



# Surrounding green, air pollution, traffic noise exposure and non-accidental and cause-specific mortality

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## ABSTRACT

**Background:** Most previous studies that investigated associations of surrounding green, air pollution or traffic noise with mortality focused on single exposures.

**Objectives:** The aim of this study was to evaluate combined associations of long-term residential exposure to surrounding green, air pollution and traffic noise with total non-accidental and cause-specific mortality.

**Methods:** We linked a national health survey (Public Health Monitor, PHM) conducted in 2012 to the Dutch longitudinal mortality database. Subjects of the survey who were 30 years or older on 1 January 2013 (n = 339,633) were followed from 1 January 2013 till 31 December 2017. We used Cox proportional hazard models to evaluate associations of residential surrounding green (including the average Normalized Difference Vegetation Index (NDVI) in buffers of 300 m and 1000 m), annual average air pollutant concentrations (including particulate matter (PM<sub>10</sub>, PM<sub>2.5</sub>), nitrogen dioxide (NO<sub>2</sub>)) and traffic noise with non-accidental, circulatory disease, respiratory disease, lung cancer and neurodegenerative disease mortality.

**Results:** We observed 26,886 non-accidental deaths over 1.627.365 person-years of follow-up. Surrounding green, air pollution and traffic noise exposure were not significantly associated with non-accidental or cause-specific mortality. For non-accidental mortality, we found a hazard ratio (HR) of 0.99 (0.98, 1.01) per IQR increase in NDVI 300 m, a HR of 0.99 (95% CI: 0.97, 1.01) per IQR increase in NO<sub>2</sub>, a HR of 0.98 (0.97, 1.00) per IQR increase in PM<sub>2.5</sub> and a HR of 0.99 (95% CI: 0.97, 1.01) per IQR increase in road-traffic noise. Analyses restricted to non-movers or excluding subjects aged 85+ years did not change the findings.

**Conclusion:** We found no evidence for associations of long-term residential exposures to surrounding green, air pollution and traffic noise with non-accidental or cause-specific mortality in a large population based survey in the Netherlands, possibly related to the relatively short follow-up period.

## 1. Introduction

In daily life, humans are exposed to a mixture of environmental exposures that can affect health. Long-term exposure to air pollution for example, has been linked with increased non-accidental, cardiovascular disease, respiratory disease and lung cancer mortality (Atkinson et al., 2018; Hoek et al., 2013; Beelen et al., 2014a; Faustini, Rapp, and Forastiere, 2014). Long-term exposure to road-traffic noise has also been associated with increased non-accidental and cardiovascular disease mortality (Halonen et al., 2015; Gan et al., 2012; Sørensen et al., 2012; Héritier et al., 2017). Surrounding green has been associated with

decreased non-accidental, cardiovascular, respiratory disease and lung cancer mortality rates (Gascon et al., 2016; James et al., 2016; Villeneuve et al., 2012; Vienneau et al., 2017; Crouse et al., 2017; Richardson et al., 2010; Richardson and Mitchell, 2010; Mitchell and Popham, 2008). Surrounding green may influence health by promoting physical activity, decreasing stress and reducing air pollution and noise (James et al., 2015).

Exposures to surrounding green, air pollution and traffic noise are generally spatially correlated (Hystad et al., 2014; Thiering et al., 2016). In general, higher levels of surrounding green tend to go together with lower levels of air pollution and traffic noise because of

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absence of air pollution and noise sources in green areas or removal of air pollutants from the air (Nowak et al., 2018; Tallis et al., 2011). Road-traffic noise is related to traffic intensity, which also affects traffic-related air pollutants, like nitrogen dioxide (NO<sub>2</sub>). However, the large majority of studies on the associations of surrounding green, air pollution or traffic noise with mortality have evaluated only one of these environmental exposures, ignoring potential confounding by or interaction with the other two.

We recently reported associations between air pollution, traffic noise and surrounding greenness with self-reported cardio-metabolic and mental health in a cross-sectional analysis of a large national survey (Klompmaker et al., 2019a, 2019b). Correlations between air pollution, noise and residential greenness were weak to moderate. For the current study, we linked this Dutch national health survey to the Dutch longitudinal mortality database. The aim of this study was to evaluate combined associations of long-term residential exposure to surrounding green, air pollution and traffic noise with non-accidental and cause-specific mortality during a five year follow-up period (2013–2017).

## 2. Methods

### 2.1. Public health monitor

In the period of September - November 2012 a Dutch national health survey (Public Health Monitor, PHM (*Gezondheidsmonitor Volwassenen GGD-en, CBS en RIVM 2012*)) that covered issues related to personal characteristics, lifestyle and socio-economic status (SES) was conducted by the 28 Public Health Services (GGD-en), Statistics Netherlands (CBS) and the National Institute for Public Health and the Environment (RIVM). Statistics Netherlands has enriched the PHM with information on standardized household income and region of origin. Standardized household income is adjusted for differences in household size and composition. The elderly ( $\geq 65$  years) were oversampled as part of the design of the PHM. Further, only individuals living in non-institutionalized households were sampled. The PHM includes information on 387,195 citizens aged  $\geq 19$  years, the response rate was 47%. More information about the PHM can be found elsewhere (Statistics Netherlands, 2015).

### 2.2. Exposure assessment

#### 2.2.1. Surrounding green

We used two different green metrics to assess surrounding green. The Normalized Difference Vegetation Index (NDVI) was used to assess surrounding greenness, i.e. average density of green vegetation within a circular buffer of the participant's residential address. The NDVI was derived from LANDSAT\_5 TM and captures the density of green vegetation at a spatial resolution of 30 m. NDVI values range between  $-1$  and  $1$ , with higher numbers indicating a higher density of green vegetation. Negative NDVI values represent water and were set to zero (Klompmaker et al., 2018). We combined cloud free images from the summer of 2010 to create a map that covers (almost) the whole country.

A highly detailed national land-use database of the Netherlands of 2010 (TOP10NL, CC-BY Kadaster, 2010, <https://www.kadaster.com/automatic-generalisation>) was used to assess surrounding green space, i.e. the proportion of green space within a buffer around the participant's residential address. TOP10NL divides the Netherlands into polygons with different classes of land-use (water, road and terrain). The terrain class is divided in 21 subclasses; eleven of these classes correspond to green areas. TOP10NL does, in contrast to NDVI, not include private green property (such as gardens) and street greenery.

Surrounding greenness and surrounding green space were assessed in buffers with a 300 and 1000 m radius for all addresses in the Netherlands. More information about the assessment of surrounding green can be found elsewhere (Klompmaker et al., 2018). Analyses to

assess surrounding green were performed in ArcGIS 10.2.2 (Esri, Redlands, CA, USA).

