, we included surrounding greenness as a linear term and analyzed the association between each NDVI exposure metric (per 0.1 unit increment) and each mortality outcome. We calculated hazard ratios (HRs) and 95% confidence intervals (CIs) by Cox Proportional Hazards models with age as the underlying time scale. Individuals were censored at death from other causes, emigration, loss to follow-up for other reasons or at the end of follow-up. Three models were a priori specified with increasing level of adjustment: *Model 1*, crude model: age (specified as the underlying time scale), sub-cohort (included as strata), sex (included as strata), calendar year of enrolment (adjusted to account for time-trends in exposure and outcome). *Model 2*, further adjusted for individual level variables: marital status (married/cohabiting, divorced, single, widowed), smoking status (never, former, current), smoking duration (years of smoking) for current smokers, smoking intensity (cigarettes/day) for current smokers, squared smoking intensity, and employment status (yes vs. no). *Model 3* (main model), further adjusted for neighborhood-level SES: mean income in 2001. The spatial scale of a "neighborhood" varied from smaller neighborhoods and city districts (CEANS, EPIC-NL, E3N, HNR and KORA) to municipalities (DNC, DCH and VHM&PP). We included strata per individual sub-cohort to account for baseline hazard heterogeneity across the sub-cohorts and to relax the proportional hazards assumption. The use of strata for sub-cohort in our pooled analysis further avoids potential bias resulting from methodological differences between cohorts. We evaluated violation of the proportional hazard assumption of the Cox Models for all covariates by test of a non-zero slope in a generalized linear regression of the scaled Schoenfeld residuals on time. All main analyses were performed in the population with complete information on Model 3 variables.

For the main Model 3, we further specified NDVI exposure metrics in quartiles, to be in line with categorical analyses reported in previous literature (Crouse et al., 2017; James et al., 2016; Ji et al., 2019; Orioli et al., 2019; Villeneuve et al., 2012; Zijlema et al., 2019). Our assessment of the exposure–response functions for both NDVI metrics and natural-cause and cardiovascular mortality using natural splines did not show much deviation from linearity (Figure S1 and Table S1). Exposure-response curves showed linearity for most of the data (between 0.2 and 0.5 NDVI values) and the counter-intuitive trend only represented less than 10% of the population.

Based on the main Model 3, BMI and physical activity were additionally adjusted for in separate extra models, as we considered BMI and physical activity could act both as mediators or potential confounders. Baseline BMI (kg/m^2) was divided into 4 categories according to the WHO recommendations (WHO 2000): underweight (<18.5), normal (18.5–24), overweight (25–29) and obese (≥30). Baseline physical activity was based on monthly or weekly basis depending on the cohort and was classified as low (once a month or less and less than 1 h/week), medium (about once a week and around 1 h/week) and high (3 times a week or more and more than 2 h/week). Considering the differences in distribution and definition of physical activity across sub-cohorts (Appendix Section 2), we decided to conduct analyses with adjustment for physical activity in two different approaches: (a) including the complete available data from all the sub-cohorts, and (b) only including data from sub-cohorts with comparable distribution (excluding E3N, DNC and EPIC-NL). Impact of adjustment for BMI or physical activity was assessed in population with complete information on the respective covariates.

We further adjusted our Main model 3 for air pollution ($PM_{2.5}$ and NO_2) and traffic noise individually in separate models, and together in one model, to investigate the association of greenness with mortality when mutually considering other environmental exposures. Impact of adjustment for air pollution or traffic noise was assessed in population with complete information on the respective covariates.

We investigated potential effect modification by baseline age (<65y and ≥65y), sex, smoking status, urbanicity, air pollution ($PM_{2.5}$ and NO_2), traffic noise, BMI and education level. Urbanicity was defined by Degree of Urbanization (DEGURBA) dataset from Eurostat (version EU27-2012 March). The participants' residence is determined as cities (as densely populated urban area where at least 50% of the population lives in urban centers), towns or suburbs (intermediate density suburban areas where less than 50% of the population lives in rural areas and less than 50% of the population lives in urban centers) and rural areas (thinly populated areas where more than 50% of the population lives in rural areas) (Eurostat 2011). The study population were mostly from urbanized areas, though especially in the VHM&PP and DNC cohorts subjects were also from less urbanized areas. We added an interactive term of the continuous NDVI exposure and quartiles or categories of each potential effect modifier separately in the main Model 3, except for sex. We replaced the strata term for sex in the main model with an interaction term and main effect for sex. We used likelihood ratio tests to assess statistical significance at the 0.05 level. We further compared effect estimates in sub-cohorts with positive and negative correlations between area-level income and NDVI exposures.

We additionally performed sensitivity analyses to investigate the possible impact of potential confounders, which were only available in some cohorts. We compared effect estimates in identical subsets of the data with and without further adjustment for the additional potential confounders. Additional potential confounders included educational level (low, medium, high), occupational class (white collar/ blue collar), the area-level unemployment rate, smoking duration and intensity for former smokers. We further evaluated robustness of our findings by performing the main analyses in datasets excluding individual cohorts one by one. We also performed analyses in population with complete information on Model 1 and Model 2 covariates respectively, to check the potential selection bias introduced by analyzing complete cases on individual and area-level covariates. To assess the sensitivity of our findings to using the 2010 exposures, we restricted analyses to follow-up periods starting from 2000, 2005, 2008 and 2010, with successively less temporal misalignment of the exposure assessment at the expense of shorter follow-up and fewer deaths, following the assessment performed for air pollution in this pooled cohort (Brunekreef et al., 2021). To assess the potential impact of not accounting for residential mobility, we compared 2010 NDVI exposures assigned to residential addresses at baseline and at the end of follow-up for participants who had information on residential history.

We performed analyses in R, version 3.4.0 and packages: *survival* (version 2.42–3), *coxme* (version 2.2–10), *Matrix* (version 1.2–14), *foreach* (version 1.4.4), *glmnet* (version 2.0–16), *multcomp* (version 1.4–8), *survey* (version 3.33–2), *splines* (version 3.4.0), *Hmisc* (version 4.1–1), *mfp* (version 1.5.2), *mice* (version 2.46.0), *VIM* (version 4.7.0), *ggplot2* (version 2.2.1), *MASS* (version 7.3–50), and *rms* (version 5.1–2). P-values less than 0.05 were used to define statistical significance.

