Environment International 179 (2023) 108136

Contents lists available at ScienceDirect

Environment International

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

Full length article

Mixtures of long-term exposure to ambient air pollution, built environment and temperature and stroke incidence across Europe

Jeroen de Bont[a,*,1], Regina Pickford[b,1], Christopher Åström[c], Fabian Colomar[d,e,f], Konstantina Dimakopoulou[g], Kees de Hoogh[h,i], Dorina Ibi[j], Klea Katsouyanni[g,k,l], Erik Melén[m], Federica Nobile[n], Göran Pershagen[a], Åsa Persson[a], Evangelia Samoli[g], Massimo Stafoggia[a,n], Cathryn Tonne[d,e,f], Jelle Vlaanderen[j], Kathrin Wolf[b], Roel Vermeulen[j], Annette Peters[b,o,p,2], Petter Ljungman[a,q,2]

[a] Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
[b] Institute of Epidemiology (EPI), Helmholtz Zentrum München – Deutsches Forschungszentrum für Gesundheit und Umwelt GmbH, Neuherberg, Germany
[c] Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden
[d] ISGlobal, Barcelona, Spain
[e] Universitat Pompeu Fabra (UPF), Barcelona, Spain
[f] CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, Spain
[g] Department of Hygiene, Epidemiology and Medical Statistics, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece
[h] Swiss Tropical and Public Health Institute, Allschwil, Switzerland
[i] University of Basel, Basel, Switzerland
[j] Institute for Risk Assessment Sciences, Utrecht University, Utrecht, Netherlands
[k] MRC Centre for Environment and Health, Environmental Research Group, Imperial College London, UK
[l] NIHR HPRU in Environmental Exposures and Health, Imperial College London, London, UK
[m] Department of Clinical Science and Education Södersjukhuset, Karolinska Institutet, Stockholm, Sweden
[n] Department of Epidemiology, Lazio Region Health Service /ASL Roma 1, Rome, Italy
[o] Chair of Epidemiology, Institute for Medical Information Processing, Biometry and Epidemiology, Medical Faculty, Ludwig-Maximilians-Universität München, Munich, Germany
[p] Munich Heart Alliance, German Center for Cardiovascular Health (DZHK e.V., partner-site Munich), Munich, Germany
[q] Department of Cardiology, Danderyd Hospital, Stockholm, Sweden

ARTICLE INFO

Handling Editor: Adrian Covaci

Keywords:
Stroke
Multiple environmental exposures
Urban exposome
Meta-analysis
Air pollution
Green space

ABSTRACT

Introduction: The complex interplay of multiple environmental factors and cardiovascular has scarcely been studied. Within the EXPANSE project, we evaluated the association between long-term exposure to multiple environmental indices and stroke incidence across Europe.

Methods: Participants from three traditional adult cohorts (Germany, Netherlands and Sweden) and four administrative cohorts (Catalonia [region Spain], Rome [city-wide], Greece and Sweden [nationwide]) were followed until incident stroke, death, migration, loss of follow-up or study end. We estimated exposures at residential addresses from different exposure domains: air pollution (nitrogen dioxide (NO_2), particulate matter < 2.5 µm ($PM_{2.5}$), black carbon (BC), ozone), built environment (green/blue spaces, impervious surfaces) and meteorology (seasonal mean and standard deviation of temperatures). Associations between environmental exposures and stroke were estimated in single and multiple-exposure Cox proportional hazard models, and Principal Component (PC) Analyses derived prototypes for specific exposures domains. We carried out random effects meta-analyses by cohort type.

Results: In over 15 million participants, increased levels of NO_2 and BC were associated with increased higher stroke incidence in both cohort types. Increased Normalized Difference Vegetation Index (NDVI) was associated with a lower stroke incidence in both cohort types, whereas an increase in impervious surface was associated with an increase in stroke incidence. The first PC of the air pollution domain ($PM_{2.5}$, NO_2 and BC) was associated

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* Corresponding author at: Institute for Environmental Medicine, Karolinska Institutet, SE-171 76 Stockholm, Sweden.
E-mail address: jeroen.de.bont@ki.se (J. de Bont).

[1] Shared first authorship.

[2] Shared last authorship.

https://doi.org/10.1016/j.envint.2023.108136
Received 14 April 2023; Received in revised form 28 July 2023; Accepted 7 August 2023

with an increase in stroke incidence. For the built environment, higher levels of NDVI and lower levels of impervious surfaces were associated with a protective effect [%change in HR per 1 unit = −2.0 (95 %CI, −5.9;2.0) and −1.1(95 %CI, −2.0; −0.3) for traditional adult and administrative cohorts, respectively]. No clear patterns were observed for distance to blue spaces or temperature parameters.

Conclusions: We observed increased HRs for stroke with exposure to $PM_{2.5}$, NO_2 and BC, lower levels of greenness and higher impervious surface in single and combined exposure models.

1. Introduction

Cardiovascular disease (CVD) accounts for 31 % of worldwide deaths (Roth et al., 2017) and stroke is one of the main causes of CVD death. Stroke is a multifactorial disease resulting from the interaction between genetic and non-genetic factors such as behavioural risk factors and environmental exposures (Tzoulaki et al., 2016).

Epidemiological studies have shown adverse effects of air pollution on stroke (de Bont et al., 2022), and to a lesser extent, studies reported a protective effect of green spaces on stroke (Liu et al., 2022). Short-term studies have reported associations between ambient air temperature and stroke (Lian et al., 2015), but the literature on long-term effects of air temperature on stroke is still limited. A recent systematic literature review on long-term exposure to temperature and health effects found in four studies on cardiovascular mortality and hospital admissions that higher winter temperature was associated with lower mortality, while the results were inconsistent for higher summer temperature (Zafeiratou et al., 2021).