#### 2.2.2. Air pollution

For each home address, long-term average concentrations of particulate matter [including particulate matter with aerodynamic diameter  $\leq 10 \mu\text{m}$  (PM<sub>10</sub>), particulate matter with aerodynamic diameter between 10 and  $2.5 \mu\text{m}$  (PM<sub>coarse</sub>), particulate matter with aerodynamic diameter  $\leq 2.5 \mu\text{m}$  (PM<sub>2.5</sub>), PM<sub>2.5</sub>absorbance (PM<sub>2.5</sub>abs), a marker of black carbon] and nitrogen dioxide (NO<sub>2</sub>) were assessed by land-use regression (LUR) models developed within the framework of the ESCAPE project (Beelen et al., 2013; Eeftens et al., 2012). NO<sub>2</sub> levels higher than  $80 \mu\text{g}/\text{m}^3$  ( $n = 18$ ) were set to  $80 \mu\text{g}/\text{m}^3$  as these values are probably due to an unrealistic combination of explanatory variables (the maximum annual average NO<sub>2</sub> concentration measured within the ESCAPE study is  $61.5 \mu\text{g}/\text{m}^3$ ). Further, we used long-term average concentrations of two Oxidative Potential (OP) metrics – electron spin resonance (OP<sup>ESR</sup>) and dithiothreitol (OP<sup>DTT</sup>) (Yang et al., 2015). OP is an intrinsic measure of PM to oxidize target molecules and thus effectively incorporates biologically relevant properties of PM (Yang et al., 2015). LUR models were based on air pollution measurements conducted in 2009. Performances of the LUR models were evaluated using leave-one out cross validation (R2LOOCV) and ranged from 0.38 for PM<sub>coarse</sub> to 0.89 for PM<sub>2.5</sub>abs (Beelen et al., 2013; Eeftens et al., 2012; Yang et al., 2015).

#### 2.2.3. Traffic noise

Residential traffic noise levels were assessed by the Standard Model Instrumentation for Noise Assessments (STAMINA). STAMINA is a model to map environmental noise in the Netherlands. This model was developed at the Dutch National Institute for Public Health and the Environment (RIVM) and uses the standard Dutch Calculation method for traffic and industrial noise (Schreurs et al., 2010). The spatial resolution of the noise maps depends on the distance between source and observation point. The lowest resolution is  $80 \times 80 \text{m}$ , and close to the source the level of detail is highest, with a resolution of  $10 \times 10 \text{m}$  (Schreurs et al., 2010).

Daily average (24 h, Lden) and night-time average (23:00–07:00 h, Lnight) road- and rail-traffic noise exposures were assessed for 2011. Since correlations between Lden and Lnight were high (spearman  $\rho = 0.99$  for road-traffic and  $0.95$  for rail-traffic noise), we only used Lden in our analyses.

### 2.3. Study population

We linked the PHM to the Dutch longitudinal mortality database, with a follow-up period from 1 January 2013 until 31 December 2017 that has been provided by Statistics Netherlands (CBS). Residential surrounding green, air pollution and road- and rail-traffic noise exposures were linked to the home address on January the 1st of 2013 of each PHM subject.

Of all subjects who completed the PHM,  $< 0.5\%$  was lost to follow-up in the period between filling in the PHM (September - November 2012) and the start of the follow-up period (1 January 2013). We included only subjects aged 30 years or older on 1 January 2013 in the cohort, in line with other studies on environmental exposures and mortality (Vienneau et al., 2017; Fischer et al., 2015; Héritier et al., 2017). Hence, approximately 9.5% of the PHM subjects and less than 0.5% of the deaths were excluded. The reason for this is that risk factors for deaths in early life (including especially infant mortality) may be different from those in later life. In most populations including our study population, the restriction did not affect the number of included events much, as mortality rates of subjects aged  $< 30$  years are low. Further, since we did not have land-use data across the border of the Netherlands, subjects with residential addresses within 1 km (largest buffer) of the border of the Netherlands were excluded from our cohort

(~2.5%), resulting in a study population of 339,633 subjects.

We linked several local and regional SES indicators to the cohort to adjust for potential confounding not accounted for by individual (SES) indicators. Regional indicators were based on NUTS 3 regions of the Netherlands ( $n = 40$ ). NUTS (Nomenclature des Unités Territoriales Statistique) is a geocode standard for referencing the subdivisions of countries for statistical purposes and is developed and regulated by Eurostat, the statistical office of the European Union. Local SES indicators were based on neighborhood level ( $n \sim 2600$ , representing on average approximately 2900 addresses). We linked mean income (mean income per income recipient), percentage of (non-western) immigrants and unemployment rate (number of people with income support per 1000 inhabitants aged 15–64 years) of 2010 at regional and neighborhood level to the study population. Further, we used a composite SES score that represents the educational, occupational and economical status at a four-digit postal code level (PC4,  $n \sim 4000$ , representing on average approximately 1800 addresses). This composite score was only available at PC4 level; hence we do not have the composite score at regional or neighborhood level.

#### 2.4. Outcome definition

We selected non-accidental mortality [International Classification of Diseases, 10th Revision (ICD-10) codes: A00-R99], circulatory disease mortality (I00-I99), respiratory disease mortality (J00-J99), lung cancer mortality (C34) and neurodegenerative disease mortality [including dementia (F00-F03), motor neuron disease (G12.2), Parkinson (G20-G22), Alzheimer (G30), MS (G35)] as our main outcomes. Secondary analyses were conducted with more specific mortality outcomes: ischemic heart disease mortality (I20-I25; IHD), cerebrovascular mortality (I60-I69), COPD mortality (J40-J44) and dementia mortality (F00-F03)].

From 2013, Statistics Netherlands (CBS) switched from manual coding of mortality statistics to an automatic system (IRIS) for the selection of the underlying cause of death. IRIS automatically selects the underlying cause of death when multiple causes of death are reported based on internationally agreed decision tables. In approximately 75% of the cases, multiple causes of death are reported (Harteloh et al.). The use of IRIS makes it easier to compare mortality statistics with other countries that use IRIS; moreover, it increases the reproducibility of the data.

#### 2.5. Statistical analyses

We imputed the missing values of potential confounding variables as a sizable number of subjects missed information on at least one potential confounder. We furthermore observed that subjects with missing data were more likely to die during follow-up (Table 1). The percentage of missing values per covariate was relatively low (Table 2), the highest percentage of missing values was found for number of glasses alcohol per week (9.1%) and cigarettes smoked per day (9.2%). In total, approximately 28% of the study population had at least one missing value on a potential confounding variable. We performed multiple imputation of missing values using chained equations (MICE package, (van Buuren and Groothuis-Oudshoorn, 2010)) to generate 15 datasets using 15 iterations. All variables used in the regression models were available in the imputation procedure, plus some auxiliary variables [degree of urbanization, medication prescription for diabetes (ATC4 code: A10B), asthma or COPD (R03A, R03B, R03C, R03D), anxiolytics (N05B), hypnotics & sedatives (N05C) and antidepressants (N06A)].

