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Air pollution and surrounding greenness in relation to ischemic stroke: A population-based cohort study

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ABSTRACT

Background: Evidence for the association between environmental exposures and ischemic stroke (IS) is limited and inconsistent. We aimed to assess the relationship between exposure to air pollutants, residential surrounding greenness, and incident IS, and to identify population subgroups particularly sensitive to these exposures.

Methods: We used data from administrative health registries of the public healthcare system in Catalonia, Spain to construct a cohort of individuals aged 18 years and older without a previous stroke diagnosis at 1st January 2016 (n = 3 521 274). We collected data on sociodemographic characteristics and cerebrovascular risk factors, and derived exposure at the participant's residence to ambient levels of fine particulate matter ($PM_{2.5}$), black carbon (BC), nitrogen dioxide (NO_2), and Normalized Difference Vegetation Index (NDVI) in a 300 m buffer as an indicator of greenness. The primary outcome was IS diagnosis at any point during the follow-up. We used Cox proportional hazards models to estimate associations between environmental exposures and incident IS and stratified analyses to investigate effect modification.

Results: Between 1st January 2016 and 31st December 2017, 10 865 individuals were admitted to public hospitals with an IS diagnosis. Median exposure levels were: 17 µg/m³ $PM_{2.5}$, 35 µg/m³ NO_2, 2.28 µg/m³ BC and 0.27 NDVI. Individuals with higher residential exposure to air pollution were at greater risk of IS: HR 1·04 (95% CI:0·99-1·10) per 5 µg/m³ of $PM_{2.5}$; HR 1.05 (95% CI:1·00-1·10) per 1 µg/m³ of BC; HR 1·04 (95% CI:1·03-1·06) per 10 µg/m³ of NO_2. Conversely, individuals with higher residential surrounding green space, had lower risk of IS (HR 0·84; CI 95%:0·7-1.0). There was no evidence of effect modification by individual characteristics.

Conclusions: Higher incidence of IS was observed in relation to long-term exposures to air pollution, particularly NO_2, in a region that meets European health-based air quality standards. Residential surrounding greenness was associated with lower incidence of IS.

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1. Introduction

Ischemic stroke (IS) remains one of the leading causes of death and disability worldwide (GBD 2019 Stroke Collaborators, 2021), and its global burden is not expected to decrease in the coming years (Wafa et al., 2020). In addition to traditional and behavioural risk factors (e.g., hypertension or low physical activity), characteristics of the physical and natural environment also influence the incidence of the disease (Feigin et al., 2016; GBD 2019 Stroke Collaborators, 2021). With more than 75% of the population in Europe living in urban areas, it is important to identify how environmental hazards concentrated in urban environments, such as air pollution or limited access to natural environments, contribute to the stroke burden and which individuals are most sensitive to exposure.

Exposure to ambient air pollution may result in several pathophysiological changes related to stroke, such as systemic inflammation, accelerated progression of atherosclerosis, and predisposition to cardiac arrhythmias. Previous studies have reported an association between long-term exposure to particulate matter with aerodynamic diameter less than 2.5 μm ($PM_{2.5}$) and stroke (Niu et al., 2021; Scheers et al., 2015; Yuan et al., 2019). As a result, $PM_{2.5}$ has been identified as a leading risk factor for stroke, accounting for an estimated 20% of the global stroke burden (GBD 2019 Stroke Collaborators, 2021). However, fewer studies have investigated the effects of common traffic-related air pollutants other than $PM_{2.5}$ on stroke such as nitrogen dioxide (NO_2) and black carbon (BC). While most previous knowledge about the effects of air pollution on stroke incidence to date are based on populations outside Europe (Niu et al., 2021), a recent multi-country study (Wolf et al., 2021) reported a positive association in a pooled analysis including populations from several European countries. The authors found no evidence of a threshold below which air pollutant concentrations are not harmful for stroke. However, much of the follow-up period covered in the included cohorts studies was more than a decade ago (Andersen et al., 2012; Atkinson et al., 2013; Korek et al., 2015; Ljungman et al., 2019; Orioli et al., 2019; Stafoggia et al., 2014; Stockfelt et al., 2017; Wolf et al., 2021), and given the strong time-trends in stroke incidence and air pollution (European Environment Agency (EEA), 2020; Wafa et al., 2020), there is a need to study the association between long-term exposure to air pollution and stroke incidence in large cohorts reflecting more recent years.

Growing evidence supports the health benefits of green space exposure (i.e., vegetation) on a range of health outcomes, including mortality (Barboza et al., 2021; Nieuwenhuijsen et al., 2017). However, the available evidence on the association between green spaces and risk of stroke is still very scarce (Orioli et al., 2019; Pereira et al., 2012; Tamosiunas et al., 2014). Mechanisms underlying an association between green space exposure and cerebrovascular health are still poorly understood, but may include benefits via immunoregulatory pathways, stress-reduction, and/or promotion of physical activity (Hartig et al., 2014; Markevych et al., 2017).

We address these gaps in the available literature using a large, population-based cohort to: 1) assess the relationship between long-term exposure to air pollution ($PM_{2.5}$, BC, and NO_2) and surrounding green space at residence and incidence of IS, and to 2) identify subgroups of the population particularly sensitive to these environmental factors.

2. Material and methods

2.1. Study design, data sources and study population

We conducted a longitudinal prospective cohort study based on the adult population of Catalonia (a northeast region of Spain) to assess the long-term effects of air pollution and green spaces at residence on incident IS and transient ischemic attack (TIA) episodes. Using record-linkage, we constructed a cohort using data collected in the health administration databases of Catalonia. All residents of Catalonia are granted universal healthcare by law, and the public healthcare system covers nearly the entire population (7.5 million inhabitants).

The Catalan Central Registry of Insured Persons collects sociodemographic information on all residents of Catalonia using a unique identifier. This identifier allows for linkage across several health administration databases including databases related to acute hospitals discharge (CMBD-HA), Pharmacy claims, and primary care (CMBD-AP), providing detailed information on comorbidity and date of diagnosis. Both CMBD databases register the information using International Classification of Diseases (ICD) codes (ICD, *Ninth Revision*, for CMDB-HA and ICD, *Tenth Revision* [ICD-10], for CMBD-AP), and Pharmacy Claims Databases use WHOCC–ATC/DDD Index codes.

We included data for all individuals aged ≥18 years (>80% population included) registered in the Catalan Central Registry of Insured Persons at Jan 1st 2016 (baseline). Individuals with a diagnosis of cerebrovascular disease (ICD 10 = G45x, I61x and I63x in the CMBD-AP) prior to January 1st, 2016 were excluded during analysis. Participants' residential addresses at baseline were geocoded. Data were managed so as to ensure anonymization in accordance with current data protection legislation (AQuAS, 2017). We received approval from our local ethics committee (code 2018/7917/I).

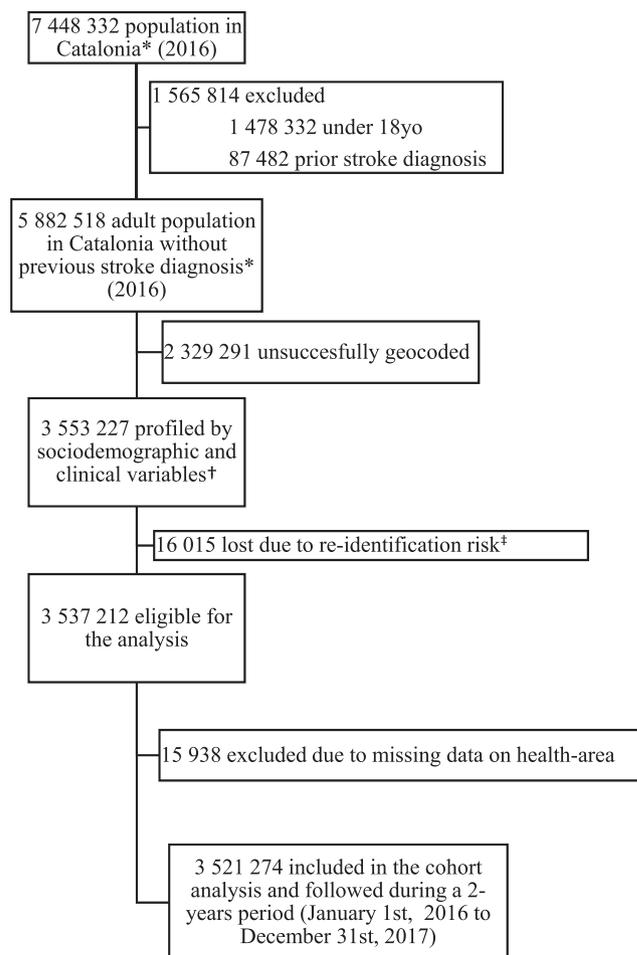The final cohort included 3 521 274 participants (Fig. 1: Study

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│ 7 448 332 population in   │
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│ 5 882 518 adult population   │
│ in Catalonia without   │
│ previous stroke diagnosis*   │
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          ├───┤ 16 015 lost due to re-identification risk‡ │
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│ 3 537 212 eligible for   │
│ the analysis   │
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          ├───┤ 15 938 excluded due to missing data on health-area │
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│ 3 521 274 included in the cohort │
│ analysis and followed during a 2-│
│ years period (January 1st, 2016 to│
│ December 31st, 2017)   │
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Fig. 1. Study population and selection process. *Individuals registered in the Central Registry of Insured Persons. †Baseline characteristics for geocoded vs non geocoded individuals are shown in Table S1 in supplemental material. Addresses could not be geocoded due to errors in the address record. ‡The Public Data Analysis for Health Research and Innovation Program of Catalonia applied a data anonymization process that ensured that the combination of data provided to the researcher did not allow the indirect identification of specific individuals.

population and selection process) and were followed for a study period of two years (January 1st, 2016 to December 31st, 2017). An extended follow up period was considered in sensitivity analyses. An extended follow up period (Jan 1st, 2015 to December 31st, 2017) was considered in sensitivity analyses including person-time from 2015.