Potential mechanisms linking long-term exposure to cold, heat and temperature variability with stroke remain poorly understood, but it seems that these exposures can activate physiopathological regulatory mechanisms (Lian et al., 2015). Hypothesised mechanisms may be an activation of the sympathetic nervous system and the renin-angiotensin system after the exposure to cold air with subsequent elevated blood pressure, while heat exposure increases skin blood flow and sweating possibly leading to hemoconcentration and hyperviscosity. Long-term exposure to high temperatures has also been associated with higher blood pressure and obesity (Zafeiratou et al., 2021). High blood pressure and obesity as well as hyperviscosity of the blood can increase the risk of ischemic stroke (Lian et al., 2015). Unstable temperatures can disrupt normal thermoregulation. Therefore, evaluating both the mean and variability of temperatures is relevant in understanding their impact on stroke risk (Lian et al., 2015).

Previous studies have mainly examined these factors in single exposure analyses. However, populations are continuously exposed to a mixture of environmental exposures, including air pollution, lack of natural environments and increased air temperature, which impact cardiovascular health (Nieuwenhuijsen, 2016). Some studies have applied multiple exposure models to account for confounding effects, but these models are prone to biased estimates due to high correlations (Dominici et al., 2010). These models also do not take their complex interplay into account and how it might affect health outcomes. New studies, which evaluate how these mixtures of environmental parameters interact, can help policymakers and urban planners to identify key aspects in the optimal urban design to reduce the number of stroke cases (Nieuwenhuijsen and Khreis, 2019).

In order to better understand the impact of environmental exposures on health, several prerequisites need to be met including adequate sample sizes of studies and replication/consistency of findings. Recent air pollution studies on health have used large European administrative cohorts (Stafoggia et al., 2022) that address any statistical power prerequisite but have not yet been used for the assessment of other environmental exposures. A limitation of these large datasets is that they are prone to residual confounding due to limited individual information. Some previous studies have shown that indirect adjustment can largely overcome this limitation (Brunekreef et al., 2021, Stafoggia et al., 2022), yet "traditional" cohorts with a wealth of individual data are needed to account for individual risk factors such as smoking and individual socioeconomic status. Moreover, a comprehensive and uniform exposure assessment across different European countries is desirable to reduce heterogeneity between studies that may result from different approaches.

The objective of this work was to assess three main domains of environmental exposures using an exposome approach (Vermeulen et al., 2020), including air pollution, built environment and ambient air temperature with respect to stroke incidence. We hypothesised that increased air pollution exposure and less green- and more grey spaces as well as higher average summer temperature and a higher fluctuation in outdoor temperature would lead to a higher risk of ischemic stroke. We include traditional adult cohorts with detailed individual information on risk factors and large administrative cohorts in our analyses and compare the results between the cohort types. This approach combines the large number of participants of the administrative cohorts with the detailed individual information available in the traditional adult cohorts while using uniform exposure assessment methods.

2. Materials and methods

The study was conducted as part of the "EXposome Powered tools for healthy living in urbAN Settings (EXPANSE)", which focuses on evaluating the complex mixture of the urban exposome on cardio-metabolic and pulmonary disease across Europe (Vlaanderen et al., 2021).

2.1. Study population

In this study, we included data from three traditional adult cohorts in Sweden (Cardiovascular Effects of Air Pollution and Noise in Stockholm [CEANS] study), the Netherlands (European Prospective Investigation into Cancer and Nutrition, the Netherlands [EPIC-NL]) and Germany (Cooperative Health Research in the Region of Augsburg [KORA]). These traditional cohort studies are rich on individual personal information on risk factors as they recruited study participants, examined them and conducted regular follow-ups on adverse health outcomes. In addition, we included data from four administrative cohorts which are formed by linking census administrative data with existing national databases of stroke incidence and mortality, individual characteristics if available, and residential history. These administrative cohorts are much larger regarding the number of participants but have less detailed personal information on the participants. The administrative cohorts included a regional cohort in Catalonia (Spain), nationwide cohorts in Greece and Sweden, and one citywide cohort in Rome, Italy. A more detailed cohort description is given in the supplement (pages 3–17).

2.2. Study design

In each cohort, we identified participants without a history of either stroke or coronary heart disease at least 3 years before enrolment in each cohort (outcome definition specified in the next section). For adult cohorts, the recruitment and baseline examinations took part between 1992 and 2004, and included adult participants above 20 years. For the administrative cohorts, we included all individuals who were above 37 years of age at baseline and were registered within the administration of each cohort. As the Greek administrative cohort included only citizens above 35 years and we wanted to remove prevalent cases, we restricted all administrative cohorts to participants above 37 years old. The baseline of the administrative cohorts varied between 2010 and 2014 and a more detailed description of participant eligibility and period of follow-up is specified in Table 1 and in the supplement (pages 3 to 17). Participants were followed-up until incident stroke or myocardial infarction, death, migration, loss of follow-up or end of the study period (up till 2011–2014 for the traditional adult cohorts and 2018–2019 for administrative cohorts), whichever came first. For the purposes of this analysis, participants with prevalent stroke or coronary heart disease and with their residential address missing at baseline were excluded.

Cohorts extracted and recoded their data according to a shared codebook for the EXPANSE project. All analyses were run locally at the respective study centres using the same code and only metadata and results were shared. The EXPANSE project, including the present analyses, was conducted in accordance with the Declaration of Helsinki. The original cohort studies were approved by the respective authorities complying with all relevant national, state, and local regulations, and written informed consent was obtained from all participants before enrolment.

2.3. *Outcome assessment: stroke definition*

We analysed incident events of stroke that occurred during the follow-up period. Stroke was defined according to the international classification of diseases (ICD), 8th, 9th and 10th revisions codes including hospitalization with principal diagnosis of ischemic, haemorrhagic or unspecified stroke (ICD8: 431–434, 436; ICD9: 431, 433.x1, 434, 436; ICD10: I61, I63, I64) and out-of-hospital deaths from cerebrovascular diseases (ICD9: 431–436; ICD10: I61-I64). Stroke occurrence was either taken from patient records (CEANS, Catalonia, Rome, Sweden), self-reported (KORA), derived by record-linkage of hospital discharge (EPIC-NL) or drug prescription (Greece). For KORA, outcome identification was accomplished by interview and inspection of medical records and death certificates. For Greece, the incidence of stroke was defined according to ICD-10 diagnosis recorded on drug prescriptions based on guidelines by the European Stroke Association (Dawson et al., 2022). Specifically, if subjects had at least one prescription with Aspirin and Dipyridamole or Clopidogrel without Aspirin, after six months of baseline, they were considered as cases. The exception to the guidelines was single use of aspirin which we excluded since the overlap with the therapy for ischemic heart disease is very large. To derive incident events, we excluded participants with a history of either stroke or coronary heart disease at least 3 years before enrolment.