Datasets were created in SAS, all analyses were performed with R 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria) (R Core Team 2016).

##### 2.5.1. Regression models

To study whether the environmental exposures were associated with

non-accidental and cause-specific mortality, we used Cox proportional hazard models. We specified *a priori* several Cox models with age as underlying time scale and increasing degrees of covariate adjustment. Model 1 included the baseline hazard stratified by sex. Model 2 was additionally adjusted for marital status, country of origin, paid occupation, standardized household income and level of education. Model 3 was additionally adjusted for physical activity, body mass index (BMI), smoking status, number of cigarettes smoked for current smokers (linear and quadratic term), alcohol status, number of glasses of alcohol for current consumers (linear and squared term). Model 4 was additionally adjusted for neighborhood mean income, neighborhood percentage of immigrants, neighborhood unemployment rate and PC4 composite SES. Model 5 (main model) was additionally adjusted for region mean income, region percentage of immigrants and region unemployment rate. Categories of covariates in the Cox models were identical to the categories presented in Table 2, except for region of origin (7 categories: Dutch native, Morocco, Turkey, Suriname, Netherlands Antilles, Other non-western, Other western), physical activity (5 categories: quintiles), SES region (5 categories: quintiles) and SES neighborhood (5 categories: quintiles) and PC4 composite SES (5 categories: quintiles).

Hazard ratios (HRs) presented in this study are based on the full (imputed) population unless otherwise stated. HRs were pooled over the 15 imputed datasets based on Rubin's rules; the HRs from all imputed datasets were averaged and the standard errors were pooled by combining the within and between imputation variance (van Buuren and Groothuis-Oudshoorn, 2010). HRs (main model) based on the complete case population ( $n = 244,814$ ) are presented in the supplement.

We plotted exposure-response curves for all exposure-outcome combinations using natural splines with 3 degrees of freedom for one of the 15 imputed datasets. To test whether the goodness-of-fit of the models with splines was significantly better than the goodness-of-fit of the linear models, we used the likelihood ratio test and defined statistical significance by a two-sided alpha level of  $p = 0.05$ . Exposure-response curves showed non-significant or small deviations from linearity for most associations (Fig. S1a–e). Hence, we decided to report results for continuous exposure terms in the main text and tables. Results for quintiles of each exposure are reported in the supplement. We quantified the linear effect of exposure to surrounding green, air pollution and traffic noise per interquartile range (IQR) to allow comparison of effect sizes across exposures.

Several studies showed that associations of surrounding green, air pollution or traffic noise with mortality differ by age (Crouse et al., 2015; Fischer et al., 2015; Héritier et al., 2017; Vienneau et al., 2017; Villeneuve et al., 2012). Hence, we performed analyses with interaction terms for age to evaluate potential effect modification by age ( $< 65$  years vs.  $\geq 65$  years).

To evaluate potential mutual confounding of exposures, we performed two-exposure regression analyses with combinations of surrounding green, air pollution and traffic noise exposures. To evaluate potential interaction effects of combined exposures, we specified interaction terms between the exposures. We assessed interaction effects by combining a continuous exposure term with quintiles of another exposure and vice versa. Interaction effects were assessed on the multiplicative scale. We hypothesized that the effect of exposure to air pollution is strongest (increased odds) in the highest road-traffic noise quintile and vice versa. Further, we expected that the effect of air pollution or road-traffic noise would be strongest (increased odds) in the lowest surrounding green quintile and that the effect of surrounding green would be strongest (decreased odds) in the lowest air pollution or road-traffic noise quintile.

As sensitivity analyses, we evaluated associations of surrounding green, air pollution and traffic noise with mortality for the non-movers (all subjects who did not move in the 5 years preceding the start of the follow-up period,  $n = 279,123$ ), for all subjects younger than 85 years

**Table 1**

Descriptive statistics of the mortality outcomes and exposures in the full (imputed) population (n = 339,633) and for the complete case population (n = 244,814).

Outcome	ICD-10 codes	Full population N (%)	Complete case population N (%)
Non-accidental mortality	- A00-R99	26,886 (7.9)	15,169 (6.2)
Circulatory disease mortality	- I00-I99	8020 (2.4)	4281 (1.7)
Ischemic heart disease mortality	- I20-I25	1986 (0.6)	1113 (0.5)
Cerebrovascular disease mortality	- I60-I69	1773 (0.5)	920 (0.4)
Respiratory disease mortality	- J00-J99	2429 (0.7)	1333 (0.5)
COPD mortality	- J40-J44	1357 (0.4)	756 (0.3)
Lung cancer mortality	- C34	2195 (0.6)	1353 (0.6)
Neurodegenerative disease mortality	- F00-F03, G12.2, G20-G22, G30, G35	2016 (0.6)	1028 (0.4)
Dementia mortality	- F00-F03	1151 (0.3)	554 (0.2)
<b>Exposure</b>	<b>Exposure indicator (unit)</b>	<b>median (IQR)</b>	<b>median (IQR)</b>
Surrounding green	- NDVI 300 m	0.52 (0.13)	0.53 (0.13)
	- NDVI 1000 m	0.57 (0.14)	0.57 (0.14)
	- TOP10NL 300 m (proportion)	0.19 (0.24)	0.19 (0.24)
	- TOP10NL 1000 m (proportion)	0.38 (0.32)	0.38 (0.32)
Air pollution	- NO <sub>2</sub> (µg/m <sup>3</sup> )	23.01 (7.61)	23.08 (7.54)
	- PM <sub>10</sub> (µg/m <sup>3</sup> )	24.41 (1.18)	24.42 (1.17)
	- PM <sub>coarse</sub> (µg/m <sup>3</sup> )	8.05 (0.77)	8.06 (0.77)
	- PM <sub>2.5</sub> (µg/m <sup>3</sup> )	16.69 (0.83)	16.67 (0.83)
	- PM <sub>2.5abs</sub> (10 <sup>-5</sup> /m)	1.24 (0.24)	1.24 (0.24)
	- OP <sup>DTT</sup> (nmol DTT/min/m <sup>3</sup> )	1.20 (0.28)	1.19 (0.27)
	- OP <sup>ESR</sup> (A.U./1000/m <sup>3</sup> )	0.89 (0.17)	0.89 (0.17)
Traffic noise	- Road-traffic noise, Lden (dB)	53.2 (7.40)	53.1 (7.30)
	- Rail-traffic noise, Lden (dB)	29.0 (8.60)	29.0 (8.70)

at baseline (n = 325,712) and younger than 75 years at baseline (n = 271,471). Further, we additionally adjusted for NUTS 1 regions (North, East, West, and South) of the Netherlands to adjust for broad regional patterns of mortality not accounted for by the potential confounders.