2.2. Sociodemographic characteristics and cerebrovascular risk factors

We obtained the sociodemographic characteristics (age, sex, healthcare management area, and individual socioeconomic status) from the Central Registry of Insured Persons for each individual. Healthcare management areas (AGA, n = 43) are territorial boundaries that are based on the aggregation of nested primary care service areas (ABS, n = 374). These geographic units are used for the operational planning, coordination, and analysis of the main flows between primary care and basic hospital care. We derived individual socioeconomic status (SES) from the predefined categories used for the co-payment system for drug dispensations (Vivanco-Hidalgo et al., 2019b): low income (<€18 000 [$US 20 468] per year); middle-high income (€18 000 to €100 000 [$US 113 710] per year); high income (>€100 000 per year); and individuals exempt of co-payment (nonworking population or people receiving non-contributory pension).

We used the 2011 Deprivation Index of the Spanish Society of Epidemiology (IP2011) as a measure of area-level deprivation (Duque et al., 2021). The index is available for the entire Catalan territory at a census tract level. There are currently more than 5000 census tracts in Catalonia. While some small municipalities may consist of only one census tract, larger cities may consist of multiple census tracts (e.g. Barcelona has more than 1000). We assigned each participant the weighted mean of the index for all census tracts falling within a 300 m buffer around each geocoded home address. This index is based on six indicators of SES: manual and temporary workers, unemployment, insufficient education overall and in young people (aged 16 to 29 years), and dwellings without access to the internet. Its values range between −1 and 1, with values close to zero being representative of average deprivation in Spain, and higher values indicating more deprivation.

We obtained information about preexisting cardiovascular risk factors (before 1st January 2016) by combining patient's active diagnosis from the CMBD-AP (hypertension ICD-10 codes I10 and I15.9; dyslipidemia ICD-10 codes E78– 78.9; diabetes mellitus ICD-10 codes E10–14.9; atrial fibrillation ICD-10 code I48; obesity ICD-10 code E66 or a body mass index registry above 30) and patients' active medication from Pharmacy Claims Databases (C02, C02K, C02L, C02N, and C02LX codes for antihypertensive agents; A10A, A10B, and A10X codes for insulin and blood glucose lowering drugs; C10A, C10B for dyslipidemia), all of them set before the start of follow-up. Smoking status was recorded using the available information in CMBD-AP based on a general practitioner's record and update of smoking use in predefined categories: non-smoker, smoker, or former-smoker. Detailed descriptions of the ascertainment methods for cardiovascular risk factors and socioeconomic status are described elsewhere (Vivanco-Hidalgo et al., 2019b).

2.3. Environmental data

We assessed individual-level exposure to ambient levels of $PM_{2.5}$, BC, and NO_2 for the study period. Our assessment of exposure to air pollution was based on land use regression models (LUR) developed in the Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) study framework for Catalonia (de Hoogh et al., 2018). In ELAPSE, standardized Europe-wide hybrid LUR models for 2010 were developed estimating annual mean $PM_{2.5}$, NO_2, and BC concentrations at 100 m spatial resolution. We first assigned to each study's participant the 2010 ELAPSE-derived annual mean NO_2, $PM_{2.5}$, and BC estimates at each individual's residential address. Then, to temporally adjust the exposures to the study period, we used 2015 annual means from time series

daily data from background reference stations for each Air Quality Zone if any available (Sistema de Vigilancia de Calidad del Aire, 2020). We used the ratio of the annual means for 2010 and 2015 to adjust the spatial estimates. This extrapolation method has been previously validated and used in studies on the assessment of the risk of air pollution on health outcomes (MacIntyre et al., 2014).

The assessment of residential surrounding greenness was based on the Normalized Difference Vegetation Index (NDVI), a satellite-based index of greenness derived from Landsat 8 Operational Land Imager (OLI) sensor data at 30 m × 30 m resolution. Its values range between 0 and 1, with higher positive numbers indicating more greenness, and low NDVI values (<0.1) usually indicating barren areas of rock and sand, or built-up areas and impervious surfaces. Given that the maximum vegetation in our study region occurs in the spring, 8 Landsat images from spring, 2016 and 2017 (May 1st, 2016; April 11th, 2017; April 18th, 2017; 12th June 2017; and 14th June 2017), were selected in order to maximize the contrast in exposure. The findings of previous studies support the stability of the greenness spatial contrast over years in the study region (Dadvand et al., 2012). Residential surrounding green space indices were quantified as the NDVI average within 300 m and 500 m buffers around each participant's residential address. We selected the 300 m buffer as our main exposure metric following the current recommendations regarding distance between residence and the nearest open public space (WHO, 2016).

In sensitivity analysis, we considered alternative exposure metrics including: 1) air pollution annual mean exposures derived from ELAPSE models for 2010 and 2015 within 300 m and 500 m buffers; 2) annual mean $PM_{2.5}$ at residence derived from the Air Pollution, Autism Spectrum Disorders and Brain Imaging Amongst Children in Europe (APACHE) study (Stafoggia et al., 2019) for the 2015 and 2014–2015 periods; 3) NDVI average within 500 m buffer around participant's residential address; 4) green space exposure defined as % of area within buffer covered by green space, within 300 m and 500 m buffers; 5) distance to green space defined as Euclidean distance from each participants' residential address to nearest green space of at least 0.5 ha; and 6) green space exposure defined as Vegetation Continuous Fields and Modified Soil-adjusted Vegetation Index. Indicators of % green space and distance to green space were based on the Map of Land Covers of Catalonia (V4, 2009) from Centre de Recerca Ecològica i Aplicacions Forestals (CREAF) (Institut Cartogràfic i Geològic de Catalunya, 2009). Based on orthophotos with a spatial resolution of 1:1000, the map contains a total of 241 simple covers, which can be hierarchically grouped into different levels. Three green spaces categories were considered: agricultural green, which included arboreal and herbaceous crops; forest green, which included sclerophyllous, deciduous and conifer forests; and urban green, which included artificial green areas and urban woodland.

Spatial variables were analysed using Geographic Information Systems software, PostgreSQL (1996–2017 The PostgreSQL Global Development Group), PostGIS (Creative Commons Attribution-Share Alike 3.0) and R (R Core Team, 2020) software (version 3.6.3).

2.4. Outcomes

The primary outcome measure was a first-ever IS or transient ischemic attack (TIA) diagnosis at any point during the follow-up. Using the CMBD-HA dataset, we identified IS and TIA patients (ICD, *Ninth revision*, codes 433.x1, 434.x, 435.x and 436.5 as a main diagnosis at discharge) hospitalized from January 1,2016 to December 31st, 2017 (end of follow-up).

2.5. Statistical analysis

Descriptive analyses of the sociodemographic, clinical, and exposure variables were performed for all participants and for subgroups with and without a first-ever stroke.

We used a Cox proportional hazards model to estimate the association between the continuous environmental exposures and incident outcomes. We used time to stroke diagnosis in weeks as the outcome variable in our hazard models. Right-censoring occurred at the first instance of: death, emigration outside the study area, or the end of the study period. HRs for air pollutants are reported as fixed increments of 5 $\mu g/m^3$ for $PM_{2.5}$ and increments of 10 $\mu g/m^3$ for NO_2 and per unit for BC and NDVI. Estimates per interquartile range (IQR) are reported in the supplemental material.