2.4. *Exposure assessment*

A uniform exposure assessment protocol was developed for all the countries within the EXPANSE project (Vlaanderen et al., 2021). The included exposures were estimated at the residential addresses at baseline. Data source and time periods of the different exposure methodologies are specified in Table S1.

2.4.1. *Ambient air pollution*

For air pollution, fine particulate matter (particulate matter with an aerodynamic diameter below 2.5 μm, $PM_{2.5}$), nitrogen dioxide (NO_2), black carbon (BC), and ozone (O_3) were included. For each pollutant, a land-use regression (LUR) model was centrally built for the year 2010 (de Hoogh et al., 2018). Model performance was evaluated using five-fold cross-validation (CV); all models performed well with an R^2 value (i.e., spatial variability of the measured concentrations that can be explained by the model) of 66 % for $PM_{2.5}$, 58 % for NO_2, 51 % for black carbon, and 60 % for O_3. Data were estimated on a 100 × 100 m spatial resolution. For the analyses, the respective exposures of these grids were assigned to the residential addresses of our cohort participants at baseline. A more detailed description of the air pollution model developed can be found in de Hoogh et al., 2018 (de Hoogh et al., 2018).

2.4.2. *Built environment*

The built environment was characterized using three different indicators: greenness, grey spaces and blue spaces. Greenness was defined using the normalized difference vegetation index (NDVI) to assess average surrounding greenness. NDVI quantifies photosynthetically active vegetation by measuring the difference between near-infrared and red light. NDVI values range from + 1.0 to −1.0. NDVI was derived from the Vegetation Indices (MOD13Q1) product of the Terra Moderate Resolution Imaging Spectroradiometer (MODIS) with 250 m × 250 m resolution in 2019 (Didan et al., 2015). Surrounding greenness for each participant was assigned as the NDVI value of the specific grid of their residential address.

Grey spaces were characterized using the impervious density map of 2015 (Copernicus Land Monitoring Service, 2021). Impervious density maps are high-resolution maps (100 m × 100 m) that represent the percentage of soil sealing per area unit. Sealed/impervious areas are characterized by the substitution of the original (semi-) natural land cover or water surface with an artificial, often impervious cover. Similar to NDVI, we assigned the % of impervious surface of each 100 × 100 m grid at the residential address.

Exposure to blue spaces was estimated as distance to nearest water body. Due to the complexity in water body features (i.e. narrow linear features such as rivers, canals, coastal path, and beaches) distance metrics are often preferred to coverage metrics (e.g. surface areas) in research concerning blue spaces (Elliott et al., 2020). Exposure to blue spaces was assessed using the EU-Hydro map developed by the CLMS (Copernicus Land Monitoring Service, 2019). This baseline map 2011–2013 for all EEA39 countries provides high-resolution data on the river network, water bodies (e.g., lakes and wide rivers), drainage network with catchment areas, drainage lines and sea/ocean water. The Euclidean distance from the residential address to the nearest blue space was calculated.

2.4.3. *Air temperature*

Daily air temperature data (degree Celsius) at a 11 × 11 km resolution, covering our cohort study areas, were extracted from the European Centre for Medium-Range Weather Forecasts (ECMWF) ERA5-Land reanalysis dataset for 2010 (European Centre, 2023). These were assigned to cohort participants by location, and subsequently aggregated to calculate season mean and standard deviation (with cold season from January to March and October to December, and warm season from April to September).

2.5. *Statistical analyses*

We applied two approaches to evaluate the effect of multiple urban exposures on stroke incidence in the following order: single exposure models to estimate specific exposure-outcome associations, and Principal Component Analyses (PCA) derived prototypes for exposures domains, i.e. group of related exposures, to capture mixtures of exposures. Analyses were harmonised by use of a common protocol and code, while results were centralised at Karolinska Institutet. In a second step, we carried out a random effects meta-analysis to pool results by cohort type. We only conducted a meta-analysis if data from all cohorts was available. We calculated I2 statistics and P values for $\chi 2$ test from Cochran's Q to quantify the heterogeneity among studies.

We first applied single exposure models to evaluate the effect of each environmental exposure on incident stroke using Cox proportional hazard models with age as underlying time variable. Age was used as time scale to account for potential confounding by age (Thiebaut and Benichou, 2004). We selected three models with successively more detailed control for individual- and area-level confounders based on previous studies (Wolf et al., 2021, Cesaroni et al., 2014; Stafoggia et al., 2014). A Directed Acyclic Graphs is provided in the supplement (Figure S1). As individual variables in the administrative cohorts were limited, the selection of the confounders differed between traditional adult cohorts and administrative cohorts. For both cohort types, model 1 included age (time scale, in years), and sex, and the cohort baseline year and subcohort if applicable, as some of the traditional adult cohorts comprised two or more subcohorts. For country-wide administrative cohorts (Greece, Catalonia and Sweden), model 1 was additionally adjusted for a dummy variable for the nomenclature of territorial units for statistics (NUTS-1). For traditional adult cohorts with detailed individual risk factor information, model 2 was further adjusted for individual lifestyle and socioeconomic information at baseline: marital status (single, married or living with partner, divorced or separated, or widowed), body-mass index, smoking status (never, former, or current) and smoking duration (years), intensity of smoking among current and former smokers (cigarettes per day) and smoking intensity squared, employment status (yes or no), and education level (primary or less, secondary, or tertiary, as per country-specific definitions). For administrative cohorts, model 2 included all individual level variables available within each cohort. Availability of these covariates differs by administrative cohort (specific adjusting variables are specified in the results section). Finally, in all cohorts, model 3 additionally included neighbourhood-level socioeconomic status. Each cohort selected the most common area-SES variable in their specific region based on previous studies. Spatial scale varied from small census/neighbourhoods (CEANS, EPIC-NL, Catalonia, Rome, Sweden) to municipalities (Greece, KORA). Model 3 was considered our main model. Participants with missing information in model 3 covariates were excluded from the analyses.