Several studies have linked existing (national) administrative databases with surrounding green, air pollution and traffic noise exposure to evaluate associations with mortality (Fischer et al., 2015; Vienneau et al., 2017; Héritier et al., 2017; Crouse et al., 2017, 2015; Villeneuve et al., 2012). These administrative cohorts have size advantages over individual cohorts, but often lack in-depth information on potential confounders, such as lifestyle factors. To assess potential confounding by missing lifestyle factors, we also ran models with adjustments for covariates that were available for all Dutch individuals in the national mortality database (age, sex, marital status, country of origin, standardized household income, region SES and neighborhood SES). Categories of these covariates were similar to the categories we used in the main model, except for standardized household income (10 categories based on quantiles of all Dutch households: < 1%, 1–5%, 5–10%, 10–25%, 25–50%, 50–75%, 75–90%, 90–95%, 95–99%, > 99%).

### 3. Results

#### 3.1. Study population and exposure distribution

Our study population consisted of 339,633 persons aged 30 years or older. We observed 26,886 non-accidental deaths, 8020 circulatory disease deaths and 2429 respiratory disease deaths over 1.627.365 person-years of follow-up (Table 1). For the complete case population (n = 244,814), percentages of non-accidental and cause-specific mortality were lower than for the full population, e.g. 6.2% non-accidental deaths compared to 7.9% in the full population (Table 1), indicating that mortality rates were generally higher for people with missing covariate information. Descriptive statistics of covariates in imputed and observed datasets are given in Table 2. The distribution of most covariates was very similar in the imputed and observed population. Due to oversampling of the elderly in the PHM, the median age (63 years) in our study population was higher than in the entire Dutch population aged 30 years or older (53 years). Further, people of Dutch origin (87% versus 81%) were overrepresented in our study population

compared to the entire Dutch population aged 30 years or older.

The variation (IQR/median) in TOP10NL surrounding green space was larger than the variation in NDVI surrounding greenness. The variation in PM<sub>10</sub>, PM<sub>coarse</sub> and PM<sub>2.5</sub> concentrations was substantially lower than the variation in the concentrations of other more traffic-related air pollutants, such as NO<sub>2</sub> and PM<sub>2.5abs</sub> (Table 1). Road-traffic noise varied less than the traffic-related air pollutants, but more than PM<sub>10</sub>, PM<sub>coarse</sub> and PM<sub>2.5</sub>. The median (IQR) exposure to NDVI 300 m, NO<sub>2</sub> and road-traffic noise were 0.52 (0.13), 23.01 (7.61) µg/m<sup>3</sup> and 53.2 (7.40) dB, respectively. The medians and IQRs of the exposures in the full population were similar to the complete case population (Table 1).

Surrounding green, air pollution and traffic noise exposures were overall moderately correlated (Fig. S2). For example, NO<sub>2</sub> was positively correlated with road-traffic noise (Spearman rho = 0.40) and negatively correlated with NDVI 300 m (Spearman rho = -0.48). NDVI 300 m was also negatively correlated with road-traffic noise (Spearman rho = -0.22). Air pollution and traffic noise were weakly negatively correlated with PC4 composite SES and mean income, while surrounding green was weakly positively correlated with both indicators (Fig. S2). For neighborhood percentage of immigrants, we found moderate to strong negative correlations with surrounding green and positive correlations with air pollution.

#### 3.2. Associations of exposures with mortality

In our main model, surrounding green, air pollution and traffic noise exposure were not associated with non-accidental, circulatory disease, respiratory disease, lung cancer or neurodegenerative disease mortality (Table 3 for linear analyses and Table S1 for quintile analyses). For non-accidental mortality, we found a HR of 0.99 (0.98, 1.01) per IQR increase in NDVI 300 m, a HR of 0.99 (95% CI: 0.97, 1.01) per IQR increase in NO<sub>2</sub> and a HR of 0.99 (95% CI: 0.97, 1.01) per IQR increase in road-traffic noise. Table S2 presents associations of air pollution and road-traffic noise with mortality expressed for more commonly used increments (per 10 µg/m<sup>3</sup> for NO<sub>2</sub>, PM<sub>10</sub> and PM<sub>2.5</sub> and per 10 dB for road-traffic noise), to facilitate easier comparison with previous studies. HRs based on the full (imputed) population were approximately similar to the HRs based on the complete case population (Table S3). Further, similar HRs (main model) in each individual



**Table 2**  
Descriptive statistics of covariates in full (imputed) population and observed data (n = 339,633).

Covariate [percentage missing]	category	Full population Percentage/median (IQR)	Observed data Percentage/median (IQR)
- Sex [0]	female	54.1	54.1
- age [0]		63 (23)	63 (23)
<b>Individual socio-economic status</b>			
- marital status [0]	married, living together	66.1	66.1
	unmarried, never married	12.4	12.4
	divorced	9.3	9.3
	widowed	12.2	12.2
- region of origin [0]	Dutch	87.1	87.1
	other western <sup>a</sup>	8.8	8.8
	other non-western <sup>b</sup>	4.1	4.1
- education [3.5]	primary or less	10.9	10.6
	lower-secondary	37.4	37.3
	higher-secondary	25.7	25.9
	University	26.0	26.3
- paid occupation [7.3]	yes	43.0	45.0
- standardized household income [0.4] <sup>c</sup>	< €15,200	9.2	9.2
	€15,200–19,399	19.9	19.9
	€19,400–24,199	21.5	21.5
	€24,200–30,999	23.5	23.6
	≥ €31,000	25.9	25.9
<b>Lifestyle factors</b>			
- smoking status [6.3]	current	18.5	18.7
	former	42.9	42.8
	never	38.6	38.4
- number of cigarettes smoked [9.2]	number of cigarettes smoked/day for current smokers	10 (13)	10 (10)
- alcohol use [3.9]	current	81.6	81.9
	former	6.3	6.2
	never	12.1	11.9
- alcohol consumption [9.1]	number of glasses/week for current consumers	6 (10.5)	6 (10.5)
- BMI [4.1]	< 18.5 kg/m <sup>2</sup>	1.0	1.0
	18.5–24.9 kg/m <sup>2</sup>	44.0	44.2
	25.0–30.0 kg/m <sup>2</sup>	40.4	40.4
	> 30.0 kg/m <sup>2</sup>	14.5	14.4
- Physical activity [9.0]	min/week	600 (960)	600 (960)
<b>Area-level socio-economic status</b>			
- PC4 (4 digit postal code) composite SES [0.2]	Based on education, income and paid occupation (year = 2010)	0.34 (1.19)	0.34 (1.19)
- Mean income neighborhood [0]	Mean income per income recipient *€ 1000 (year = 2010)	29.4 (4.9)	29.4 (4.9)
- Unemployment rate neighborhood [0.0]	Number of people with income support per 1000 inhabitants of 15–64 years (year = 2010)	24.0 (9.0)	24.0 (9.0)
- Percentage of immigrants neighborhood [0]	Percentage non-western immigrants (year = 2010)	5.0 (10.0)	5.0 (10.0)
- Income region [0]	Mean income per income recipient (year = 2010)	34.4 (2.7)	34.4 (2.7)
- Unemployment rate region [0]	Number of people with income support per 1000 inhabitants of 15–64 years (year = 2010)	24.5 (7.3)	24.5 (7.3)
- Percentage of immigrants region [0]	Percentage non-western immigrants (year = 2010)	8.4 (5.4)	8.4 (5.4)

<sup>a</sup> Other western: Europe, North America, Oceania, Indonesia, Japan.