3. Results

3.1. Study population and surrounding greenness

Fourteen percent (14.1%) of the total population was excluded from all main analyses due to missing information on greenness exposure (0.3%), individual-level covariates (12%), or neighborhood-level mean income (1.8%). Hence, the total pooled study population in the main model (Model 3) comprised 327,388 individuals who experienced 47,179 natural deaths during 6,374,370 person-years of follow-up (Table 1). The mean age at baseline ranged from 42.1 to 73.8 years across the individual sub-cohorts (Table 2). The excluded population was slightly younger (baseline age 45.7 ± 14.7 y) than the Model 3 population (baseline age 48.8 ± 13.4 y). The proportion of females in the excluded population (62.4%) was slightly lower than in the Model 3 population (66.3%). The detailed information on missing data within each individual sub-cohort was extensively reported in Chen et al. (2021).

The mean NDVI in the pooled cohort was 0.33 (SD 0.10) and 0.34 (SD 0.10) in the 300-m grid and 1-km buffer, respectively (Figure S2). The variation in NDVI exposure between the individual sub-cohorts was substantial (Fig. 1). For NDVI 300-m the Swedish SNACK cohort located in the Stockholm center had the lowest value of 0.12 (SD 0.10), whereas the French national E3N cohort had the highest value of 0.41 (SD 0.12). A similar distribution was observed for NDVI 1-km.

Overall, locations with higher greenness had lower levels of $PM_{2.5}$, NO_2 and traffic noise (Table S2). The correlation coefficient between neighborhood mean income and greenness varied considerably from −0.71 in the Swedish SNACK cohort to 0.32 in the Danish DCH cohort (Table S3). NDVI metrics in the 300-m grid and 1-km buffer were moderately to highly correlated in all cohorts with Spearman correlation coefficients ranging from 0.61 to 0.89 across sub-cohorts (Table S3).

3.2. Association between greenness and mortality: Single exposure models

NDVI 300-m and NDVI 1-km were inversely associated with natural-cause mortality with a HR of 0.95 (95% CI: 0.94, 0.96) and 0.94 (95% CI: 0.93, 0.95) per increment of 0.1 unit, respectively (Table 3). Consistent results were observed when specifying NDVI metrics in quartiles for natural-cause mortality. For both NDVI metrics, the HRs were lowest in the highest (fourth) quartile [HR = 0.89 (95% CI: 0.86, 0.91) for NDVI 300-m and HR = 0.87 (95% CI: 0.84, 0.89) for NDVI 1-km] and highest in the second quartile [HR = 0.92 (95% CI: 0.90, 0.95) for NDVI 300-m and HR = 0.94 (95% CI: 0.92, 0.96) for NDVI 1-km] compared to the first quartile.

For cause-specific mortality, lower mortality risk with higher NDVI exposure was found, most pronounced for diabetes mortality with a HR of 0.86 (95% CI: 0.79, 0.94) and 0.80 (95% CI: 0.72, 0.89) for NDVI 300-m and NDVI 1-km, respectively (Table 3). The effect estimates for NDVI 300-m and NDVI 1-km with cardiovascular, cerebrovascular, ischemic heart disease, respiratory, COPD, and lung cancer mortality were similar as for natural-cause mortality but with wider 95% CI, probably related to lower number of deaths (Table 3). For cause-specific mortality, analyses with NDVI in quartiles differed somewhat from specifying linear NDVI metrics. The cardiovascular, cerebrovascular, and ischemic heart disease mortality rates were almost identically reduced compared to the lowest quartile for individuals in the second to fourth quartile of NDVI 300-m. For NDVI 1-km, those living in the highest quartile had considerably lower risk of mortality than those in the lowest quartiles. The risk of respiratory mortality with NDVI 300-m and NDVI 1-km was lower for the individuals in the highest quartile [HR = 0.93 (95% CI: 0.83, 1.05) and HR = 0.91 (95% CI: 0.80, 1.03), respectively], than in the second quartile [HR = 0.98 (95% CI: 0.89, 1.08) and HR = 0.93 (95% CI: 0.84, 1.02), respectively], but higher than in the 3rd quartile [HR = 0.83 (95% CI: 0.75, 0.93) and HR = 0.84 (95% CI: 0.75, 0.94), respectively]. A similar pattern was observed for lung cancer and COPD mortality. As for diabetes mortality, individuals in the 3rd quartile of NDVI 300-m presented the lowest mortality rate, while for the NDVI 1-km exposure only the individuals living in the highest quartile presented a significantly decreased mortality risk (Table 3).

The association with NDVI was evident for all the studied outcomes in Model 1, which was adjusted only for age, sex, and year of baseline visit (Table S4). We found that adjustments for individual level covariates attenuated the associations of NDVI 300-m and NDVI 1-km with

Table 2
Baseline characteristics on the major covariates of the participants from the ELAPSE pooled cohort included in the main model (Model 3).