We applied PCA based on three a priori defined domains: 1) air pollution (including $PM_{2.5}$, NO_2, BC and warm-season O_3); 2) built environment (including NDVI, impervious surfaces and distance to blue spaces); and 3) ambient temperature (including mean and standard deviation temperatures during cold and warm season). We applied PCAs by domains rather all exposures together in a PCA, because we expected that by domains, we would get interpretable and comparable PCAs across cohorts. The PCAs were applied to reduce the dimension of the data and the correlation between the exposures. Once we applied the PCA for each domain for each cohort, we selected the number of principal components that explained at least 80 % of the variance. The identified principal components were used in the Cox regression models as a linear variable. We evaluated violation of the proportional hazards assumption of the Cox models for all covariates by investigating the scaled Schoenfeld residuals against time, and applying the global test from the R survival package.

2.5.1. Sensitivity analyses

We conducted several sensitivity analyses to assess the robustness of our results. First, we developed two-exposure models selecting one exposure of each domain (NO_2, NDVI and mean air temperature during warm season, as in priori are the most common exposures in the literature) in order to evaluate possible confounding effects of the spatially correlated exposures. Secondly, we evaluated the effect of each exposure and PCA by tertiles to check for possible nonlinear associations between the components and stroke incidence. We also applied a multicomponent analysis including the same components of each domain (bi-component), bi-components additionally adjusted for the components of each specific domain, and all components in one model. All statistical analyses were conducted in R, version 3.4.0, using the following packages: *FactoMineR, survival, ggplot2, metafor,* and *mixmeta.*

3. Results

The number of participants ranged between 7,600 and 28,700 for the traditional adult cohorts and between 1.5 and 6 million for the administrative cohorts (Table 1). The Greek and Rome administrative cohort had the lowest exclusion of individuals (1.8 % and 0.4 %, respectively), whereas the largest exclusion was done in EPIC-NL (21.2 %) (supplement information pages 3–17). The percentage of stroke cases within the populations varied between 0.8 % and 6.5 %. Overall, we were able to include a total of 15,319,062 participants with 94,796,772 person-years at risk of which 519,666 (3.4 %) developed a stroke event. Regarding the mean age at baseline, KORA and EPIC-NL were the youngest cohorts (49.4 and 50.6 years, respectively) and the Greece cohort the oldest (60.3 years). The percentage of females ranged from 77 % in EPIC-NL to 48 % in the Swedish cohort.

The exposure levels differed across European areas, irrespective of the cohort type (Table S2). For most air pollutants, the Swedish cohorts had the lowest levels, whereas participants of the southern European cohorts but also EPIC-NL were exposed to comparatively high levels. Regarding the built environment, the cohorts from north and the middle of Europe had the highest NDVI values. Impervious surface was by far the lowest in the two Swedish cohorts while the highest levels were seen in the southern European ones. Distance to water was lowest in the Swedish cohorts and the Dutch cohort. The furthest average distance from blue spaces was seen for the Rome cohort.

Mean warm and cold season temperature were highest in the southern European cohorts. The standard deviation of the warm season temperature was much higher in the Greek administrative cohort than in any other cohort while the standard deviation of the cold season was highest in the two Swedish cohorts and in Greece.

The correlations between the air pollution indicators and built environment indicators followed similar patterns across most of the cohorts. High positive correlations were found between the air pollutants (except for O_3) and with impervious surfaces, whereas negative correlations were found between the pollutants and NDVI. The air pollution and built environment indicators were differently correlated with the temperature indicators within each cohort (Figure S2).

3.1. Associations of specific exposures with stroke incidence

For the single exposure models, the associations for $PM_{2.5}$ differed between traditional adult cohorts with detailed individual risk factor

Table 1.D

escription of the included traditional adult and administrative cohorts in the present analyses.

Characteristics	*Traditional cohorts*			*Administrative cohorts*			
	CEANS	*EPIC-NL*	*KORA*	*Catalonia*	*Greece*	*Rome*	*Sweden*
Cohort details							
Recruitment	*1992–2004*	*1993–1997*	*1994–2001*	*2015*	*2014*	*2011*	*2010*
End of follow-up	*2011*	*2010*	*2011–2014*	*2020*	*2019*	*2018*	*2018*
N	*19,274*	*28,730*	*7,616*	*3,546,305*	*6,121,421*	*1,539,784*	*4,321,054*
Persons-year risk	*250,217.4*	*438,937.7*	*116,258.8*	*17,018,691.6*	*29,640,819.6*	*10,000,055.8*	*37,303,538.1*
Stroke cases, N (%)	*802 (4.2)*	*691 (2.4)*	*329 (4.3)*	*28,175 (0.8)*	*400,479 (6.5)*	*26,710 (1.7)*	*63,906 (1.5)*
Baseline characteristics							
Age baseline, mean (SD)	*56.0 (11.1)*	*50.6 (11.2)*	*49.4 (13.8)*	*56.2 (13.8)*	*60.3 (15.4)*	*59.0 (14.4)*	*58.9 (13.8)*
Female, N%	*11,227 (58.3)*	*22,168 (77.2)*	*3,890 (51.1)*	*1,874,062 (52.8)*	*3,215,769 (52.5)*	*851,394 (55.3 %)*	*2,240,187 (51.8 %)*

Abbreviations: CEANS, Cardiovascular Effects of Air Pollution and Noise in Stockholm study; EPIC-NL, The European Prospective Investigation into Cancer and Nutrition- Netherlands; KORA, Cooperative Health Research in the Augsburg Region.

information and administrative cohorts, however the effects of NO_2 and BC were positive for both types of cohorts [% change in HR per 10 ug/m^3 NO_2 = 8.9 (95 %CI, −0.4; 18.9) and 2.1 (95 %CI, 0.7; 3.5)], respectively (Fig. 1). Warm summer ozone, on the other hand, was negatively associated with stroke incidence. This trend was similar across all cohorts, except for Rome which did not show statistically significant associations [HR % change per 10 μg/m^3 = 0.8 (95 %CI, −3.7; 5.5)].