<sup>b</sup> Other non-western: Africa, Latin America, Asia (including Turkey, excluding Indonesia and Japan).

<sup>c</sup> Standardized household income is adjusted for differences in household size and composition.

imputed dataset were observed.

In our minimally adjusted models, we found inverse associations of surrounding green and positive associations of air pollution with almost all mortality outcomes (Fig. S3a–e). In general, associations attenuated but remained significant after adjustments for individual SES (model 2, m2). Additional adjustments for lifestyle factors attenuated associations substantially and most associations lost significance (model 3, m3). After adjustments for individual SES and lifestyle factors, additional adjustments for neighborhood and PC4 SES (model 4, m4) and region SES (model 5, m5) barely affected the associations. Road- and rail-traffic noise were not associated with any mortality outcome in our minimally adjusted models (Fig. S3a–e). In the model adjusted only for the covariates that were available for the entire Dutch population (age, sex, marital status, country of origin, standardized household income, region SES, PC4 SES and neighborhood SES), associations were similar to associations of our main model for air pollution and traffic noise (Fig. 1 and Fig. S4, model labelled as “cov all”). For surrounding green, inverse associations with non-accidental and respiratory disease mortality were found in this less adjusted model. For example, for

respiratory disease mortality we found a HR of 0.94 (95% CI: 0.89, 1.00) for an IQR increase in NDVI 300 m.

We found no indications for effect modification by age for non-accidental mortality (Table S4). For circulatory disease, respiratory disease, lung cancer and neurodegenerative disease mortality, associations for non-elderly differed from associations for elderly (Table S4). However, there was no consistent pattern of differences in associations between non-elderly and elderly subjects across causes of death. For example, for respiratory disease mortality an IQR increase in NO<sub>2</sub> was associated with a HR of 1.11 (95% CI: 0.90–1.38) for the non-elderly and a HR of 0.88 (95% CI: 0.71, 1.09) for the elderly, whereas for circulatory disease mortality, an IQR increase in NO<sub>2</sub> was associated with a HR of 0.93 (95% CI: 0.81, 1.05) for the non-elderly and a HR of 1.05 (95% CI: 0.92, 1.19) for the elderly.

In the sensitivity analyses where we excluded movers or subjects aged 85+, we found similar HRs as in the full study population (Fig. 1 and Fig. S4). In the analyses where we excluded subjects aged 75+, associations were slightly different with wider confidence intervals: HRs more below 1 for air pollution and traffic noise for non-accidental

**Table 3**

Associations of surrounding green, air pollution and traffic noise with non-accidental, circulatory disease, respiratory disease, lung cancer and neurodegenerative disease mortality in the full (imputed) population.<sup>a</sup>

Exposure (IQR)	Non-accidental mortality HR (95% CI)	Circulatory disease mortality HR (95% CI)	Respiratory disease mortality HR (95% CI)	Lung cancer mortality HR (95% CI)	Neurodegenerative disease mortality HR (95% CI)
NDVI 300 m (0.13)	0.99 (0.98, 1.01)	1.01 (0.98, 1.05)	0.98 (0.92, 1.04)	1.03 (0.97, 1.09)	0.98 (0.92, 1.04)
NDVI 1000 m (0.14)	0.99 (0.97, 1.01)	1.00 (0.97, 1.04)	0.99 (0.92, 1.06)	1.03 (0.96, 1.11)	0.97 (0.90, 1.05)
TOP10NL 300 m (0.24)	1.01 (0.99, 1.02)	1.03 (1.00, 1.06)	0.99 (0.93, 1.05)	1.03 (0.97, 1.09)	1.02 (0.96, 1.09)
TOP10NL 1000 m (0.32)	1.00 (0.98, 1.03)	1.02 (0.97, 1.06)	1.03 (0.95, 1.12)	1.02 (0.94, 1.11)	1.00 (0.92, 1.10)
NO <sub>2</sub> (7.61 µg/m <sup>3</sup> )	0.99 (0.97, 1.01)	0.97 (0.93, 1.01)	0.98 (0.91, 1.06)	1.03 (0.96, 1.11)	1.02 (0.94, 1.11)
PM <sub>10</sub> (1.18 µg/m <sup>3</sup> )	1.00 (0.98, 1.01)	0.99 (0.96, 1.02)	0.97 (0.92, 1.02)	0.99 (0.94, 1.05)	1.00 (0.95, 1.06)
PM <sub>coarse</sub> (0.77 µg/m <sup>3</sup> )	1.00 (0.99, 1.02)	0.99 (0.96, 1.02)	0.98 (0.92, 1.04)	0.99 (0.93, 1.05)	1.02 (0.96, 1.09)
PM <sub>2.5</sub> (0.83 µg/m <sup>3</sup> )	0.98 (0.97, 1.00)	0.98 (0.95, 1.01)	0.98 (0.93, 1.04)	1.02 (0.97, 1.08)	0.95 (0.90, 1.01)
PM <sub>2.5</sub> abs (0.24 µg/m <sup>3</sup> )	0.99 (0.97, 1.01)	0.98 (0.96, 1.01)	0.97 (0.92, 1.03)	1.00 (0.95, 1.05)	0.97 (0.92, 1.03)
OP <sup>PIV</sup> (0.28 nmol DTT/min/m <sup>3</sup> )	0.98 (0.96, 1.00)	0.97 (0.94, 1.01)	1.01 (0.94, 1.08)	1.03 (0.96, 1.11)	0.98 (0.91, 1.05)
OP <sup>ESR</sup> (0.17 A.U./1000/m <sup>3</sup> )	1.00 (0.98, 1.02)	0.99 (0.96, 1.01)	0.96 (0.91, 1.02)	1.04 (0.98, 1.09)	1.00 (0.95, 1.06)
Road-traffic noise, Lden (7.40 dB)	0.99 (0.97, 1.01)	0.99 (0.96, 1.02)	0.95 (0.90, 1.00)	0.97 (0.92, 1.03)	0.97 (0.91, 1.02)
Rail-traffic noise, Lden (8.60 dB)	0.99 (0.97, 1.00)	0.98 (0.95, 1.01)	1.03 (0.98, 1.09)	0.99 (0.94, 1.04)	0.98 (0.92, 1.03)

<sup>a</sup> Results are presented as HR (95% CI) per interquartile range increase. We used models with age as underlying time scale, stratified by sex and adjusted for marital status, region of origin, education, paid occupation, standardized household income, physical activity, BMI, smoking status, cigarettes smoked, alcohol status, glasses alcohol, PC4 composite SES, mean income neighborhood, unemployment neighborhood, percentage of immigrants neighborhood, mean income region, unemployment region and percentage of immigrants region.

and circulatory disease mortality and slightly above unity for air pollution and respiratory and lung cancer mortality. Additional adjustment for region of the Netherlands (four levels) barely affected the HRs of the main model (Fig. 1 and Fig. S4, model labelled as “adj area”).