Study	Mean Baseline age (SD) years	% Woman	% Current smokers	Cigarettes/day[a]	Years of smoking[a]	% Not employed	% Married/cohabiting	Mean Income[b]
CEANS	56.6 (11.8)	58	22	13.1 (7.7)	33.7 (11.1)	31	71	25.3 (5.6)
SDPP	47.1 (4.9)	61	26	13.5 (7.4)	27.9 (8.6)	9	84	24.3 (4.2)
SIXTY	60.0 (0)	52	21	13.4 (7.6)	36.3 (9.9)	32	74	24.7 (6.9)
SALT	57.9 (10.7)	56	21	12.7 (8)	37.9 (9.3)	36	67	25.3 (6.6)
SNACK	73.8 (10.9)	64	14	11.6 (8.2)	43.8 (13.8)	78	44	28.6 (2.2)
DCH	56.7 (4.4)	52	36	16.4 (9)	36.3 (7.7)	22	72	20.2 (3.4)
DNC	53.6 (8.3)	100	34	13.7 (8)	30.4 (9.5)	22	70	19.1 (2.5)
DNC-1993	56.2 (8.4)	100	37	13.9 (8.2)	31.6 (9.9)	30	68	19.2 (2.6)
DNC-1999	47.9 (4.2)	100	29	13.3 (7.3)	27.1 (7.1)	5	76	19.0 (2.4)
EPIC-NL	49.5 (11.8)	75	29	15.0 (8.7)	28.9 (11.2)	39	70	12.6 (1.6)
MORGEN	42.9 (11.2)	55	35	15.7 (8.6)	24.8 (10.6)	31	65	12.2 (1.6)
PROSPECT	57.7 (6.0)	100	23	13.7 (8.7)	36.8 (7.6)	49	77	13.1 (1.4)
HNR	59.6 (7.8)	50	24	18.6 (12.1)	34.5 (9.4)	60	75	25.2 (8.2)
E3N	53.0 (6.8)	100	13	11.4 (9.2)	28.7 (7.6)	32	83	11.2 (3.0)
VHM&PP	42.1 (15.0)	56	20	15.6 (8.9)	13.4 (8.3)	30	69	22.9 (1.7)
KORA	49.4 (13.9)	51	21	16.1 (9.6)	24.7(11.8)	43	80	37.3 (6.0)
S3	49.5 (14.0)	51	20	16.5 (9.5)	25.2 (12.1)	45	80	36.7 (4.4)
S4	49.3 (13.9)	51	23	15.8 (9.6)	24.2 (11.5)	41	79	38.0 (7.3)
Pooled cohort	48.8 (13.4)	66	24	15.1 (8.9)	25.5 (13.1)	30	72	20.1 (5.8)

Abreviations: CEANS, Cardiovascular Effects of Air Pollution and Noise in Stockholm; SDPP, The Stockholm Diabetes Preventive Program; SIXTY, The Stockholm cohort of 60-yearolds; SALT, Screening Across the Lifespan Twin Study; SNAC-K, The Swedish National Study of Aging and Care in Kungsholmen; DCH, Diet, Cancer and Health; DNC, Danish Nurses Cohort; EPIC-NL, European Prospective Investigation into Cancer and Nutrition, the Netherlands; MORGEN, Monitoring Project on Risk Factors and chronic diseases in the Netherlands; HNR, Heinz Nixdorf Recall study; E3N, Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale; VHM&PP, Vorarlberg Health Monitoring and Prevention Programme.

[a] Among current smokers, mean (SD).

[b] Neighborhood Mean Income: Euros × 1000, year 2001, mean (SD).

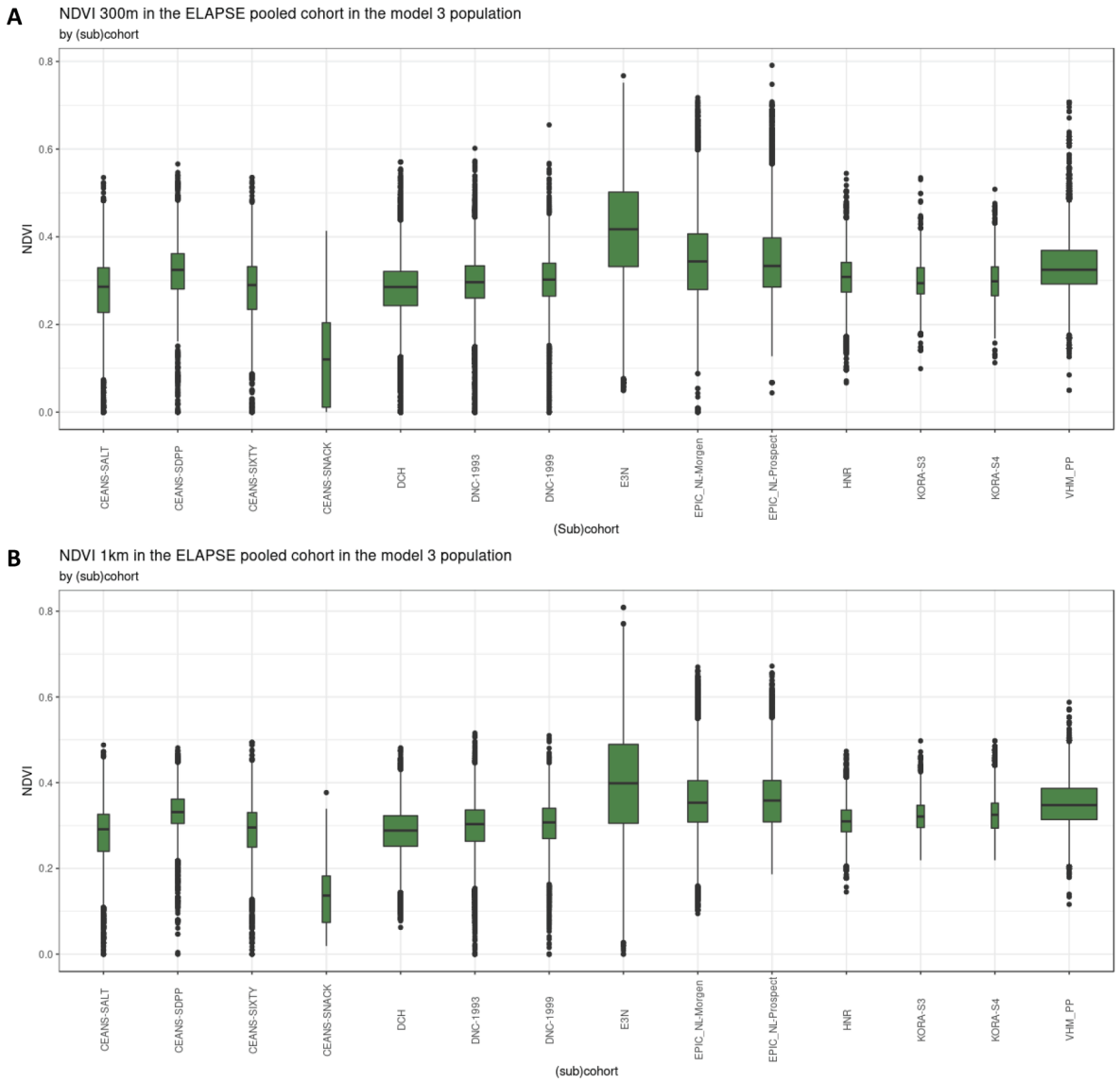

Fig. 1. Distribution of the Normalized Difference Vegetation Index (NDVI) inside radii of 300-m **(A)** and 1-km **(B)** from participants' residential addresses of individuals included in model 3 for each individual sub-cohort in the ELAPSE pooled cohort, with negative NDVI values recoded to zero. The width of boxplots indicates the population size. The boundary of the box closest to zero indicates the 25th centile of the distribution (P25); furthest from zero – P75; bold horizontal line inside the box – P50; whiskers indicate P5 and P95.

natural-cause and cause-specific mortality (Model 2 versus Model 1 in Table S4). Adjustments for neighborhood-level SES factors did not affect the HRs (Model 2 versus Model 3 in Table S4).