We modelled associations for each environmental factor as follows: a) Model 1, adjusted for age (fitted as a penalized spline) and sex; b) Model 2, Model 1 plus smoking status, and SES; and c) Model 3, Model 2 plus area-level deprivation. These models were pre-defined based on a priori theoretical assumptions about the relationship between the covariates and the outcome (Newby et al., 2015; Stafoggia et al., 2014). We considered cardiometabolic disorders such as hypertension, diabetes mellitus or obesity as potential mediators of the associations between air pollutants and green space exposure and ischemic stroke (Newby et al., 2015; Yang et al., 2020) and therefore did not adjust for them in the main analysis (mediator adjusted models were fit in exploratory analysis). We assessed the proportional hazards assumption of our models by visual inspection of score residuals plotted against event time. In sensitivity analysis, we accounted for residual spatial autocorrelation by adding a random intercept for each healthcare management area (AGA) to Model 3 (Model 4). We defined Model 3 as the main model since much of the spatial variability in exposure was adjusted for by the random intercept for healthcare area.

In sensitivity analyses, we explored the shape of the exposure-response function by modelling the exposure of interest using penalized splines. We adjusted our main model (model 3) for population density. We fit bi-exposure models to assess potential confounding due to correlations between exposures. We explored sensitivity of estimates from our main model to different exposure metrics, exposure windows, and extended follow-up time (start of follow-up 1st January 2015). We explored potential interactions between air pollutants and NDVI by fitting model 3 including cross-product terms and by estimating the effects of air pollution according to NDVI categories.

We used stratified analyses to explore effect modification by the covariates used in the main model, comparing younger individuals (under 65y) vs older (above 65y), smokers vs non-smokers (including non-smokers and former-smoker), and individuals with low (co-payment exempt and low income) vs middle-high SES (middle-high and high income).

All analyses were conducted in R (R Core Team, 2020) software (version 4.0.1).

The data that support the findings of this study are available from the corresponding author on reasonable request.

3. Results

We followed-up 3 521 274 participants between January 1st, 2016 to December 31st, 2017, resulting in 6 886 074 person-years for the analyses and 10 865 individuals admitted to public hospitals with the diagnosis of IS or TIA.

Individuals with stroke were older, more likely to be men, had a higher prevalence of cardiovascular risk factors (i.e., hypertension, diabetes, dyslipidaemia, and arterial fibrillation), and were more likely to have low SES (Table 1).

Median $PM_{2.5}$, NO_2, and BC levels in the study area were respectively 17 $\mu g/m^3$, 35 $\mu g/m^3$, and 2·3 $\mu g/m^3$ with a large exposure range for a European setting. For $PM_{2.5}$ and NO_2, most of the population were under annual safety levels set by the European Union at 25 $\mu g/m^3$ for $PM_{2.5}$ and 40 $\mu g/m^3$ for NO_2. However, they largely exceed the current WHO recommendations recently set to 5 $\mu g/m^3$ for $PM_{2.5}$ and 10 $\mu g/m^3$ for NO_2 (World Health Organization, 2021). No standard has been established for annual BC exposure levels by international environmental

Table 1
Characteristics and environmental exposures of study population.

Characteristics	Overall n = 3 521 274	Without IS during the follow-up **n** = 3 510 409 (99.7%)	IS during the follow-up n = 10 865 (0.3%)
Age	47 (36, 62)	47 (36, 62)	76 (65, 83)
Sex (Male)	1 695 734 (48%)	1 690 007 (48%)	5 727 (53%)
Obesity	723 526 (21%)	719 291 (20%)	4 235 (39%)
Smoking			
Non-smoker	2 529 403 (72%)	2 521 809 (72%)	7 594 (70%)
Smoker	630 733 (18%)	629 249 (18%)	1 484 (14%)
Former-smoker	361 138 (10%)	359 351 (10%)	1 787 (16%)
Hypertension	679 059 (19%)	672 034 (19%)	7 025 (65%)
Diabetes	223 870 (6·4%)	220 748 (6·3%)	3 122 (29%)
Dyslipidemia	873 724 (25%)	867 495 (25%)	6 229 (57%)
Arterial fibrillation	59 529 (1·7%)	58 206 (1·7%)	1 323 (12%)
Individual socioeconomic status			
Low	2 341 134 (66%)	2 333 066 (66%)	8 068 (74%)
Middle-High	957 130 (27%)	954 930 (27%)	2 200 (20%)
High	25 447 (0·7%)	25 416 (0·7%)	31 (0·3%)
Exempt	141 124 (4·0%)	140 647 (4·0%)	477 (4·4%)
Area-level deprivation	−0·47 (-0·89, −0·07)	−0·47 (-0·89, −0·07)	−0·41 (-0·83, −0·03)
$PM_{2.5}$ ($\mu g/m^3$)	17·02 (15·62, 18·01)	17·02 (15·62, 18·01)	17·08 (15·67, 18·06)
NO_2 ($\mu g/m^3$)	35 (23, 41)	35 (23, 41)	36 (23, 42)
BC ($\mu g/m^3$)	2·28 (2·00, 2·70)	2·28 (2·00, 2·70)	2·31 (2·00, 2·71)
NDVI	0·27 (0·22, 0·35)	0·27 (0·22, 0·35)	0·26 (0·21, 0·34)

Data are median (IQR) and n (%).
IS, Ischemic Stroke; $PM_{2.5}$, Particulate Matter with aerodynamic diameter less than 2.5 μm; NO_2, Nitrogen dioxide; BC, Black Carbon; NDVI, Normalized Difference Vegetation Index.

agencies. Fig. 2 shows the geographical distribution of air pollutants, NDVI and ischemic stroke cases during the follow-up period in the study area. Higher levels of air pollutants and lower levels of NDVI are observed in urban areas of Catalonia, with particularly high levels of $PM_{2.5}$, NO_2, and BC in the metropolitan area of Barcelona (comprising approximately 3 million inhabitants). Distributions of the environmental exposures and their correlations are presented in Fig. S1.

Individuals with a higher residential exposure to air pollution were at greater risk of presenting with an IS during the study period (Model 3, Fig. 3 and Table S2): HR for fixed 5 $\mu g/m^3$ increments in $PM_{2.5}$ 1·04 (95% CI: 0·99-1·1); HR for fixed 10 $\mu g/m^3$ increments in NO_2 1·04 (95% CI: 1·03-1·06); and HR for 1 $\mu g/m^3$ increments in BC 1·05 (95% CI: 1-1·1).. We observed evidence of a protective association between a higher average exposure to green spaces (NDVI) in a 300 m buffer around residential address and IS (Model 3, Fig. 3 and Table S2): (HR 0·84; CI 95%: 0·7- 1).

The results of the exploratory analysis for the mediator adjusted models are shown in Table S3.