For COPD and dementia mortality, we found no associations of surrounding green, air pollution and traffic noise in the full (imputed) population (Table S5). We found some (significant) positive associations of air pollution with cerebrovascular disease mortality and (mostly significant) negative associations of air pollution with ischemic heart disease mortality. Surrounding green and traffic noise were not associated with cerebrovascular disease or ischemic heart disease mortality.

In multi-exposure models, associations of exposures with mortality were similar to associations in single-exposure models (Table S7). For example, in a single-exposure model the HR for an IQR increase in NDVI 300 m for respiratory disease mortality was 0.98 (95% CI: 0.92, 1.04), in a model additionally adjusted for NO<sub>2</sub> the HR was 0.97 (95% CI: 0.91, 1.03) and in a model additionally adjusted for road-traffic noise the HR was 0.97 (95% CI: 0.91, 1.03). We found no indications for multiplicative interaction effects in the hypothesized directions between combinations of exposure variables and mortality. Some interaction terms were significant, but there was no clear pattern of interaction effects (Table S8). For example, an IQR increase in road-traffic noise in the lowest NDVI 300 m quintile was associated with a decreased risk on circulatory mortality (HR = 0.92, 95% CI: 0.86, 0.97). In the highest NDVI 300 m quintile, an IQR increase in road-traffic noise was associated with an increased risk on circulatory mortality (HR = 1.12, 95% CI: 1.03, 1.21).

#### 4. Discussion

Residential surrounding green, air pollution and traffic noise were not significantly associated with total non-accidental, circulatory disease, respiratory disease, lung cancer and neurodegenerative disease mortality over a five year follow-up period, in a large Dutch study population with individual lifestyle data.

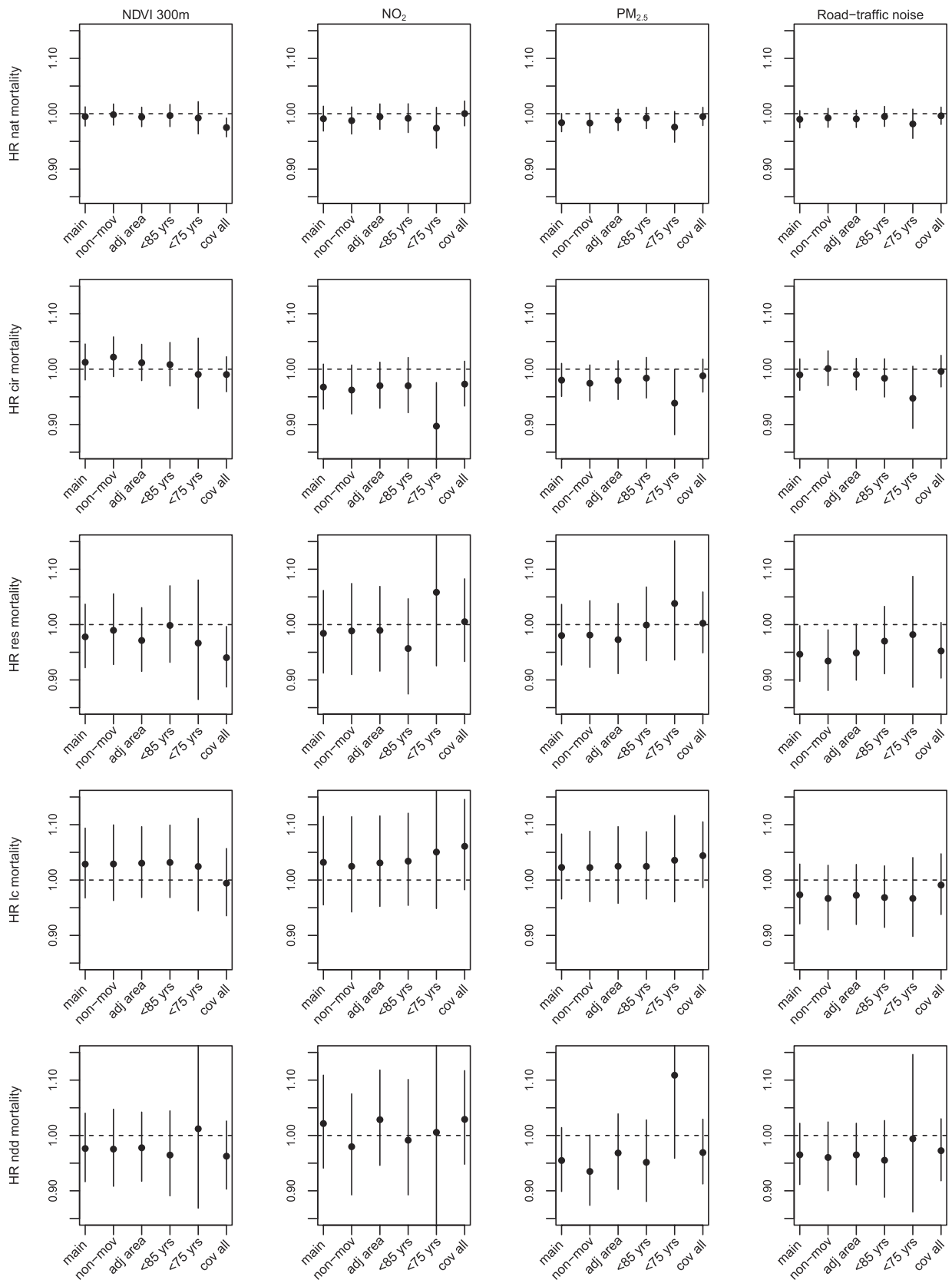
##### 4.1. Comparison with previous studies