3.3. Adjustment for air pollution and traffic noise

After adjusting for air pollution, the associations of surrounding greenness and natural-cause mortality attenuated but remained statistically significant (Table 4). The HRs of NDVI 300-m became closer to unity when adjusted for $PM_{2.5}$ [HR = 0.97 (%95 CI: 0.96, 0.98)] and NO_2 [HR = 0.98 (95% CI: 0.96, 0.99)]. Similarly, the HRs of NDVI 1-km attenuated from 0.94 (95% CI: 0.93, 0.95) to 0.97 (%95 CI: 0.95, 0.98) and 0.98 (95% CI: 0.96, 0.99) when adjusted for $PM_{2.5}$ and NO_2, respectively. After adjusting for air pollution, the associations of surrounding greenness and cause-specific mortality outcomes attenuated and became statistically nonsignificant except for diabetes mortality. Attenuation was stronger upon adjustment for NO_2 than for $PM_{2.5}$. HRs were attenuated to essentially unity for cardiovascular disease, ischemic heart disease and COPD mortality. The association between greenness and diabetes mortality slightly attenuated but remained statistically significant after adjusting for $PM_{2.5}$.

In the subset of the pooled cohort with available information on traffic noise, we observed similar attenuation of the association between greenness and mortality after adjusting for air pollution. Further adjustment for traffic noise in a model with air pollution hardly affected the association of surrounding greenness with mortality (Table S5).

3.4. Adjustment for BMI and physical activity

The distribution of NDVI was similar across the BMI categories in the complete study population (Figure S3), as well as in the individual cohorts (Figure S4). Consistently, the association between surrounding greenness and natural-cause mortality remained robust with adjustment for the individual level BMI or physical activity (Table S5). Likewise, the effect estimates for cause-specific mortality were robust to inclusion of the BMI in the model. We observed comparable results for physical activity adjustment with both approaches (i.e., (a) complete data and (b) E3N, DNC and EPIC-NL excluded data).

Table 3
Hazard ratios and 95% confidence intervals for Normalized Difference Vegetation Index (NDVI) in the 300-m grid and 1-km buffer and natural-cause and cause-specific mortality in the pooled ELAPSE cohort applying the main model 3 (N = 327,388).

Underlying cause of death	Cases	Continuous (per 0.1 unit)	Quartile 1 as reference (NDVI 300-m: 0–0.28; NDVI 1-km: 0–0.29)		
			Quartile 2 (300-m: 0.28–0.32; 1-km: 0.29–0.33)	Quartile 3 (300-m: 0.32–0.37; 1-km: 0.33–0.38)	Quartile 4 (300-m: 0.37–0.79; 1-km: 0.38–0.81)
		HR[a] (95% CI)	HR[a] (95% CI)	HR[a] (95% CI)	HR[a] (95% CI)
Natural-cause	47,179				
NDVI 300-m		0.95 (0.94, 0.96)	0.92 (0.90, 0.95)	0.90 (0.88, 0.93)	0.89 (0.86, 0.91)
NDVI 1-km		0.94 (0.93, 0.95)	0.94 (0.92, 0.96)	0.93 (0.90, 0.95)	0.87 (0.84, 0.89)
Cardiovascular	15,633				
NDVI 300-m		0.97 (0.95, 0.99)	0.89 (0.85, 0.93)	0.90 (0.86, 0.95)	0.90 (0.86, 0.95)
NDVI 1-km		0.96 (0.93, 0.98)	0.93 (0.89, 0.97)	0.95 (0.91, 1.00)	0.87 (0.83, 0.92)
Cerebrovascular	3,774				
NDVI 300-m		0.97 (0.92, 1.01)	0.90 (0.82, 0.98)	0.88 (0.80, 0.97)	0.89 (0.81, 0.99)
NDVI 1-km		0.94 (0.89, 0.99)	0.95 (0.86, 1.04)	0.94 (0.86, 1.04)	0.84 (0.76, 0.94)
Ischemic heart disease	7,294				
NDVI 300-m		0.97 (0.94, 1.00)	0.91 (0.85, 0.97)	0.90 (0.84, 0.96)	0.90 (0.84, 0.97)
NDVI 1-km		0.94 (0.91, 0.98)	0.93 (0.86, 0.99)	0.95 (0.88, 1.02)	0.84 (0.78, 0.91)
Diabetes	1,042				
NDVI 300-m		0.86 (0.79, 0.94)	0.83 (0.71, 0.98)	0.78 (0.66, 0.93)	0.80 (0.66, 0.96)
NDVI 1-km		0.80 (0.72, 0.89)	0.91 (0.76, 1.09)	0.91 (0.76, 1.09)	0.73 (0.59, 0.90)
Respiratory	2,885				
NDVI 300-m		0.95 (0.90, 1.00)	0.98 (0.89, 1.08)	0.83 (0.75, 0.93)	0.93 (0.83, 1.05)
NDVI 1-km		0.94 (0.89, 1.00)	0.93 (0.84, 1.02)	0.84 (0.75, 0.94)	0.91 (0.80, 1.03)
Lung cancer	3,813				
NDVI 300-m		0.96 (0.92, 1.00)	0.97 (0.90, 1.06)	0.94 (0.86, 1.03)	0.93 (0.84, 1.03)
NDVI 1-km		0.95 (0.90, 1.00)	0.94 (0.86, 1.02)	0.89 (0.81, 0.98)	0.90 (0.81, 1.01)
COPD	1,720				
NDVI 300-m		0.96 (0.90, 1.02)	0.97 (0.86, 1.10)	0.86 (0.75, 0.99)	0.96 (0.82, 1.13)
NDVI 1-km		0.94 (0.87, 1.02)	0.88 (0.77, 1.00)	0.84 (0.73, 0.97)	0.92 (0.78, 1.09)

Abbreviations: NDVI, Normalised Difference Vegetation Index; CI, confidence interval; HR, hazard ratio; COPD, Chronic Obstructive Pulmonary Disease.
[a] Hazard ratios are adjusted for study (strata), age, sex (strata), year of baseline visit, smoking status, duration, intensity, intensity^2, marital status, employment status, and 2001 mean income at neighborhood level.