In sensitivity analyses, there was no evidence of non-linear associations between any of the exposures and stroke incidence, which is consistent with previous studies (Wolf et al., 2021). Positive, statistically significant associations for NO_2 and IS were consistent in models adjusted for population density (Fig. S2), across all bi-exposure models (Fig. S3 and Table S4), across the different exposure windows and
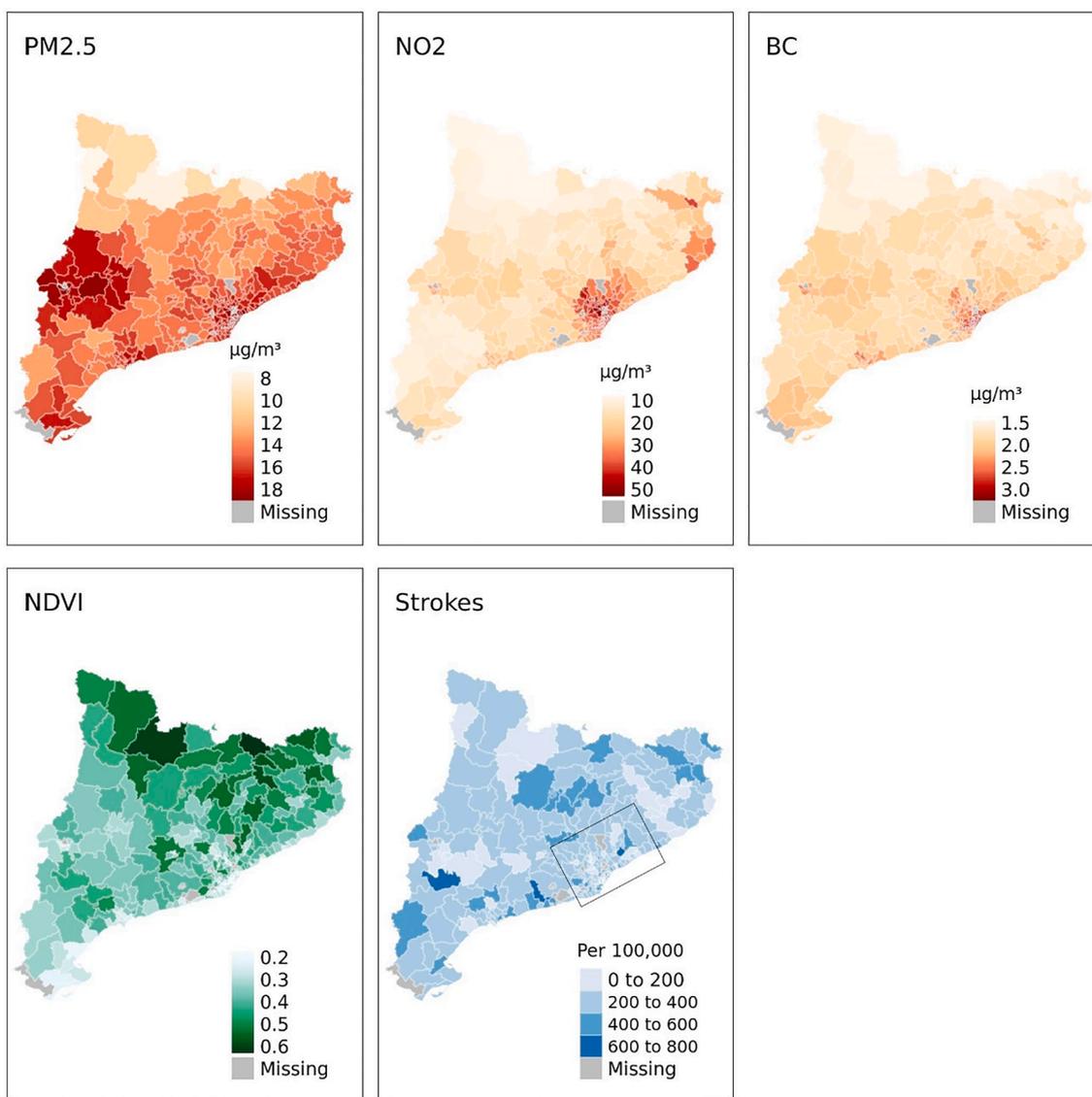
Fig. 2. Geographical distribution of air pollutants (PM₂.₅, NO₂, and BC)*, greenness (NDVI) and ischemic stroke cases[†] in the study cohort. *Distribution of the derived individual exposures for the study participants. [†]Ischemic stroke (IS) cases occurring between 1st January 2016 to 31st December 2017, per 100 000 population. Data is shown as crude estimates. The black square outlines the metropolitan area of Barcelona (around 3M inhabitants). PM₂.₅, Particulate Matter with aerodynamic diameter less than 2.5 μm; NO₂, Nitrogen dioxide; BC, Black Carbon; NDVI, Normalized Difference Vegetation Index.

follow-up periods assessed (Fig. S4). Compared to NO₂, associations between other air pollutants and IS were more sensitive to adjustment for population density, different exposure metrics, and to the inclusion of person-time from the same year as the exposure estimates (i.e. 2015) (Figures S2 and S4). Overall, the pattern of associations were similar for green space exposure metrics except for distance to green space (Fig. S4). Protective associations were slightly attenuated when person-time from 2015, which preceded the green space exposure data (2016, 2017) was included. There was some indication that the effect of BC on IS was highest among participants with higher exposure to residential surrounding green space (Table S5, Fig. S5).

Associations of annual PM₂.₅, NO₂, BC, and NDVI with IS by subgroups are presented in Fig. 4 (and Table S6). There was no evidence of effect modification by age, smoking, or SES.

4. Discussion

In this large population-based cohort study, long-term exposure to NO₂ was significantly associated with higher incidence of IS and

associations were consistent across multiple sensitivity and bi-exposure analyses. BC and PM₂.₅ were positively associated with IS in our main analysis, but confidence intervals included the null, and results were more sensitive to the model specification. Residential surrounding greenness (NDVI) was related with a lower incidence of IS. Associations across subgroups were consistent, with no evidence of effect modification by participants characteristics. To our knowledge, this is the largest study in Europe to specifically analyse the long-term association of air pollution with stroke incidence (Andersen et al., 2012; Atkinson et al., 2015; Korek et al., 2015; Ljungman et al., 2019; Orioli et al., 2019; Stafoggia et al., 2014; Stockfelt et al., 2017; Wolf et al., 2021), and one of the few to assess the effect of green spaces (Orioli et al., 2019; Pereira et al., 2012; Tamosiunas et al., 2014).

Postulated mechanistic pathways linking air pollution to cerebrovascular disease include systemic inflammatory responses, systemic oxidative stress, predisposition to cardiac arrhythmias, vascular endothelial cell injury, and a prothrombotic state, acute arterial vasoconstriction, and atherosclerotic progression manifesting as increased risk of either IS or TIA (Münzel et al., 2018). Estimates from our main model
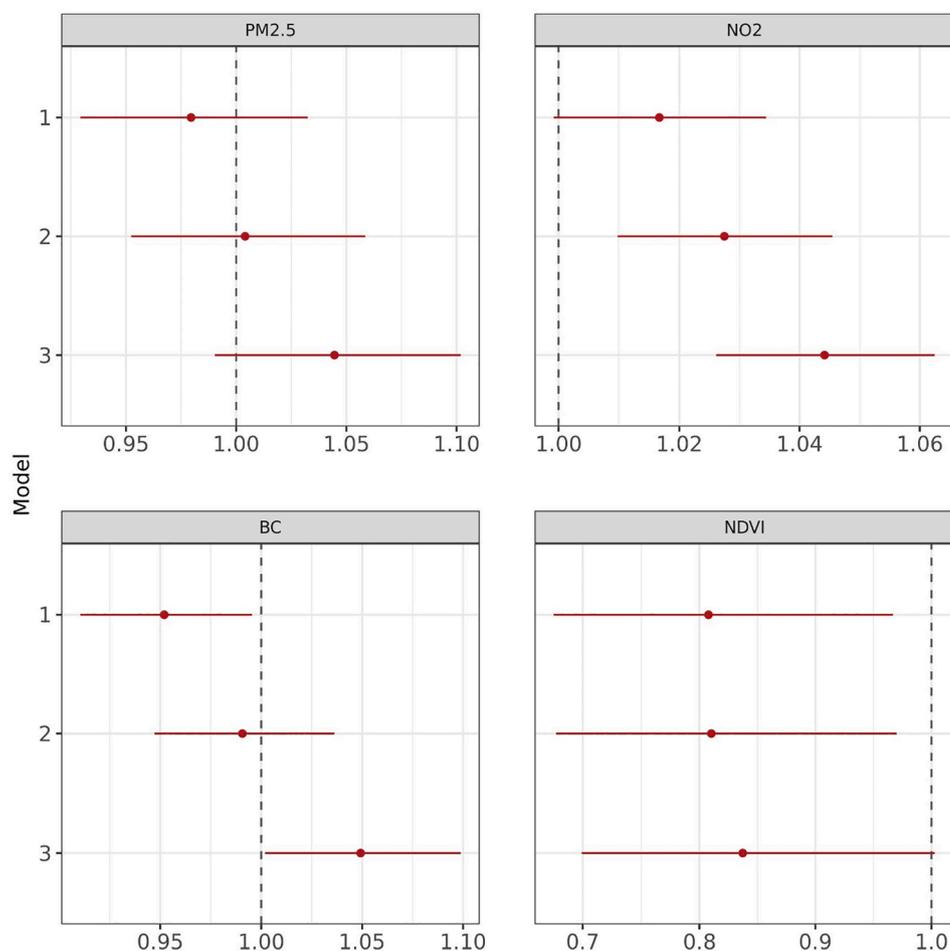
Fig. 3. Hazard ratios and 95% CI for the sequentially adjusted single-exposure models. Association between Particulate Matter with aerodynamic diameter less than 2.5 μm ($PM_{2.5}$), Nitrogen Dioxide (NO_2), black carbon (BC), and Normalized Difference Vegetation Index (NDVI) and incident stroke are modelled as follows: Model 1, adjusted for age (fitted as a penalized spline) and gender; Model 2, Model 1, plus smoking status, and the individual socioeconomic status; Model 3, Model 2 plus neighbourhood socioeconomic status. The point-estimates are represented by dots and their 95% confidence intervals as horizontal lines.

indicate a positive association between $PM_{2.5}$ exposure and IS risk but with a lower magnitude of point estimate than those reported in recent publications (Niu et al., 2021; Wolf et al., 2021). In contrast to $PM_{2.5}$, the epidemiological evidence regarding the long-term effects of NO_2 and BC, both considered good indicators of near-road traffic pollution, is still limited (Atkinson et al., 2013; Ljungman et al., 2019; Stafoggia et al., 2014; Wolf et al., 2021). We observed robust associations between NO_2 and incidence of IS. Previous studies exploring the relation between NO_2 and IS have mainly focused on short-term exposures, and there is a lack of consistency in the few reported long-term effects of NO_2 on the disease. Our results from bi-exposure models indicate that associations between NO_2 and IS were not due to confounding by other air pollutants or residential surrounding green space. However, potential confounding of the effects of one traffic-related pollutant by others is a challenge in observational epidemiology (Atkinson et al., 2015). Epidemiological studies have often relied on NO_2 as a proxy of traffic-related air pollution in general, because NO_2 measurements are available in many countries, and the variability of traffic related air pollution mixture appears to be well characterised by NO_2 (Levy et al., 2014). Due to lack of exposure data on ultrafine particles and other gaseous pollutants, we were not able to disentangle the effect of NO_2 from that of traffic-related co-pollutants. Our findings are consistent with growing evidence of the association of NO_2 with several health outcomes (e.g. cardiovascular and respiratory outcomes and mortality) in studies spanning different decades and countries covering diverse traffic-related pollutant mixtures, suggesting that it is unlikely that observed health effects of NO_2 can be attributed solely to confounding by a co-pollutant (Forastiere and Peters, 2021). Consistent with other studies (Wolf et al., 2021), we observed positive associations between air pollution and incident stroke

below current European limit values.