Consistent across cohort types, for the built environment, we observed that an increase of NDVI decreased the risk of developing a stroke [HR %change per 0.1 unit increase = −5.9 (95 %CI, −10.6; −0.9)] for traditional adult cohorts and −1.0 (95 %CI, −1.9; −0.1) for the administrative cohorts, whereas an increase in impervious surface was associated with increase of stroke incidence (Fig. 1 and Table S3). The protective effect of NDVI was stronger in the traditional adult cohorts compared to the administrative cohorts, but the association with impervious surface was clearer in the administrative cohorts. (Fig. 1). However, looking at the single cohorts, neither a clear pattern could be detected between the cohorts, nor a clear trend for the traditional adult cohorts (table S3).

Regarding ambient air temperature, increased levels of temperature during the warm season within the study regions were associated with a very small increased risk of incident stroke for the administrative cohorts [% change in HR per 1 °C = 1.4 (95 %CI, 1.1; 1.6)] while the estimate for the traditional adult cohort was also positive however with a very large confidence interval. Further, we did not find statistically significant associations with stroke incidence for increased temperatures during the cold season and increased daily variability of temperatures during the warm and cold season. Through all results, the heterogeneity of the meta-analytic estimates was mostly around 0 % in the traditional cohorts but in the admin cohorts it varied between 70 and 98 % (table S3).

In the sensitivity analyses, the effects estimates changed substantially after adjusting for area-based SES variables in the administrative cohorts, but not in the adult cohorts (table S3). We further observed in most exposures stronger effect in the highest tertile (T3) compared to the second tertile, indicating possible linear associations between the components and stroke incidence (Figure S3). We observed some nonlinear trends for $PM_{2.5}$, distance to water and most temperature values in both cohort designs. In bi-exposure models, the meta-analytic estimates remained mostly similar (Table S4). Adjusting NO_2 for NDVI attenuated the associations slightly in the traditional adult cohorts but less so in the administrative cohorts, while adjusting the model for mean temperature increased the estimate for the traditional adult cohorts. Adjusting for NO_2 in the NDVI model slightly attenuated the effects while adding mean temperature to the model slightly increased the estimate in both cohort types.

In the traditional adult cohorts, the models are adjusted for subcohort (strata), age (timescale), sex (strata), and year of baseline visit, marital status, body-mass index, smoking (status, duration, intensity, intensity squared), employment status, education, and area-level socioeconomic status (2001 mean income on a neighbourhood level for CEANS and EPIC-NL, and percentage of households with low income, estimated income < 1250 € for KORA.

In the administrative cohorts, the models were adjusted for at least the following covariates: age (timescale) and sex (strata). The availability of the covariates differs by administrative cohorts. The following covariates were adjusted for each individual administrative cohort:

- Catalonia: age(timescale), sex, smoking, individual income, psca index, percentage of foreigners at census, population density at census.
- Greece: age(timescale), sex, NUTS1 areas country-wide (4 levels: Attica / Aegean Islands, Crete / North Greece / Central Greece)) & 4 area-level variables: tertiary education rate, unemployment rate, degree of urbanicity in 3 categories: 1. Cities (densely populated areas), 2. Towns and Suburbs (intermediate density areas) and 3. Rural areas (thinly populated areas) and married rate. For the Greater Area of Athens and other large municipalities (population