3.5. Effect modification analysis

We found stronger associations between greenness exposure and natural-cause mortality in population with baseline age below 65 yr compared to the elderly (Fig. 2A, Table S6). Associations of greenness with natural-cause mortality did not differ by sex, smoking status, and levels of urbanicity (Fig. 2B-D). Further interaction analyses showed no statistically significant differences in the association between greenness and natural-cause mortality by air pollution, traffic noise, education level and BMI (Table S6, Figure S5). Similar HRs were observed in sub-cohorts with positive or negative correlations between NDVI and area-level income (Table S6).

3.6. Sensitivity analyses

The sensitivity analyses did not alter the main findings. Identical HRs were observed for analyses performed in the full population and population with complete information on individual- and area-level variables (Table S7), suggesting little selection bias was introduced by missing data. Additional adjustments for potential confounders in the subset of respective cohorts with the available information did not change the results (Table S8). No deviation from the main analysis was found when incorporating smoking and marital status as strata, which were the variables violating the proportional hazard assumption (Table S9). The effect estimate for the association between NDVI 1-km and natural-cause mortality was sensitive to exclusion of the large VHM&PP cohort, which contributed almost half (47%) of the natural-cause mortality cases [HR = 0.97 (95% CI: 0.95, 0.99)]; as well as to exclusion of DCH cohort [HR = 0.96 (95 %CI: 0.94, 0.98)] and E3N cohort [HR = 0.92 (95 %CI: 0.91, 0.94)] (Table S10). Importantly, these cohorts together accounted for 73% of the total natural-cause mortality cases. When restricting analyses to participants with follow-up period to after year 2000 (69% of total person-years at risk, 84% of total deaths), after year 2005 (46% of total person-years at risk, 64% of total deaths), after year 2008 (32% of total person-years at risk, 47% of total deaths), and after year 2010 (23% of total person-years at risk, 33% of total deaths), we observed robust associations between NDVI exposures and natural-mortality with wider confidence intervals (Table S11). For the majority of participants who had information on residential history (i.e., cohorts CEANS, DCH, EPIC-NL and VHM&PP; N = 243,510), correlations between NDVI exposures assigned to residential addresses at baseline and end of follow-up were high (Pearson correlation coefficients 0.75 and 0.82 for NDVI in 300-m grid and 1-km buffer, respectively).

4. Discussion

In this analysis of a large pooled cohort covering 14 sub-cohorts from Europe, higher levels of surrounding greenness exposure were associated with lower risk of natural-cause mortality. The associations remained even after adjusting for the spatially correlated environmental exposures air pollution and traffic noise. Inverse associations were also observed for cardiovascular, cerebrovascular, ischemic heart disease, diabetes, respiratory, lung cancer and COPD mortality with wider confidence intervals sometimes include unity. Associations with cause-specific mortality were less stable after adjustment for air pollution.

4.1. Comparison with previous studies

(a) Natural-cause mortality

The effect estimates for natural-cause mortality derived from the single exposure model were particularly comparable to the estimates found in a cohort study conducted in Hong Kong (Wang et al., 2017). Wang and colleagues estimated a HR of 0.96 (95% CI: 0.93, 0.99) per 0.1 increase in NDVI in a 300-m buffer and natural-cause mortality after adjusting for individual and area-level variables. A study that followed

Table 4
Associations of Normalized Difference Vegetation Index (NDVI) in the 300-m grid and 1-km buffer with natural-cause mortality and cause specific mortality from single and two-exposure models with adjustment for air pollution ($PM_{2.5}$ and NO_2).

		Complete case with Air Pollution exposure (N = 327,388)		
Underlying cause of death	Cases	Single-exposure	Adjusted for $PM_{2.5}$	Adjusted for NO_2
		HR[a] (95% CI)	HR[a] (95% CI)	HR[a] (95% CI)
Natural-cause	47,179			
NDVI 300-m		0.95 (0.94, 0.96)	0.97 (0.96, 0.98)	0.98 (0.96, 0.99)
NDVI 1-km		0.94 (0.93, 0.95)	0.97 (0.95, 0.98)	0.98 (0.96, 0.99)
Cardiovascular	15,633			
NDVI 300-m		0.97 (0.95, 0.99)	0.99 (0.97, 1.01)	1.00 (0.98, 1.03)
NDVI 1-km		0.96 (0.93, 0.98)	1.00 (0.97, 1.03)	1.01 (0.97, 1.04)
Cerebrovascular	3,774			
NDVI 300-m		0.97 (0.92, 1.01)	0.98 (0.94, 1.03)	0.99 (0.94, 1.04)
NDVI 1-km		0.94 (0.89, 0.99)	0.97 (0.91, 1.03)	0.96 (0.90, 1.03)
Ischemic heart disease	7,294			
NDVI 300-m		0.97 (0.94, 1.00)	0.98 (0.95, 1.02)	1.01 (0.97, 1.04)
NDVI 1-km		0.94 (0.91, 0.98)	0.98 (0.93, 1.02)	1.00 (0.95, 1.05)
Diabetes	1,042			
NDVI 300-m		0.86 (0.79, 0.94)	0.90 (0.82, 0.99)	0.93 (0.84, 1.03)
NDVI 1-km		0.80 (0.72, 0.89)	0.86 (0.76, 0.97)	0.87 (0.76, 1.00)
Respiratory	2,885			
NDVI 300-m		0.95 (0.90, 1.00)	0.95 (0.90, 1.00)	0.98 (0.93, 1.04)
NDVI 1-km		0.94 (0.89, 1.00)	0.94 (0.88, 1.01)	0.99 (0.92, 1.07)
Lung cancer	3,813			
NDVI 300-m		0.96 (0.92, 1.00)	0.98 (0.94, 1.03)	0.98 (0.93, 1.03)
NDVI 1-km		0.95 (0.90, 1.00)	0.99 (0.93, 1.04)	0.98 (0.92, 1.04)
COPD	1,720			
NDVI 300-m		0.96 (0.90, 1.02)	0.97 (0.91, 1.04)	1.01 (0.93, 1.08)
NDVI 1-km		0.94 (0.87, 1.02)	0.97 (0.88, 1.06)	1.02 (0.92, 1.12)

Abbreviations: NDVI, Normalised Difference Vegetation Index; CI, confidence interval; HR, hazard ratio; COPD, Chronic Obstructive Pulmonary Disease.