Conversely, we observed residential surrounding green space to be related with lower risk of stroke. Available evidence on the association between surrounding green space with stroke is still scarce; the few available studies provide some evidence that green space exposure is related to lower stroke admissions (Orioli et al., 2019; Pereira et al., 2012), milder initial stroke severity (Vivanco-Hidalgo et al., 2019a) and with higher survival rates after acute ischemic stroke (Wilker et al., 2014). The pattern of protective associations between diverse measures of surrounding residential green space and IS was consistent, providing additional support for a hypothesized association. No association was observed for distance to nearest green space however, suggesting that access to green space may be less relevant for IS. Exposure to green spaces is postulated to provide a beneficial effect on health through different mechanisms, such as mental restoration and stress reduction, increased physical activity, improved social contacts/cohesion, and exposure to an enriched microbiome (Hartig et al., 2014; Markevych et al., 2017; Nieuwenhuijsen et al., 2017), some of which (especially physical activity) are known to exert a protective effect on stroke risk (O'Donnell et al., 2016; Yusuf et al., 2020). Exposure to green space has also been linked to mechanisms known to be involved in the occurrence of IS and TIA such as immunoregulatory pathways (Rook, 2013), lower levels of sympathetic activation, reduced oxidative stress and increased angiogenic capacity (Yeager et al., 2018). In addition, green spaces have been described to mitigate exposure to air pollution (Markevych et al., 2017; Nieuwenhuijsen et al., 2017), which could lead to a reduction in the air pollution-related risk of cardiovascular disease. NDVI is a good proxy for general greenness in cities, but it might not be the best indicator to reflect the promotion of physical activities and social
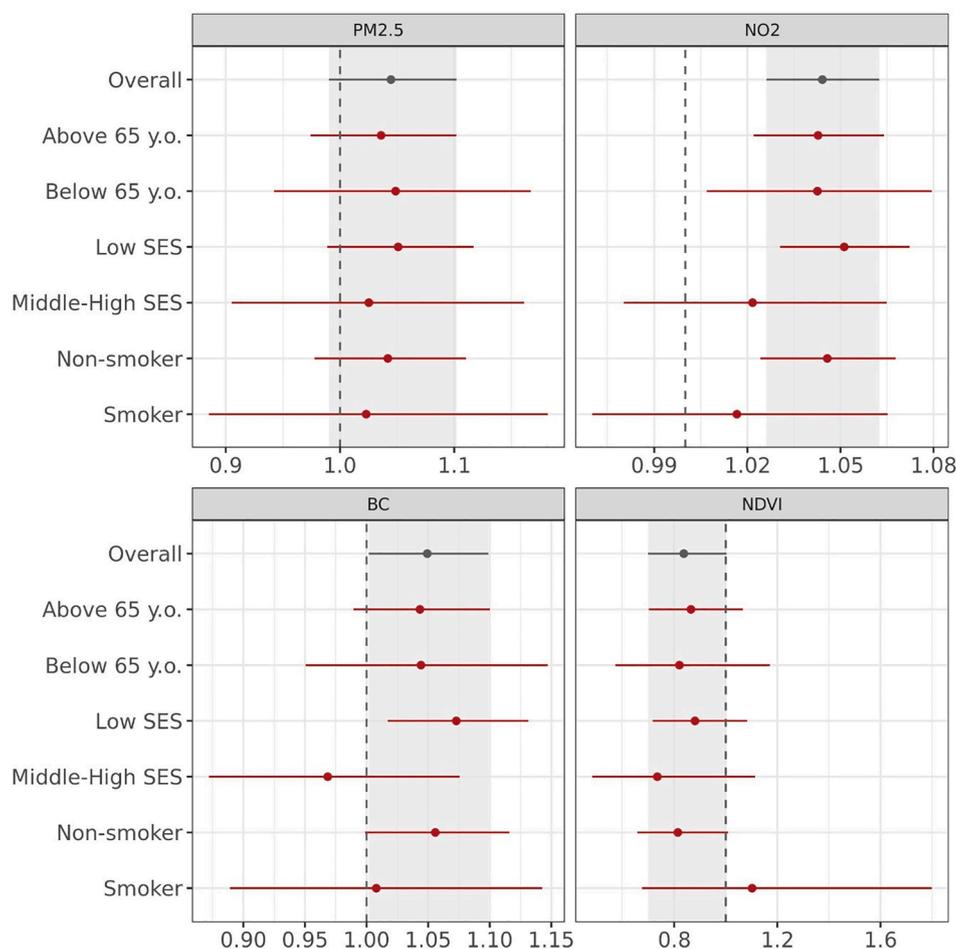
Fig. 4. Association of $PM_{2.5}$, NO_2, BC, and NDVI with IS stratified by participant characteristics. The point-estimates are represented by dots and their 95% confidence intervals as horizontal lines. Shading represents the confidence interval for our main model (Model 3). Subgroup analysis estimations were retrieved from our main model. $PM_{2.5}$, Particulate Matter with aerodynamic diameter less than 2.5 μm; NO_2, Nitrogen dioxide; BC, Black Carbon; NDVI, Normalized Difference Vegetation Index; SES: individual socioeconomic status.

interactions compared to other greenness indicators that are more representative of public and open green spaces (Nieuwenhuijsen et al., 2017). However, general greenness might be more widespread in the city than public green spaces, and hence have a larger impact (Barboza et al., 2021). The observed lack of association between distance to green spaces and stroke might suggest that the predominant effect is through the activation of immunoregulatory pathways, or reduction of stress due to nature viewing (for which small amounts of green may be sufficient) (Gascon et al., 2016). However, there is a need for further studies to understand the underlying mechanisms linking greenness and stroke incidence.

Previous studies on air pollution and greenness in relation to IS have suggested modification of the exposure-stroke association by individual characteristics, primarily age, SES or smoking (Stafoggia et al., 2014). However, our estimates were consistent among population subgroups and did not provide evidence of effect modification.

While we considered several air pollutants and multiple exposure metrics for green space, we did not consider the influence of other potentially relevant environmental determinants that have been linked to cerebrovascular health, such as noise or exposure to blue spaces (Gascon et al., 2017; van Kempen et al., 2018). Road traffic is an important source of both noise and air pollution, and the two exposures are correlated, raising questions about the extent of mutual confounding and combined effects without conclusive results to date (Beelen et al., 2009; Cai et al., 2018; Sørensen et al., 2014). In addition, green spaces have been described to mitigate both air pollution and noise exposure. Blue spaces have also been described to exert beneficial effects on general health and cardiovascular outcomes although the evidence to date is inconsistent (Gascon et al., 2017). Further studies are needed not

only to assess the impact of other environmental determinants on stroke, but also to understand the complex interactions between them, for example, using an Exposome-based approach.

Our study has several strengths. This is one of the few studies that have evaluated simultaneously the effect of different environmental factors (air pollutants and green spaces) on stroke (Orioli et al., 2019). Our prospective cohort study includes follow-up over relatively recent years compared to other studies (Andersen et al., 2012; Atkinson et al., 2013; Korek et al., 2015; Ljungman et al., 2019; Orioli et al., 2019; Stafoggia et al., 2014; Stockfelt et al., 2017; Wolf et al., 2021), providing better reflection of the current context, which may not be captured by studies covering earlier periods due to strong time trends in stroke incidence and air pollution in Europe. Its nationwide population-based approach, including nearly the entire population, reduces the risk of selection bias. The incidence of stroke and the distribution of cerebrovascular risk factors observed in our cohort are consistent with those reported in previous epidemiological studies (European Heart Network, 2018), suggesting that findings from this cohort are likely to have good generalisability to other populations in Europe. In contrast to many previous cohort studies in Europe (Atkinson et al., 2013; Ljungman et al., 2019; Orioli et al., 2019; Stafoggia et al., 2014; Stockfelt et al., 2017; Wolf et al., 2021) and worldwide (Niu et al., 2021; Verhoeven et al., 2021; Yuan et al., 2019), we have not included haemorrhagic strokes in our outcome definition. Given the differences in pathophysiological mechanisms underlying stroke subtypes, restricting our analysis to ischemic stroke is more likely to shed light on potential underlying pathways.