A systematic review presented evidence that living in areas with higher amounts of residential green was inversely associated with cardiovascular diseases mortality (Gascon et al., 2016). In this review,

results for non-accidental mortality were less consistent and no studies found associations with lung cancer mortality (Gascon et al., 2016). More recently published studies reported inverse associations of surrounding green with non-accidental, cardiovascular, respiratory, IHD and stroke mortality (Vienneau et al., 2017; Crouse et al., 2017; James et al., 2016), but not with neurodegenerative disease mortality (James et al., 2016). However, several of these studies used an administrative cohort to evaluate associations of surrounding green, with limited ability to adjust for potential confounders such as lifestyle factors (Crouse et al., 2017; Vienneau et al., 2017; Villeneuve et al., 2012). Our results showed that HRs for surrounding greenness based on models with adjustment only for covariates that were available for the entire Dutch population were different from HRs based on models with adjustment for all covariates, including lifestyle factors, for non-accidental and respiratory disease mortality outcomes. For respiratory disease mortality for example, we found a HR of 0.98 (95% CI: 0.92, 1.04) per IQR increase in NDVI 300 m in our main model and a HR of 0.94 (95% CI: 0.89, 1.00) in our model with adjustments for covariates that were available for the entire population only. This suggests that the lack of adjustments for lifestyle factors could lead to an overestimation of the association of surrounding green in the Netherlands. Whether this applies to other study areas and populations depends primarily on the typically complex correlation between surrounding green and lifestyle.

Contrary to our findings, reviews of long-term air pollution exposure and mortality indicated that air pollution (mainly NO<sub>2</sub> and PM<sub>2.5</sub>) is associated with non-accidental, cardio-vascular disease, respiratory disease and lung cancer mortality (Hoek et al., 2013; Atkinson et al., 2018). Meta-analyses showed HRs of 1.02 (95% CI: 1.01, 1.03) per 10 µg/m<sup>3</sup> increase in NO<sub>2</sub> and of 1.06 (95% CI: 1.04, 1.08) per 10 µg/m<sup>3</sup> increase in PM<sub>2.5</sub> for non-accidental mortality (Atkinson et al., 2018; Hoek et al., 2013). Substantial heterogeneity in effect estimates of individual studies was reported for almost all causes of death (Hoek et al., 2013; Atkinson et al., 2018). Some studies, such as Crouse et al. (2015) and Fischer et al. (2015) reported positive associations of NO<sub>2</sub> and PM<sub>2.5</sub> with non-accidental mortality, others, such as Beelen et al. (2014) and Lipsett et al. (2011) found no associations in line with our study. Possible explanations for the heterogeneity in effect estimates are differences in exposure definition and misclassification, adjustment for potential confounding factors and in study population characteristics.

There are a few studies that investigated associations of road-traffic noise with mortality, mainly cardiovascular disease mortality (Gan



(caption on next page)

**Fig. 1.** Associations of surrounding green, air pollution and traffic noise with non-accidental (nat), circulatory disease (cir), respiratory disease (res), lung cancer (lc) and neurodegenerative disease (nnd) mortality in sensitivity models based in the full (imputed) population.<sup>a,b</sup> <sup>a</sup>Results are presented as HR (95% CI) per inter-quartile range increase. We used models with age as underlying time scale, stratified by sex and adjusted for marital status, region of origin, education, paid occupation, standardized household income, physical activity, BMI, smoking status, cigarettes smoked, alcohol status, glasses alcohol, PC4 composite SES, mean income neighborhood, unemployment neighborhood, percentage of immigrants neighborhood, mean income region, unemployment region and percentage of immigrants region. <sup>b</sup>main = main model, non-mov = subset analyses with only non-movers, adj area = m5 additionally adjusted for region (NUTS 1) of the Netherlands, < 85 yrs = subset analyses with subjects aged < 85 years, < 75 yrs = subset analyses with subjects aged < 75 years, cov all = model with adjustments for covariates that were available for all Dutch individuals in the national mortality database (Models with age as underlying timescale, stratified by sex and adjusted for marital status, country of origin, standardized household income, PC4 composite SES, mean income neighborhood, unemployment neighborhood, percentage of immigrants neighborhood, mean income region, unemployment region and percentage of immigrants region).

et al., 2012; Halonen et al., 2015; Sørensen et al., 2012; Héritier et al., 2017; Beelen et al., 2009; van Kempen et al., 2018). Beelen et al. (2009) reported associations of road-traffic noise with cardiovascular diseases in a Dutch cohort. However, associations were only found in the highest noise category (> 65 dB), suggesting a non-linear relationship. In the recent WHO evaluation, some evidence for an association of road traffic noise with ischemic heart disease mortality (and disease) was found, but associations were heterogeneous (van Kempen et al., 2018). We found no associations of traffic noise on circulatory disease, ischemic heart disease and cerebrovascular disease mortality, even in our minimally adjusted models. Further, no indications for a threshold level in analyses with categories of traffic noise or splines were found.

#### 4.2. Potential reasons for lack of associations

We do not have a clear explanation for the lack of a relationship between surrounding green, air pollution or traffic noise and mortality. The lack of an association could either be due to the absence of true associations between the exposures and mortality in this study population, or methodological issues such as the relatively short follow-up period, characteristics of our study population and confounder adjustment.

Effect estimates of environmental exposures on mortality are generally modest in size. Therefore, a large sample size with a sufficient number of events is needed to observe associations with environmental exposures. We followed 339,633 subjects with more than 25,000 deaths from 2013 till 2018. The number of events (deaths) was large – except for specific mortality outcomes such as lung cancer mortality – because of the large study population. However, the follow-up period was relatively short and may not have been sufficient to capture subtle differences in event rates across exposure ranges. Hart et al. for example found stronger associations of black smoke with incident lung cancer in a Dutch cohort of 120,852 subjects with a follow-up period of 17.3 years compared to the same cohort with a follow-up period 11.3 years (Hart et al., 2015). We note that for PM<sub>2.5</sub> and PM<sub>10</sub>, confidence intervals of HRs expressed per 10 µg/m<sup>3</sup> were relatively wide (Table S2), related to the short follow-up and the small exposure contrast for these pollutants. For the other exposures, confidence intervals were smaller related to the larger exposure contrast.

In the PHM, the elderly (65+ years) were oversampled as part of the design. Therefore, the median age in our study population was higher (63 years) compared to the median age in the full Dutch population aged 30 years or older (53 years). Several studies reported associations of surrounding green, air pollution and traffic noise in older age groups; however, the highest effect estimates were generally found in the younger age groups (Crouse et al., 2015; Fischer et al., 2015; Héritier et al., 2017; Vienneau et al., 2017, 2012). This could be related to an increase in the baseline hazard with age, which may translate into lower HRs on the multiplicative scale for the elderly compared to the non-elderly (Girerd et al., 2016; Rod et al., 2012). Hence, the over-representation of the elderly in our study population might have contributed to the fact that we did not observe associations of environmental exposures with mortality. We, however, did not observe indications of effect modification by age in our study. This is likely due to the small number of deaths in the younger age groups over the

relatively short follow-up period (Table S9).