[a] Hazard ratios are adjusted for study (strata), age, sex (strata), year of baseline visit, smoking status, duration, intensity, intensity^2, marital status, employment status, and 2001 mean income at neighborhood level.

female nurses from 11 states in the United States (James et al., 2016) and a large prospective study from Barcelona, Spain (Nieuwenhuijsen et al., 2018), found negative associations between surrounding greenness and natural-cause mortality, yet with stronger effect estimates compared to our results [HR = 0.88 (95% CI: 0.82, 0.94) for a 0.1 unit increase in cumulative NDVI in the 250-m area and HR = 0.92 (95% CI: 0.89, 0.97) for a 0.1 unit increase in NDVI in a 300-m area, respectively]. Also, three studies from Europe (Bauwelinck et al., 2021; Klompmaker et al., 2021; Orioli et al., 2019) reported comparable results although they found a slightly weaker association than in the present study [HR = 0.97 (95% CI: 0.96, 0.98) per IQR increase (0.24) in NDVI in a 500-m area; HR = 0.97 (95% CI: 0.97, 0.98) per IQR increase (0.14) in NDVI in a 300-m area; and HR = 0.99 (95% CI: 0.98, 0.99) for NDVI in the 300-m, respectively]. In China, Ji et al. (2019) reported that individuals in the highest quartile of greenness in the 250-m area had 27% lower mortality than those in the lowest quartile (HR = 0.73 (95% CI: 0.70, 0.76)). In contrary, our findings differed from those of Klompmaker et al. (2020) reporting no association between surrounding green and non-accidental mortality, with a HR of 0.99 (95% CI: 0.98, 1.01) per IQR increase (0.13) in NDVI in a 300-m area.

The differences in the magnitude of the estimates between studies may be either due to different study populations, follow-up period, exposure misclassification error, or adjustment of covariates. Most of the studies performed using administrative datasets were not able to control for some potentially important confounders due to limited data on individual level lifestyle factors (Bauwelinck et al., 2021; Klompmaker et al., 2021; Orioli et al., 2019). Additionally, the non-linear association observed in the spline analyses could partly explain the differences across studies, as a linear estimate may not be the best summary of the association.

Surrounding green was overall moderately negatively correlated with air pollution and traffic noise, suggesting that confounding or mediation between the three environmental exposures is possible (Crouse et al., 2017; Gascon et al., 2018; Klompmaker et al., 2019; Ramirez-Rubio et al., 2019; Thiering et al., 2016). Previous studies that investigated associations of surrounding green with mortality have considered air pollution and traffic noise as mediators (James et al., 2016; Orioli et al., 2019), while others have considered them as potential confounders (Bauwelinck et al., 2021; Crouse et al., 2017; Klompmaker et al., 2021; Nieuwenhuijsen et al., 2018; Vienneau et al., 2017; Villeneuve et al., 2012). In the present study, we included air pollution and traffic noise in the analysis as potential confounders. We found that the association of greenness with natural-cause mortality reduced substantially but remained after adjusting for $PM_{2.5}$ and NO_2. The findings are in line with two studies from Canada (Crouse et al., 2017; Villeneuve et al., 2012), a cohort study from Spain (Nieuwenhuijsen et al., 2018), and two recent studies from Belgium and the Netherlands (Bauwelinck et al., 2021; Klompmaker et al., 2021) that showed evidence of a negative association between greenness and natural-cause mortality after adjusting for air pollution as confounder. Similar results were observed in a study from Switzerland (Vienneau et al., 2017) after adjusting for both PM_{10} and traffic noise as confounders in the same model [HR = 0.94 (95%: 0.93, 0.95) per IQR increase (0.14) in NDVI in the 500-m area]. Additionally, Nieuwenhuijsen et al., (2018) and Klompmaker et al., (2021) observed inverse association of greenness with mortality after adjusting for traffic noise as potential confounder.

(b) Cause-specific mortality

We observed decreased risk associated with greenness exposure for all the studied cause-specific mortality in single exposure models: cardiovascular, cerebrovascular, ischemic heart disease, diabetes, respiratory, lung cancer and COPD mortality. Our findings on cardiovascular, ischemic heart disease, and cerebrovascular mortality were similar to those observed in Rome (Orioli et al., 2019), in Switzerland (Vienneau et al., 2017) and China (Wang et al., 2017), while a stronger association was found for respiratory mortality in previous studies conducted in USA (James et al., 2016) and Canada (Crouse et al., 2017; Villeneuve et al., 2012). Overall, our effect estimates for cause-specific mortality were highly comparable to those reported for the Dutch national cohort except for lung cancer mortality (Klompmaker et al. 2021). Our findings are incongruent with those from the Belgian cohort, where no association between greenness and cardiovascular, ischemic heart disease and cerebrovascular disease mortality was reported (Bauwelinck et al. 2021). Yet, both of the previous mentioned studies were conducted in administrative cohorts and were not able to adjust for individual lifestyle factors in the analysis. Despite the relatively low number of cases, we found a strong significant association between surrounding greenness and diabetes mortality that was not observed in USA (James et al.,