The limitations must also be acknowledged. First, our data covered a relatively short follow-up period of two years, and we did not have

annual average exposure data for several years prior to the start of follow-up for all exposures. Consequently, we were unable to explore in detail the role of different windows of exposure. However, associations between air pollution estimated by the ELAPSE model and IS were fairly consistent in sensitivity analyses comparing exposures from 2010 and 2015. Sensitivity analysis, which extended the follow-up period by including person-time from 2015 led to some attenuation of estimates other than those of NO_2, particularly those based on coincident exposure periods (e.g. 2015) or exposures measured after 2015 (green space). Although the spatial distribution of long-term average air pollution and green space is likely to be fairly stable from year to year, our results suggest the timing of exposure could be relevant. Second, we did not explicitly account for duration of residence before baseline or change of residence during the two-year follow-up, except for emigration outside Catalonia (which was used as a censoring event). However, approximately 1% of participants changed primary care service area per year, suggesting that the influence of exposure measurement error by not accounting for residential mobility is likely to be small. Third, we defined our outcome variable in terms of hospital admissions for IS and may not have captured milder IS cases. In addition, we did not have information about patients attending private health services; however, this is estimated to be a small number of IS cases since >90% of the population uses the public system. Fourth, detailed data on individual-level socioeconomic factors were not available in this administrative cohort. While we derived an individual-level socioeconomic indicator based on co-payment status, the categories are broad, especially for the intermediate group (>18 000 €). Fifth, the ELAPSE model for $PM_{2.5}$ and BC were based on fewer measurements compared to NO_2. This could have resulted in less spatial variation in estimates for these pollutants and may explain why the associations for $PM_{2.5}$ and BC were less precise compared to those for NO_2. Furthermore, the exposure models are likely to have greater error in rural compared to urban areas due to the relative lack of monitoring stations outside of urban areas. Finally, we consider model 3 as the main model for the analysis and interpretation of the results, which does not rule out the potential for spatial autocorrelation affecting the results. Model 4 (Table S2), while better accounting for potential spatial autocorrelation, has the trade-off of significantly reduced exposure variability.

5. Conclusions

In conclusion, our study provides new evidence of positive associations between ambient air pollution, specifically NO_2, at levels below European standards and incident IS and a protective effect of residential surrounding greenness. The increasing stroke burden globally suggests that currently high-risk and population-wide primary stroke prevention strategies are not sufficient (GBD 2019 Stroke Collaborators, 2021). This prospective study adds new knowledge supporting the important role of the physical and natural environment on stroke, which has important implications for primary stroke prevention. Further studies are needed to understand the underlying mechanisms linking greenness and stroke incidence.

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.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2022.107147.

References

Andersen, Z.J., Kristiansen, L.C., Andersen, K.K., Olsen, T.S., Hvidberg, M., Jensen, S.S., Ketzel, M., Loft, S., Sørensen, M., Tjønneland, A., Overvad, K., Raaschou-Nielsen, O., 2012. Stroke and long-term exposure to outdoor air pollution from nitrogen dioxide: A cohort study. Stroke 43 (2), 320–325. https://doi.org/10.1161/STROKEAHA.111.629246.

AQuAS, 2017. Programa públic d'analítica de dades per a la recerca i la innovació en salut a Catalunya [WWW Document]. URL http://aquas.gencat.cat/web/.content/minisite/aquas/publicacions/2017/Programa_analitica_dades_PADRIS_aquas2017.pdf.

Atkinson, R.W., Carey, I.M., Kent, A.J., van Staa, T.P., Anderson, H.R., Cook, D.G., 2013. Long-Term Exposure to Outdoor Air Pollution and Incidence of Cardiovascular Diseases. Epidemiology 24, 44–53. https://doi.org/10.1097/EDE.0b013e318276ccb8.

Atkinson, R.W., Carey, I.M., Kent, A.J., van Staa, T.P., Anderson, H.R., Cook, D.G., 2015. Long-term exposure to outdoor air pollution and the incidence of chronic obstructive pulmonary disease in a national English cohort. Occup. Environ. Med. 72 (1), 42–48. https://doi.org/10.1136/oemed-2014-102266.

Barboza, E.P., Cirach, M., Khomenko, S., Iungman, T., Mueller, N., Barrera-Gómez, J., Rojas-Rueda, D., Kondo, M., Nieuwenhuijsen, M., 2021. Green space and mortality in European cities: a health impact assessment study. Lancet. Planet. Heal. 5 (10), e718–e730. https://doi.org/10.1016/S2542-5196(21)00229-1.

Beelen, R., Hoek, G., Houthuijs, D., Van Den Brandt, P.A., Goldbohm, R.A., Fischer, P., Schouten, L.J., Armstrong, B., Brunekreef, B., 2009. The joint association of air pollution and noise from road traffic with cardiovascular mortality in a cohort study. Occup. Environ. Med. 66, 243–250. https://doi.org/10.1136/oem.2008.042358.

Cai, Y., Hodgson, S., Blangiardo, M., Gulliver, J., Morley, D., Fecht, D., Vienneau, D., de Hoogh, K., Key, T., Hveem, K., Elliott, P., Hansell, A.L., 2018. Road traffic noise, air pollution and incident cardiovascular disease: A joint analysis of the HUNT, EPIC-Oxford and UK Biobank cohorts. Environ. Int. 114, 191–201. https://doi.org/10.1016/j.envint.2018.02.048.

Dadvand, P., Sunyer, J., Basagaña, X., Ballester, F., Lertxundi, A., Fernández-Somoano, A., Estarlich, M., García-Esteban, R., Mendez, M.A., Nieuwenhuijsen, M.J., 2012. Surrounding greenness and pregnancy outcomes in four Spanish birth cohorts. Environ. Health Perspect. 120 (10), 1481–1487. https://doi.org/10.1289/ehp.1205244.

de Hoogh, K., Chen, J., Gulliver, J., Hoffmann, B., Hertel, O., Ketzel, M., Bauwelinck, M., van Donkelaar, A., Hvidtfeldt, U.A., Katsouyanni, K., Klompmaker, J., Martin, R.V., Samoli, E., Schwartz, P.E., Stafoggia, M., Bellander, T., Strak, M., Wolf, K., Vienneau, D., Brunekreef, B., Hoek, G., 2018. Spatial PM2.5, NO2, O3 and BC models for Western Europe – Evaluation of spatiotemporal stability. Environ. Int. 120, 81–92. https://doi.org/10.1016/j.envint.2018.07.036.

Duque, I., Domínguez-Berjón, M.F., Cebrecos, A., Prieto-Salceda, M.D., Esnaola, S., Calvo Sánchez, M., Marí-Dell'Olmo, M., 2021. Deprivation index by enumeration district in

Spain, 2011. Gac. Sanit. 35, 113–122. https://doi.org/10.1016/j.gaceta.2019.10.008.

European Environment Agency (EEA), 2020. Air quality in Europe - 2020 report, EEA Report.

European Heart Network, 2018. CVD Statistics 2017 [WWW Document]. Eur. Hear. Netw. URL https://ehnheart.org/cvd-statistics/cvd-statistics-2017.html (accessed 8.23.21).

Feigin, V.L., Roth, G.A., Naghavi, M., Parmar, P., Krishnamurthi, R., Chugh, S., Mensah, G.A., Norrving, B.o., Shiue, I., Ng, M., Estep, K., Cercy, K., Murray, C.J.L., Forouzanfar, M.H., 2016. Global burden of stroke and risk factors in 188 countries, during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet Neurol. 15 (9), 913–924. https://doi.org/10.1016/S1474-4422(16)30073-4.

Forastiere, F., Peters, A., 2021. Invited Perspective: The NO2 and Mortality Dilemma Solved? Almost There! Environ. Health Perspect. 129 (12) https://doi.org/10.1289/EHP10286.

Gascon, M., Triguero-Mas, M., Martínez, D., Dadvand, P., Rojas-Rueda, D., Plasència, A., Nieuwenhuijsen, M.J., 2016. Residential green spaces and mortality: A systematic review. Environ. Int. 86, 60–67. https://doi.org/10.1016/j.envint.2015.10.013.