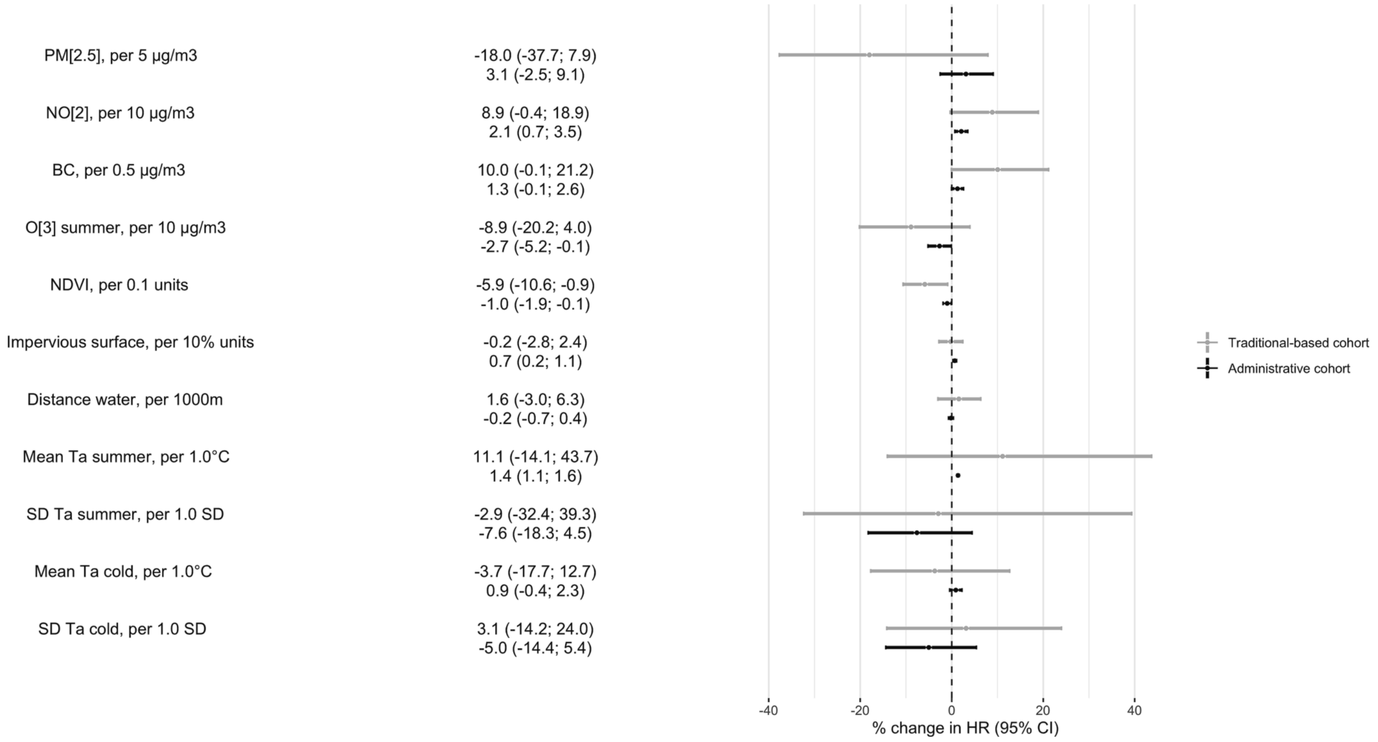

Fig. 1. Association between multiple environmental exposures and stroke incidence in single-exposure analyses (HRs for each cohort are shown in Table S3). Abbreviations: BC, Black carbon; CI, confidence interval; HR, hazard ratio; NDVI, Normalized Difference Vegetation Index; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; O_3, ozone during summer month; $PM_{2.5}$, particulate matter with an aerodynamic diameter of<2.5 μm; Ta, temperature; SD, Standard deviation.

greater than 100,000 inhabitants) in Greece, the aforementioned variables were available at square-block level. For the rest of the areas in Greece, the variables were available at municipality unit level.

- Rome: age(timescale), sex, place of birth, education, employment status, marital status, citizenship, deprivation index on a census block level and unemployment rate, percentage of graduates and house prices on a neighbourhood level.
- Sweden: age(timescale), sex, living condition, education level, district mean income, portion of people with high school or higher education in district, area.

3.2. *Combined effects of exposures per domain*

The first air pollution PC (PC-1) explained between 75 % and 92 % of the variability across cohorts (table S5). In all cohorts, the four pollutants contributed similarly to PC-1 with positive loadings for PM$_{2.5}$, NO$_2$ and BC and a negative loading for O$_3$ with the exception of EPIC-NL for which PM$_{2.5}$ in the first component was negative and for Greece and Sweden, with no loading for O$_3$. For CEANS, EPIC-NL, Greece, and Sweden a second component was included (constituting positive loadings for PM$_{2.5}$ and O$_3$, and for Sweden only O$_3$ was included) (Table S5).

Similarly, for the built environment the principal components did not differ between the cohorts. The first component included a positive loading for NDVI and a negative loading for impervious surface, explaining between 57 % and 64 % of variability across cohorts. Distance to water contributed to the second component explaining between 24 % and 34 % of the variability (Table S5).

The components of the temperature domain were slightly different across cohorts. In most cohorts, the first component included positive loadings for all four temperature parameters, explaining between 67 % and 94 % of the variability. In EPIC-NL, the loading for winter temperature was negative. KORA did not include standard deviation of temperature during winter times and Rome did not include mean temperature during warm period. However, these exposure variables were reflected in the second component as the first did not explain more than 80 %. Therefore, for all cohorts except for CEANS and EPIC-NL a second component was added (Table S5).

In addition, the correlations between the air pollution and built environment component domains were similar across cohorts, but the temperature correlations between the other components differed for each cohort (Figure S4).

An increased exposure to the PC-1 of air pollution was consistently associated with an increase in stroke incidence in both cohort types. The effects were higher for the traditional adult [% change in HR per 1 unit = 2.4 (95 %CI, −0.8; 5.7)] compared to the administrative cohorts [% change in HR per 1 unit = 0.8 (95 %CI, −0.2;1.8)]. (Fig. 2 and Table S6). In contrast, an increased exposure to a mixture of PM$_{2.5}$ and O$_3$ was associated with a decreased risk of stroke incidence in the cohorts that included the second PCA (CEANS, EPIC-NL, Greece and Sweden).

For the built environment, higher levels of NDVI and lower levels of impervious surfaces (PC-1) were consistently associated with a protective effect on stroke incidence for both cohort types [%change in HR per 1 unit = −2.0 (95 %CI, −5.9;2.0) and −1.1 (95 %CI, −2.0; −0.3) for traditional adult and administrative cohorts, respectively]. No association were seen for the second component, reflecting distance to blue spaces, neither statistically significant associations were observed for the any of the temperature principal components with stroke incidence nor a consistent trend across cohorts. Similar as in the single exposure models, the heterogeneity varied between the exposures and studies, and were generally higher for the administrative cohorts.

Regarding the PCA sensitivity analyses, we observed in most PCAs stronger effect in the highest tertile (T3) compared to the second tertile, indicating possible linear associations between the components and stroke incidence (Figure S5). A nonlinear trend was observed in the second built environment indicator, reflecting blue spaces (Figure S5).