Survey respondents might be healthier than the general population. An American study for example showed that survey respondents generally have lower mortality rates than the general population (Keyes et al., 2018). This could be due to the fact that in general heavy alcohol and cigarette consumers and less physically active people are less likely to respond to surveys (Ahacic et al., 2013; Roberts et al., 1996; Wild et al., 2001). In the PHM, only individuals living in non-institutionalized settings were sampled. Moreover, ethnic minorities and people in the lowest household income categories were under-represented in our study population compared to the full Dutch population. The sampling procedure might have caused some selection bias, as frail subjects and/or subjects with regular or digital literacy problems might not be able to complete the questionnaire.

Fischer et al. (2015) recently reported positive associations of air pollution with non-accidental, circulatory disease, respiratory disease and lung cancer mortality outcomes in the Netherlands. They used the full Dutch population aged 30+ years (n = 7.1 million, excluding movers 5 years before start of follow-up) and reported 668,206 deaths during 7 years of follow-up. Therefore, potential selection bias and the limited number of events in the complete population and in the younger age groups were no issues in their study. We note that they used a different LUR model to predict air pollutant concentrations and adjusted for a different set of potential confounders which may have resulted in different effects estimates compared to our study.

Current developments in treatment of diseases, medication, medical technology and rehabilitation programs make it possible to live longer with a disease. The majority of incident cerebrovascular and coronary events is currently non-fatal. This may complicate the assessments of associations of environmental exposures with mortality as the time period from exposure via disease/event to mortality increases. Beelen et al. (2014) found no associations of air pollution with cardiovascular disease mortality in the ESCAPE project, while Stafoggia et al. (2014) and Cesaroni et al. (2014) found clear associations with incidence of cerebrovascular and coronary events in a subset of 11 cohorts in the ESCAPE project, using the same exposure models and statistical methods.

For non-accidental, respiratory disease and lung cancer mortality, associations were found with surrounding green and air pollution in models adjusting for age, sex and individual SES. Adjustment for lifestyle factors such as smoking, physical activity and BMI reduced HRs for both air pollution and surrounding green to unity (Fig. S3). It is unlikely that these adjustments represent an over-adjustment, as they are clearly identified risk factors. The relationship between environmental exposures and lifestyle is likely through SES for which we adjusted in the epidemiological analysis. We previously observed that adjustment for individual SES did not fully remove the relationship between air pollution exposure and lifestyle factors (Strak et al., 2017), probably because of the difficulty to fully characterize SES. We note that adjustment for physical activity might be an over-adjustment in analyses of surrounding green, as physical activity could be on the causal pathway from surrounding green to mortality. This would apply more for circulatory mortality than for respiratory disease and thus does not fit the observed pattern. We do not believe that the inclusion of neighborhood and region SES variables is a potential over-adjustment



as HRs of models with adjustments only for individual SES and lifestyle factors were similar to HR of models with additional adjustments for neighborhood and regional SES variables. To reduce possible selection bias, we imputed missing values of potential confounding variables. The missing data were not completely at random as subjects with missing data were more likely to die during follow-up. We assumed that the missing data were conditionally at random; after controlling for the variables included in the imputation procedure, any remaining missing data is completely at random. We believe this assumption is reasonable as all individual SES, lifestyle factors, neighborhood SES, region SES, exposures, mortality outcomes plus some auxiliary variables (degree of urbanization and medication prescription) were available in the imputation procedure. Associations of exposures with mortality outcomes were similar between the full (imputed) population and complete case population. Further, we observed similar HRs (main model) in each individual imputed dataset, indicating no major differences in adjustments for covariates between the imputed datasets.

#### 4.3. Strengths and limitations

Strengths of this study include the longitudinal study design, the large population size (> 300,000 subjects) with national coverage and the ability to adjust for socio-economic status and lifestyle factors. We used multiple indicators of surrounding green, air pollution and traffic noise exposure and all indicators were linked to the residential address of the subjects. Moreover, all environmental exposures were assessed between 2009 and 2011, i.e. relatively closely before the time the survey was conducted (2012). Several studies showed that the spatial variation of surrounding green, air pollution and traffic noise exposure levels remain stable over periods of about 10 years in Western countries (Vienneau et al., 2017; Fecht et al., 2016; Eeftens et al., 2011; Crouse et al., 2017). De Hoogh et al. (2018) reported high correlations ( $R^2 \sim 0.9$ ) between AirBase NO<sub>2</sub> measurements in 2000, 2005 and 2010 in the Netherlands. Eeftens et al. reported excellent agreement between LUR models developed independently using data obtained 8 years apart in the Netherlands. The models explained about 80% of the spatial variation of the measurements performed in the other time period, despite changing population density, total vehicle kilometers and combustion engine developments. In addition, measurements showed that traffic noise levels in the Netherlands in 2013, 2014 and 2015 barely differed (Jabben et al., 2016, 2015). For surrounding green, there no formal assessment is available for the Netherlands, but given the limited spatial developments in the Netherlands, we expect that the findings for other developed Western countries apply in the Netherlands as well. Further, the underlying cause of death was automatically coded by IRIS based on internationally agreed decision tables.

This study has several limitations. The relatively short follow-up period might not be sufficient to capture subtle differences in event rates related to environmental exposures. We did not have information about time spent at home, workplace address and other time-activity data, which may also lead to exposure measurement error and potentially to an underestimation of the effects. The contrast in exposure was small for PM<sub>2.5</sub> and PM<sub>10</sub>, but more substantial for NO<sub>2</sub> and other pollutants. Information on individual SES and lifestyle variables were only available at the start of the follow-up. However, given the relatively short follow-up period, we do not think that this will lead to biased effect estimates.

#### 5. Conclusion

We found no evidence for associations of long-term residential exposures to surrounding green, air pollution and traffic noise with non-accidental, circulatory disease, respiratory disease, lung cancer and neurodegenerative disease mortality in a large survey, possibly related to the relatively short follow-up period.

#### CRedit authorship contribution statement

**Jochem O. Klompmaker:** Formal analysis, Writing - original draft, Investigation. **Gerard Hoek:** Conceptualization, Supervision, Writing - review & editing. **Lizan D. Bloemsma:** Writing - review & editing. **Marten Marra:** Data curation. **Alet H. Wijga:** Writing - review & editing. **Carolien van den Brink:** Writing - review & editing, Investigation. **Bert Brunekreef:** Supervision, Writing - review & editing. **Erik Lebret:** Supervision, Writing - review & editing. **Ulrike Gehring:** Writing - review & editing. **Nicole A.H. Janssen:** Conceptualization, Supervision, 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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#### Competing financial interests

The authors declare that they have no actual or potential competing financial interests.

#### Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2019.105341>.

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