Gascon, M., Zijlema, W., Vert, C., White, M.P., Nieuwenhuijsen, M.J., 2017. Outdoor blue spaces, human health and well-being: A systematic review of quantitative studies. Int. J. Hyg. Environ. Health 220 (8), 1207–1221. https://doi.org/10.1016/j.ijheh.2017.08.004.

GBD 2019 Stroke Collaborators, 2021. Global, regional, and national burden of stroke and its risk factors, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. Lancet Neurol. 20, 1–26. https://doi.org/10.1016/S1474-4422(21)00252-0.

Hartig, T., Mitchell, R., de Vries, S., Frumkin, H., 2014. Nature and Health. Nature and Health. 35 (1), 207–228.

Institut Cartogràfic i Geològic de Catalunya, 2009. Mapa de cobertes del sòl. Institut Cartogràfic i Geològic de Catalunya [WWW Document]. URL https://www.icgc.cat/Descarregues/Mapes-en-format-d-imatge/Cobertes-del-sol (accessed 1.23.22).

Korek, M.J., Bellander, T.D., Lind, T., Bottai, M., Eneroth, K.M., Caracciolo, B., De Faire, U.H., Fratiglioni, L., Hilding, A., Leander, K., Magnusson, P.K.E., Pedersen, N. L., Östenson, C.G., Pershagen, G., Penell, J.C., 2015. Traffic-related air pollution exposure and incidence of stroke in four cohorts from Stockholm. J. Expo. Sci. Environ. Epidemiol. 25, 517–523. https://doi.org/10.1038/jes.2015.22.

Levy, I., Mihele, C., Lu, G., Narayan, J., Brook, J.R., 2014. Evaluating Multipollutant Exposure and Urban Air Quality: Pollutant Interrelationships, Neighborhood Variability, and Nitrogen Dioxide as a Proxy Pollutant. Environ. Health Perspect. 122 (1), 65–72.

Ljungman, P.L.S., Andersson, N., Stockfelt, L., Andersson, E.M., Nilsson Sommar, J., Eneroth, K., Gidhagen, L., Johansson, C., Lager, A., Leander, K., Molnar, P., Pedersen, N.L., Rizzuto, D., Rosengren, A., Segersson, D., Wennberg, P., Barregard, L., Forsberg, B., Sallsten, G., Bellander, T., Pershagen, G., 2019. Long-term exposure to particulate air pollution, black carbon, and their source components in relation to ischemic heart disease and stroke. Environ. Health Perspect. 127 (10), 107012. https://doi.org/10.1289/EHP4757.

MacIntyre, E.A., Gehring, U., Mölter, A., Fuertes, E., Klümper, C., Krämer, U., Quass, U., Hoffmann, B., Gascon, M., Brunekreef, B., Koppelman, G.H., Beelen, R., Hoek, G., Birk, M., de Jongste, J.C., Smit, H.A., Cyrys, J., Gruzieva, O., Korek, M., Bergström, A., Agius, R.M., de Vocht, F., Simpson, A., Porta, D., Forastiere, F., Badaloni, C., Cesaroni, G., Esplugues, A., Fernández-Somoano, A., Lerxundi, A., Sunyer, J., Cirach, M., Nieuwenhuijsen, M.J., Pershagen, G., Heinrich, J., 2014. Air pollution and respiratory infections during early childhood: An analysis of 10 European birth cohorts within the ESCAPE project. Environ. Health Perspect. 122 (1), 107–113. https://doi.org/10.1289/ehp.1306755.

Markevych, I., Schoierer, J., Hartig, T., Chudnovsky, A., Hystad, P., Dzhambov, A.M., de Vries, S., Triguero-Mas, M., Brauer, M., Nieuwenhuijsen, M.J., Lupp, G., Richardson, E.A., Astell-Burt, T., Dimitrova, D., Feng, X., Sadeh, M., Standl, M., Heinrich, J., Fuertes, E., 2017. Exploring pathways linking greenspace to health: Theoretical and methodological guidance. Environ. Res. 158, 301–317. https://doi.org/10.1016/j.envres.2017.06.028.

Münzel, T., Gori, T., Al-Kindi, S., Deanfield, J., Lelieveld, J., Daiber, A., Rajagopalan, S., 2018. Effects of gaseous and solid constituents of air pollution on endothelial function. Eur. Heart J. 39, 3543. https://doi.org/10.1093/EURHEARTJ/EHY481.

Newby, D.E., Mannucci, P.M., Tell, G.S., Baccarelli, A.A., Brook, R.D., Donaldson, K., Forastiere, F., Franchini, M., Franco, O.H., Graham, I., Hoek, G., Hoffmann, B., Hoylaerts, M.F., Künzli, N., Mills, N., Pekkanen, J., Peters, A., Piepoli, M.F., Rajagopalan, S., Storey, R.F., 2015. Expert position paper on air pollution and cardiovascular disease. Eur. Heart J. https://doi.org/10.1093/eurheartj/ehu458.

Nieuwenhuijsen, M.J., Khreis, H., Triguero-Mas, M., Gascon, M., Dadvand, P., 2017. Fifty shades of green. Epidemiology 28, 63–71. https://doi.org/10.1097/EDE.0000000000000549.

Niu, Z., Liu, F., Yu, H., Wu, S., Xiang, H., 2021. Association between exposure to ambient air pollution and hospital admission, incidence, and mortality of stroke: an updated systematic review and meta-analysis of more than 23 million participants. Environ. Health Prev. Med. 26 (1) https://doi.org/10.1186/s12199-021-00937-1.

O'Donnell, M.J., Chin, S.L., Rangarajan, S., Xavier, D., Liu, L., Zhang, H., Rao-Melacini, P., Zhang, X., Pais, P., Agapay, S., Lopez-Jaramillo, P., Damasceno, A., Langhorne, P., McQueen, M.J., Rosengren, A., Dehghan, M., Hankey, G.J., Dans, A. L., Elsayed, A., Avezum, A., Mondo, C., Diener, H.-C., Ryglewicz, D., Czlonkowska, A., Pogosova, N., Weimar, C., Iqbal, R., Diaz, R., Yusoff, K., Yusufali, A., Oguz, A., Wang, X., Penaherrera, E., Lanas, F., Ogah, O.S., Ogunniyi, A., Iversen, H.K., Malaga, G., Rumboldt, Z., Oveisgharan, S., Al Hussain, F., Magazi, D., Nilanont, Y., Ferguson, J., Pare, G., Yusuf, S., 2016. Global and regional effects of

potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. Lancet 388 (10046), 761–775. https://doi.org/10.1016/S0140-6736(16)30506-2.

Orioli, R., Antonucci, C., Scortichini, M., Cerza, F., Marando, F., Ancona, C., Manes, F., Davoli, M., Michelozzi, P., Forastiere, F., Cesaroni, G., 2019. Exposure to residential greenness as a predictor of cause-specific mortality and stroke incidence in the rome longitudinal study. Environ. Health Perspect. 127 (2), 027002. https://doi.org/10.1289/EHP2854.

Pereira, G., Foster, S., Martin, K., Christian, H., Boruff, B.J., Knuiman, M., Giles-Corti, B., 2012. The association between neighborhood greenness and cardiovascular disease: an observational study, 466. https://doi.org/10.1186/1471-2458-12-466.

R Core Team, 2020. R: A language and environment for statistical computing.

Rook, G.A., 2013. Regulation of the immune system by biodiversity from the natural environment: An ecosystem service essential to health. Proc. Natl. Acad. Sci. USA. https://doi.org/10.1073/pnas.1313731110.

Scheers, H., Jacobs, L., Casas, L., Nemery, B., Nawrot, T.S., 2015. Long-Term Exposure to Particulate Matter Air Pollution Is a Risk Factor for Stroke: Meta-Analytical Evidence. Stroke 46, 3058–3066. https://doi.org/10.1161/STROKEAHA.115.009913.

Sistema de Vigilancia de Calidad del Aire, 2020. Datos de calidad del aire [WWW Document]. URL https://www.miteco.gob.es/es/calidad-y-evaluacion-ambiental/temas/atmosfera-y-calidad-del-aire/calidad-del-aire/evaluacion-datos/datos/Default.aspx (accessed 8.5.21).

Sørensen, M., Lühdorf, P., Ketzel, M., Andersen, Z.J., Tjønneland, A., Overvad, K., Raaschou-Nielsen, O., 2014. Combined effects of road traffic noise and ambient air pollution in relation to risk for stroke? Environ. Res. 133, 49–55. https://doi.org/10.1016/j.envres.2014.05.011.