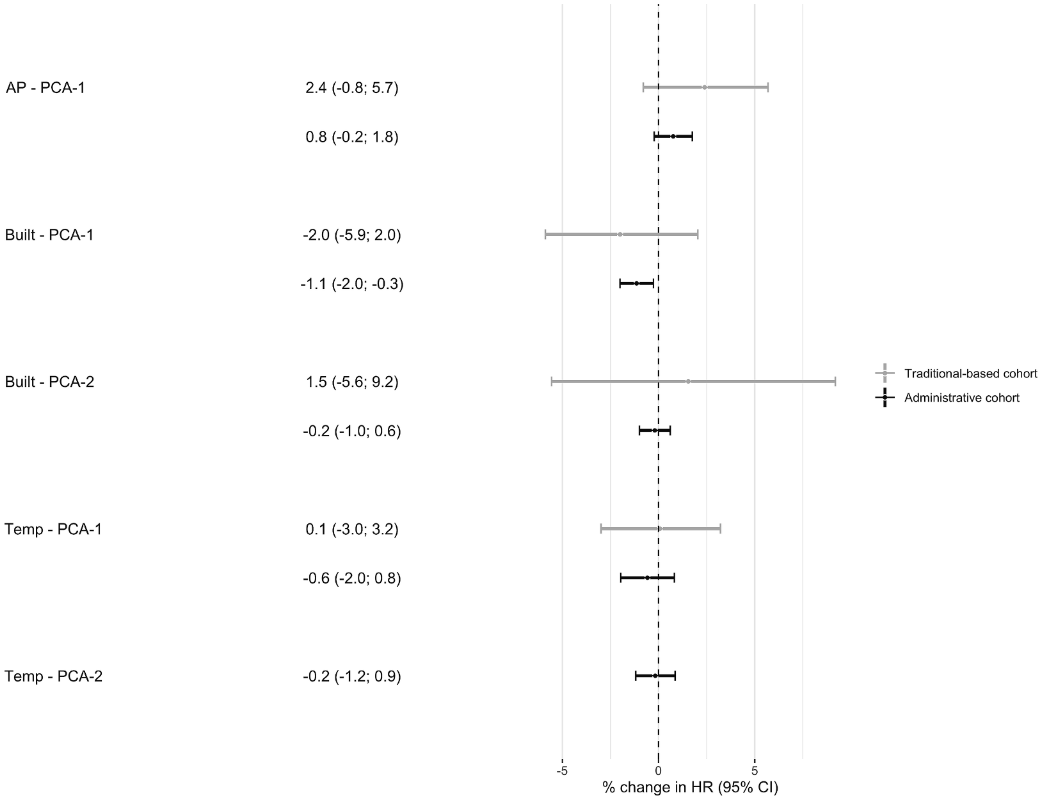

Fig. 2. Meta-analyses: association between environmental exposures and PCA analyses (HRs for all PC-domains are shown in Table S6). Abbreviations: AP, air pollution domain; Built, built environment domain; CI, confidence interval; HR, hazard ratio; temp, temperature domain; PCA, principal component.

In the bi-component and multicomponent analyses, only the mixture of high green and low grey spaces remained statistically significant with stroke incidence (Table S7). The effects of air pollution were attenuated and no longer statistically significant. Similar as in the single exposure model, adjusting air pollution domain for the built environment domain attenuated the associations slightly in the traditional adult cohorts but less so in the administrative cohorts, while adjusting the model for mean temperature increased the estimate for the traditional adult cohorts.

In the traditional adult cohorts, the models are adjusted for subcohort (strata), age (timescale), sex (strata), and year of baseline visit, marital status, body-mass index, smoking (status, duration, intensity, intensity squared), employment status, education, and area-level socioeconomic status (2001 mean income on a neighbourhood level for CEANS and EPIC-NL, and percentage of households with low income, estimated income < 1250 € for KORA.

In the administrative cohorts, the models were adjusted for at least the following covariates: age (timescale) and sex (strata). The availability of the covariates differs by administrative cohorts. The following covariates were adjusted for each individual administrative cohort:

- Catalonia: age(timescale), sex, smoking, individual income, psca index, percentage of foreigners at census, population density at census.
- Greece: age(timescale), sex, NUTS1 areas country-wide (4 levels: Attica / Aegean Islands, Crete / North Greece / Central Greece)) & 4 area-level variables: tertiary education rate, unemployment rate, degree of urbanicity in 3 categories: 1. Cities (densely populated areas), 2. Towns and Suburbs (intermediate density areas) and 3. Rural areas (thinly populated areas) and married rate. For the Greater Area of Athens and other large municipalities (population greater than 100,000 inhabitants) in Greece, the aforementioned variables were available at square-block level. For the rest of the areas in Greece, the variables were available at municipality unit level.
- Rome: age(timescale), sex, place of birth, education, employment status, marital status, citizenship, deprivation index on a census block level and unemployment rate, percentage of graduates and house prices on a neighbourhood level.
- Sweden: age(timescale), sex, living condition, education level, district mean income, portion of people with high school or higher education in district, area.

4. Discussion

In this exposome analysis we included data of more than 15 million participants from three traditional adult and four administrative cohorts across Europe. We observed increased HRs for stroke incidence with long-term exposure to NO_2 and BC in single exposure models for all cohorts, while for $PM_{2.5}$ a positive association was only seen in the administrative cohorts. Warm season O_3 was negatively associated with incidence of stroke. Analyses of air pollution mixtures in association with stroke incidence, derived from principal component analysis, were in line with the results of the single pollutant models. In fact, moving from single air pollutants to PCAs made the results more consistent between the study types. This suggests that being exposed to a mixture of air pollutants increases the risk of stroke. Protective effects were seen for higher levels of greenness and lower levels of impervious surface at the participants' home address. This finding emphasises that the built urban environment has an impact on stroke incidence. No clear patterns could be observed for distance to blue spaces or long-term exposure to different temperature parameters.

In this extensive European-wide analysis, we implemented a standardized data acquisition approach for exposure data, allowing for uniform analyses across all cohorts across Europe. We were further able to compare the results for administrative cohorts contributing very large sample sizes with those of traditional adult cohort studies, which, although lower in number, provide deep individual information on the participants. In both types of cohorts, we conducted a comprehensive assessment using two complementary steps to evaluate the association between multiple environmental exposures and stroke incidence. Firstly, we systematically examined associations with single exposures while accounting for multiple exposures. Subsequently, we investigated the effects of exposure mixtures. Across both single exposure and most multiple exposure models, consistent associations were observed between air pollution, green spaces, and grey spaces with stroke incidence in both cohort designs. However, some associations with NO_2, particularly in the traditional cohorts, were attenuated after adjusting for greenspaces, suggesting that green space characteristics may partially explain these associations. Given that NO_2 serves as an indicator of traffic-related pollution, it might be more sensitive to adjustments for other urban exposures. This suggests that future studies should take account of multiple urban exposures in urban settings. However, it is important to note that single and multiple exposure models have limitations in capturing complex mixtures of environmental exposures, as a few highly correlated exposures in the same model can lead to collinearity issues and biased estimates. To overcome this challenge and to account for exposure mixtures while reducing correlations, we employed principal component analyses (PCA) within specific domains. We chose domain-specific analyses because including more exposures into one domain would have complicated the interpretation of results even further. In fact, the loadings and variance were quite consistent across the different cohorts, especially for PCA-1 of air pollution (mixture of air pollutants), PCA-1 (mixture of high green and low grey spaces) and PCA-2 (increased distance to blue spaces) of the built environment. Although direct comparisons between the different models are not feasible, both approaches resulted in similar trends, with single exposure and PCA-based mixture models showing associations with stroke incidence. The consistency of these results holds significant implications for informing new policies aimed at improving stroke health. Such policies should not solely focus on individual aspects of the urban environment but rather consider multiple factors, including reducing air pollution and grey areas while increasing green spaces.