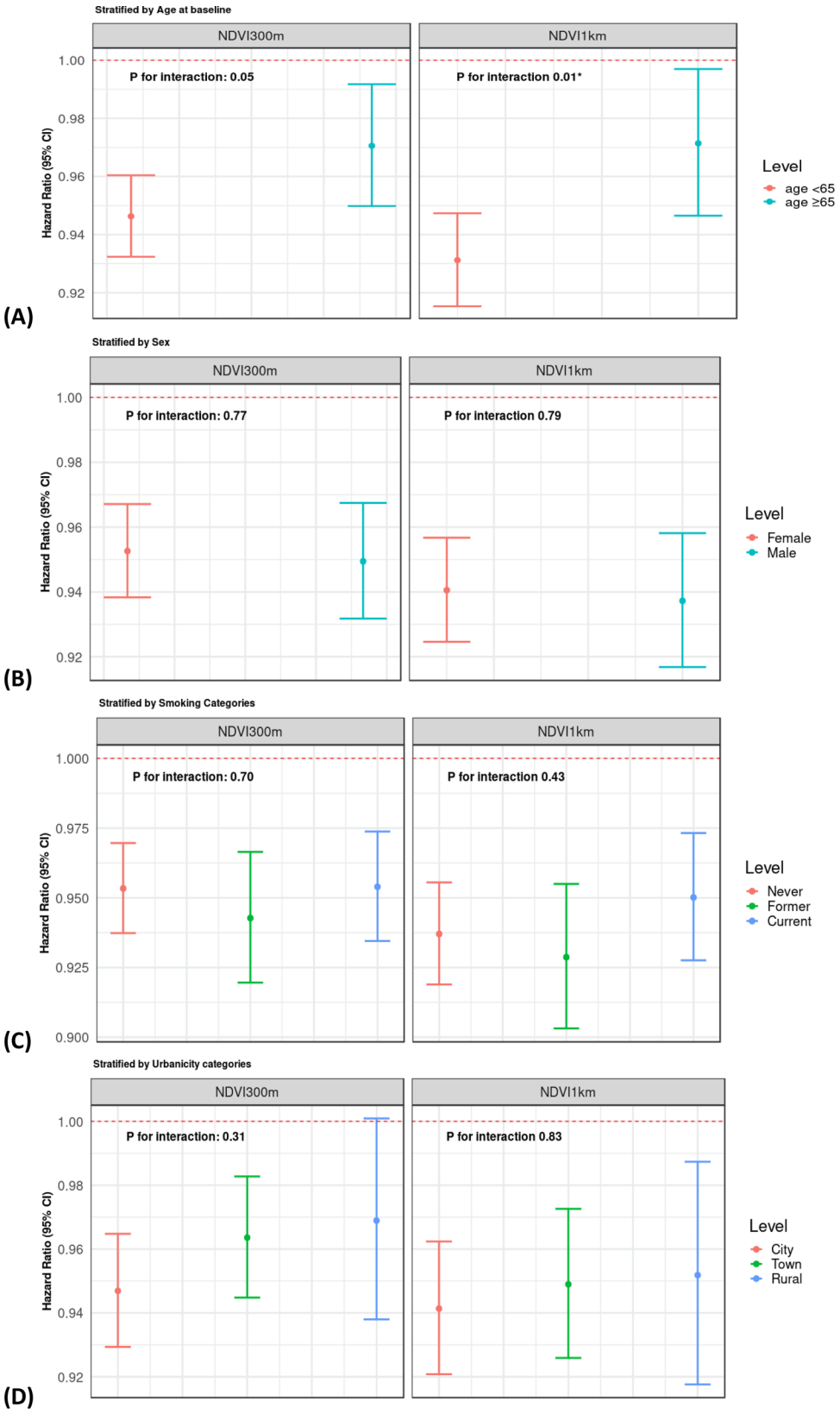

Fig. 2. Hazard ratios and 95% confidence intervals (CI) for a 0.1 unit increase in Normalized Vegetation Index (NDVI) in the 300-m grid and 1-km buffer and natural-cause mortality in the ELAPSE pooled cohort (N = 327,388) stratified by **(A)** age at baseline (N = 327,388), **(B)** sex (N = 327,388), **(C)** smoking categories (N = 327,388) and **(D)** urbanicity categories (N = 326,661). Hazard ratios are adjusted for study (strata), age, sex (strata), year of baseline visit, smoking status, duration, intensity, intensity^2, marital status, employment status, and 2001 mean income at neighborhood level, except when stratifying variable.

2016) and has not been analyzed in any other previous study. After adjusting for air pollution, effect estimates for some causes attenuated to unity, suggesting there is no association with greenness.

(c) Effect modification

Studies have attempted to examine the interactions between air pollution and greenness on mortality with inconsistent findings (Crouse et al., 2019; de Keijzer et al., 2017; Kim et al., 2019; Yitshak-Sade et al., 2019). A recent study in China found individuals living with higher air pollution were more likely to benefit from greenness exposure (Ji et al.,

2020). A study conducted in Spain also found interactions between air pollutants and greenness on natural-cause mortality (de Keijzer et al., 2017). In the present study, we found no significant evidence for multiplicative interactions between surrounding green and air pollution exposures on natural-cause mortality. We did observe an indication of monotonically decreasing associations between NDVI 1-km and natural-cause mortality in quartiles of $PM_{2.5}$ exposures (attenuated HRs for greenness in the higher $PM_{2.5}$ quartiles). Because $PM_{2.5}$ is a regional pollutant and the pollution levels showed a north–south increasing trend, the analysis stratified by quartiles of $PM_{2.5}$ concentrations may reflect different regions of the pooled cohort. This hypothesis is supported by the lack of interaction between NO_2 and greenness – as NO_2 is more locally varied and there is more overlap in NO_2 exposures across sub-cohorts than in $PM_{2.5}$.

Evidence regarding effect modification by age and sex in the association between greenness and mortality is still inconclusive (James et al., 2015; Markevych et al., 2017; Nieuwenhuijsen et al., 2017). In the present study, we observed stronger beneficial associations in younger individuals which is in line with two Canadian (Villeneuve et al., 2012; Crouse et al., 2017), and four European studies (Vienneau et al., 2017; Orioli et al., 2019; Klompmaker et al., 2021, Bauwelinck et al., 2021). We found no effect modification by sex, while opposite was observed in several previous studies (Bauwelinck et al., 2021; Crouse et al., 2017; Ji et al., 2020; Orioli et al., 2019; Vienneau et al., 2017).

Although several previous studies observed stronger associations with greenness in the individuals with higher social status compared to the lower (Ji et al., 2020; Vienneau et al., 2017), we found no effect modification by SES in the present study.