Stafoggia, M., Bellander, T., Bucci, S., Davoli, M., de Hoogh, K., de' Donato, F., Gariazzo, C., Lyapustin, A., Michelozzi, P., Renzi, M., Scortichini, M., Shtein, A., Viegi, G., Kloog, I., Schwartz, J., 2019. Estimation of daily PM 10 and PM 2.5 concentrations in Italy, 2013–2015, using a spatiotemporal land-use random-forest model. Environ. Int. 124, 170–179. https://doi.org/10.1016/j.envint.2019.01.016.

Stafoggia, M., Cesaroni, G., Peters, A., Andersen, Z.J., Badaloni, C., Beelen, R., Caracciolo, B., Cyrys, J., de Faire, U., de Hoogh, K., Eriksen, K.T., Fratiglioni, L., Galassi, C., Gigante, B., Havulinna, A.S., Hennig, F., Hilding, A., Hoek, G., Hoffmann, B., Houthuijs, D., Korek, M., Lanki, T., Leander, K., Magnusson, P.K., Meisinger, C., Migliore, E., Overvad, K., Östenson, C.G., Pedersen, N.L., Pekkanen, J., Penell, J., Pershagen, G., Pundt, N., Pyko, A., Raaschou-Nielsen, O., Ranzi, A., Ricceri, F., Sacerdote, C., Swart, W.J.R., Turunen, A.W., Vineis, P., Weimar, C., Weinmayr, G., Wolf, K., Brunekreef, B., Forastiere, F., 2014. Long-term exposure to ambient air pollution and incidence of cerebrovascular events: Results from 11 European cohorts within the ESCAPE project. Environ. Health Perspect. 122, 919–925. https://doi.org/10.1289/ehp.1307301.

Stockfelt, L., Andersson, E.M., Molnár, P., Gidhagen, L., Segersson, D., Rosengren, A., Barregard, L., Sallsten, G., 2017. Long-term effects of total and source-specific particulate air pollution on incident cardiovascular disease in Gothenburg. Sweden. Environ. Res. 158, 61–71. https://doi.org/10.1016/j.envres.2017.05.036.

Tamosiunas, A., Grazuleviciene, R., Luksiene, D., Dedele, A., Reklaitiene, R., Baceviciene, M., Vencloviene, J., Bernotiene, G., Radisauskas, R., Malinauskiene, V., Milinaviciene, E., Bobak, M., Peasey, A., Nieuwenhuijsen, M.J., 2014. Accessibility and use of urban green spaces, and cardiovascular health: Findings from a Kaunas cohort study. Environ. Heal. A Glob. Access Sci. Source 13. https://doi.org/10.1186/1476-069X-13-20.

van Kempen, E., Casas, M., Pershagen, G., Foraster, M., 2018. WHO environmental noise guidelines for the European region: A systematic review on environmental noise and cardiovascular and metabolic effects: A summary. Int. J. Environ. Res. Public Health 15, 1–59. https://doi.org/10.3390/ijerph15020379.

Verhoeven, J.I., Allach, Y., Vaartjes, I.C.H., Klijn, C.J.M., de Leeuw, F.E., 2021. Ambient air pollution and the risk of ischaemic and haemorrhagic stroke. Lancet Planet. Heal. 5, e542–e552. https://doi.org/10.1016/S2542-5196(21)00145-5/ATTACHMENT/5BB99858-DAC5-4F15-9688-5729F42B8230/MMC1.PDF.

Vivanco-Hidalgo, R.M., Avellaneda-Gómez, C., Dadvand, P., Cirach, M., Ois, Á., Gómez González, A., Rodriguez-Campello, A., de Ceballos, P., Basagaña, X., Zabalza, A., Cuadrado-Godia, E., Sunyer, J., Roquer, J., Wellenius, G.A., 2019a. Association of residential air pollution, noise, and greenspace with initial ischemic stroke severity. Environ. Res. 179, 108725 https://doi.org/10.1016/j.envres.2019.108725.

Vivanco-Hidalgo, R.M., Ribera, A., Abilleira, S., 2019b. Association of Socioeconomic Status With Ischemic Stroke Survival. Stroke 50, 3400–3407. https://doi.org/10.1161/STROKEAHA.119.026607.

Wafa, H.A., Wolfe, C.D.A., Emmett, E., Roth, G.A., Johnson, C.O., Wang, Y., 2020. Burden of Stroke in Europe: Thirty-Year Projections of Incidence, Prevalence, Deaths, and Disability-Adjusted Life Years. Stroke 51, 2418–2427. https://doi.org/10.1161/STROKEAHA.120.029606.

WHO, W.H.O., 2016. Urban Green Spaces and Health: a Review of Evidence. WHO Reg. Off. Eur. 80.

Wilker, E.H., Wu, C.D., McNeely, E., Mostofsky, E., Spengler, J., Wellenius, G.A., Mittleman, M.A., 2014. Green space and mortality following ischemic stroke. Environ. Res. 133, 42–48. https://doi.org/10.1016/j.envres.2014.05.005.

Wolf, K., Hoffmann, B., Andersen, Z.J., Atkinson, R.W., Bauwelinck, M., Bellander, T., Brandt, J., Brunekreef, B., Cesaroni, G., Chen, J., de Faire, U., de Hoogh, K., Fecht, D., Forastiere, F., Gulliver, J., Hertel, O., Hvidtfeldt, U.A., Janssen, N.A.H., Jørgensen, J.T., Katsouyanni, K., Ketzel, M., Klompmaker, J.O., Lager, A., Liu, S., MacDonald, C.J., Magnusson, P.K.E., Mehta, A.J., Nagel, G., Oftedal, B., Pedersen, N. L., Pershagen, G., Raaschou-Nielsen, O., Renzi, M., Rizzuto, D., Rodopoulou, S., Samoli, E., van der Schouw, Y.T., Schramm, S., Schwarze, P., Sigsgaard, T., Sørensen, M., Stafoggia, M., Strak, M., Tjønneland, A., Verschuren, W.M.M.,

Vienneau, D., Weinmayr, G., Hoek, G., Peters, A., Ljungman, P.L.S., 2021. Long-term exposure to low-level ambient air pollution and incidence of stroke and coronary heart disease: a pooled analysis of six European cohorts within the ELAPSE project. Lancet Planet. Heal. 5, e620–e632. https://doi.org/10.1016/s2542-5196(21)00195-9.

World Health Organization, 2021. WHO global air quality guidelines: particulate matter (PM2.5 and PM10), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide. World Health Organization.

Yang, B.Y., Hu, L.W., Jalaludin, B., Knibbs, L.D., Markevych, I., Heinrich, J., Bloom, M.S., Morawska, L., Lin, S., Jalava, P., Roponen, M., Gao, M., Chen, D.H., Zhou, Y., Yu, H. Y., Liu, R.Q., Zeng, X.W., Zeeshan, M., Guo, Y., Yu, Y., Dong, G.H., 2020. Association Between Residential Greenness, Cardiometabolic Disorders, and Cardiovascular Disease Among Adults in China. JAMA Netw. Open 3, e2017507. https://doi.org/10.1001/jamanetworkopen.2020.17507.

Yeager, R., Riggs, D.W., DeJarnett, N., Tollerud, D.J., Wilson, J., Conklin, D.J., O'Toole, T.E., McCracken, J., Lorkiewicz, P., Xie, Z., Zafar, N., Krishnasamy, S.S., Srivastava, S., Finch, J., Keith, R.J., DeFilippis, A., Rai, S.N., Liu, G., Bhatnagar, A., 2018. Association between residential greenness and cardiovascular disease risk. J. Am. Heart Assoc. 7 https://doi.org/10.1161/JAHA.118.009117.

Yuan, S., Wang, J., Jiang, Q., He, Z., Huang, Y., Li, Z., Cai, L., Cao, S., 2019. Long-term exposure to PM2.5 and stroke: A systematic review and meta-analysis of cohort studies. Environ. Res. https://doi.org/10.1016/j.envres.2019.108587.

Yusuf, S., Joseph, P., Rangarajan, S., Islam, S., Mente, A., Hystad, P., Brauer, M., Kutty, V. R., Gupta, R., Wielgosz, A., AlHabib, K.F., Dans, A., Lopez-Jaramillo, P., Avezum, A., Lanas, F., Oguz, A., Kruger, I.M., Diaz, R., Yusoff, K., Mony, P., Chifamba, J., Yeates, K., Kelishadi, R., Yusufali, A., Khatib, R., Rahman, O., Zatonska, K., Iqbal, R., Wei, L., Bo, H., Rosengren, A., Kaur, M., Mohan, V., Lear, S.A., Teo, K.K., Leong, D., O'Donnell, M., McKee, M., Dagenais, G., 2020. Modifiable risk factors, cardiovascular disease, and mortality in 155 722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. Lancet 395, 795–808. https://doi.org/10.1016/S0140-6736(19)32008-2.