4.2. Strengths and limitations

A major strength of this study is the large sample size obtained by pooling 14 sub-cohorts with lifestyle data across Europe. Also, we were able to include a broad range of potential confounders that were harmonized across sub-cohorts (Chen et al., 2021; Strak et al., 2021), including detailed information on participants' lifestyle factors, which are usually not available in the administrative cohorts. We decided not to adjust for BMI and physical activity in the main model because we considered them as potential mediators rather than confounders. James et al., (2016) and Lachowycz and Jones (2014) showed evidence that greenness affects mortality partly through physical activity. We nevertheless observed robust association between surrounding greenness and natural-cause mortality after including BMI or physical activity as potential confounders in the sensitivity analyses. However, the interpretation of the analysis adjusting for physical activity may be limited by the lack of temporal trend information and highly different definitions across individual sub-cohorts.

In this study, we used NDVI to objectively characterize the general greenness exposure of the study participants. Despite its extensive use, NDVI only measures the quantity of green vegetation and does not provide information on the quality of greenness. Previous studies have shown that health effects of greenness may differ by the types of greenness (Hartig et al., 2014; Lee & Maheswaran, 2011). Furthermore, even if there is no clear consensus about the most appropriate scale at which to measure greenness (Mitchell et al., 2011), we followed the recent literature and explored greenness inside 300-m grid and radius of 1-km from participants' residential addresses as a measure of surrounding greenness easily accessible. We observed similar findings by applying the two metrics. The use of the 2010 NDVI measure at baseline residential addresses in cohorts that span several years may increase exposure misclassification error, which is likely non-differential, and may have resulted in underestimated effect estimates. However, our sensitivity analyses showed stable effect estimates when restricting analyses to follow-up periods starting from 2000, 2005, 2008 and 2010, with successively less temporal misalignment of the exposure assessment. Furthermore, we observed high correlations between NDVI measure in years 2005, 2010, 2015 and 2020, supporting our assumption of stable patterns in NDVI over time. We also observed high correlations between 2010 NDVI assigned to residential addresses at baseline and at the end of follow-up for participants who had information on residential history, suggesting bias introduced by not accounting for residential mobility is low. The findings are consistent with a previous study from the United Kingdom reporting correlations of 0.69 and 0.81 between NDVI exposures for 5-year periods including moving (de Keijzer et al., 2018). We previously documented that the spatial structure of $PM_{2.5}$ and NO_2 exposure models were robust at the west-European scale over time (de Hoogh et al., 2018). We furthermore documented that when we restricted the start of follow-up to year 2000, 2005, 2008 and 2010, effect estimates were almost identical as in the analysis of the full study period (Brunekreef et al., 2021). Road-traffic noise data were not harmonized across cohorts and we did not evaluate temporal stability of the noise exposure estimates, which is available for about a third of the study population. Given that noise emissions from road traffic have changed less in the past decades than air pollution emissions, we suspect that noise levels are likely at least as stable as air pollution levels over time. We were not able to adjust for access to health care in the present study. As access to health care is typically related to individual and area-level SES, we expected that adjusting for individual level SES and area-level mean income in the model would have taken care of the confounding by access to health care. Furthermore, healthcare services are covered for almost full population in the countries studied in the present study, according to an European Commission report (Baeten et al., 2018). There may be differences in coding of causes of mortality between countries. Potential differences in coding would unlikely have biased our associations, as we used strata for sub-cohort in the analysis. We furthermore only could use the underlying cause of death.

4.3. Conclusions

We found evidence of a negative association between surrounding greenness and natural-cause mortality after adjusting for several individual and area-level variables, as well as the spatially correlated environmental exposures air pollution and traffic noise in a large pooled study population. The negative associations were also observed for cardiovascular, cerebrovascular, ischemic heart disease, diabetes, respiratory, lung cancer and COPD mortality, though with more uncertainty especially after adjusting for air pollution.

Author contribution

Ainhoa Bereziartua: Conceptualization, Data curation, Formal analysis, Investigation, Visualization, Writing – original draft; **Jie Chen:** Conceptualization, Data curation, Formal analysis, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing; **Kees de Hoogh:** Writing – review & editing; **Sophia Rodopoulou:** Methodology, Visualization, Writing – review & editing; **Zorana J. Andersen:** Writing – review & editing; **Tom Bellander:** Writing – review & editing; **Jørgen Brandt:** Writing – review & editing; **Daniela Fecht:** Writing – review & editing; **Francesco Forastiere:** Writing – review & editing; **John Gulliver:** Writing – review & editing; **Ole Hertel:** Writing – review & editing; **Barbara Hoffmann:** Writing – review & editing; **Ulla Arthur Hvidtfeldt:** Writing – review & editing; **W. M. Monique Verschuren:** Writing – review & editing; **Karl-Heinz Jöckel:** Writing – review & editing; **Jeanette T. Jørgensen:** Writing – review & editing; **Klea Katsouyanni:** Methodology, Writing – review & editing; **Matthias Ketzel:** Writing – review & editing; **Norun Hjertager Krog:** Writing – review & editing; **Boel Brynedal:** Writing – review & editing; **Karin Leander:** Writing – review & editing; **Shuo Liu:** Writing – review & editing; **Petter Ljungman:** Writing – review & editing; **Elodie Faure:** Writing – review & editing; **Patrik K.E. Magnusson:** Writing – review & editing; **Gabriele Nagel:** Writing – review & editing; **Göran**

Pershagen: Writing – review & editing; **Annette Peters:** Writing – review & editing; **Ole Raaschou-Nielsen:** Writing – review & editing; **Matteo Renzi:** Writing – review & editing; **Debora Rizzuto:** Writing – review & editing; **Evangelia Samoli:** Methodology, Writing – review & editing; **Yvonne T. van der Schouw:** Writing – review & editing; **Sara Schramm:** Writing – review & editing; **Gianluca Severi:** Writing – review & editing; **Massimo Stafoggia:** Writing – review & editing; **Maciej Strak:** Writing – review & editing; **Mette Sørensen:** Writing – review & editing; **Anne Tjønneland:** Writing – review & editing; **Gudrun Weinmayr:** Writing – review & editing; **Kathrin Wolf:** Writing – review & editing; **Emanuel Zitt:** Writing – review & editing; **Bert Brunekreef:** Funding acquisition, Investigation, Project administration, Writing – review & editing; **Gerard Hoek:** Conceptualization, Investigation, Project administration, Supervision, Visualization, Writing – review & editing.

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.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2022.107341.

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