Most of the associations were consistent across cohort type and statistical approaches, but we also found some heterogeneity and inconsistencies in the results. In the meta-analyses, we observed significant heterogeneity among the administrative cohorts, whereas the traditional cohorts showed minimal heterogeneity (Table S3). This discrepancy can be attributed to the administrative cohorts having very narrow confidence intervals due to the large sample size, and despite the effect estimates being very similar, they did not overlap across the cohorts. We also found some inconsistencies in the results, specifically for $PM_{2.5}$, where the meta-analysis for the traditional adult cohorts showed a negative association with stroke incidence. This was not in line with our hypotheses and the result also differed from the administrative cohorts. Results for the single cohorts revealed that these negative associations were driven by the Swedish CEANS study and the Dutch EPIC-NL study, while the German KORA showed a positive association. Interestingly, of the administrative cohorts, the Swedish cohort also showed negative associations. Hence, in this case, the country-wide study was in accordance with the study that was limited to only Stockholm in Sweden. There is a geographical gradient across Sweden for $PM_{2.5}$, with higher levels in the southern parts of the country, which is to some extend attributable to differences in the importance of long-range transport. As there are geographic differences in the incidence of stroke in the opposite direction, which might not be fully captured by the covariates included in the adjustment, this would contribute to explaining the inverse associations with $PM_{2.5}$ in the Swedish nationwide cohort. The negative association for EPIC-NL is in line with previous analyses (Wolf et al., 2021). Also, the confidence intervals for these associations are wide and therefore the estimate cannot be considered precise and should be interpreted with caution.

4.1. Air pollution

In a recent umbrella review, de Bont et al. summarised systematic reviews and meta-analyses on ambient air pollutants and cardiovascular health (de Bont et al., 2022). The authors concluded that while for short-term effects of PM and NO_2 the strength of the evidence for stroke is sufficient, for long-term effects the evidence is still limited for PM, and unclear for NO_2 since no reviews are available yet.

Other large studies on long-term effects of $PM_{2.5}$ show stronger effects compared to our results of the administrative cohorts [2.8, (−2.9; 8.8)], however with effect estimates in the same range. For example, Stafoggia et al. (Stafoggia et al., 2014) found a positive association of 1.19 (0.88;1.62) in the ESCAPE study which included 11 European cohorts; Cai (Cai et al., 2018) showed HRs of 1.14 (0.65;1.99) in analyses in a Norwegian and two English cohorts, both per 5 $\mu g/m^3$ increase in annual $PM_{2.5}$. However, also no associations for $PM_{2.5}$ (Ljungman et al., 2019, Carlsen et al., 2022) have been reported. Regarding NO_2 and stroke incidence, in the analyses by Cai et al. (Cai et al., 2018) the association, showing an increase of 1.03 (95 %CI, 0.64; 1.12) per 10 $\mu g/m^3$ increase in NO_2, was similar to the results of our administrative cohorts [1.9 (95 %CI, 0.4; 6.0)] however with smaller confidence intervals, while in our traditional adult cohorts the association were higher with a larger confidence interval [8.9 (95 %CI, −0.4; 18.9)]. Some studies also revealed null associations for NO_2 (Stafoggia et al., 2014, Olaniyan et al., 2022). For BC, the number of studies is limited, and results are inconsistent (Alexeeff et al., 2018, Ljungman et al., 2019, Carlsen et al., 2022).

In the ELAPSE study, including 137.148 participants from six European cohorts, the incidence of stroke was associated with $PM_{2.5}$ (HR 1.10 [95 % CI 1.01; 1.21] per 5 $\mu g/m^3$ increase), NO_2 (1.08 [95 %CI, 1.04; 1.12] and BC (1.06 [95 %CI, 1.02; 1.10] each per 10 $\mu g/m^3$ increase in pooled analyses (Wolf et al., 2021). The three traditional adult cohorts we investigated in our analysis were also part of the ELAPSE analyses. While ELAPSE comprised specifically cohorts with exposure to low ambient air pollution levels, we covered cohorts across a broader exposure distribution. Moreover, we also included administrative cohorts. The associations of our analyses are comparable however somewhat smaller than the results of the ELAPSE study. Similar to our results, warm-season O_3 was negatively associated with an increase in stroke in the ELAPSE study. Other larger studies in the USA (Danesh Yazdi et al., 2019) and Canada (Olaniyan et al., 2022), however, found positive associations between the exposure to O_3 and the incidence of stroke. A possible explanation might be the different strength of the correlation of O_3 with $PM_{2.5}$. While it was positive in both North American studies (Pearson's r = 0.6 in Canada and r = 0.2 in the USA), we observed mostly moderate negative correlations with $PM_{2.5}$ (Spearman's r values 0.4 for Sweden to –0.9 in Catalonia) and highly negative correlations with NO_2 (0.3 for Greece and rest was negative from to −0.2 to −0.9 in Catalonia).

In a real-life setting, people are exposed to a mixture of air pollutants. To better capture this in our analyses, we additionally used a combined air pollution parameter determined by PCA. The strength of this approach is that we can estimate the association of the combined mixture without being sensitive to the correlation between specific pollutants. In general, the first air pollution component was similar in all cohorts with positive loadings for $PM_{2.5}$, NO_2 and BC and a negative loading for O_3. Using this first component as exposure, we found positive associations in most cohorts, indicating that long-term exposure to this mix of air pollutants was associated with an increase in the incidence of stroke.

A limited number of studies has considered air pollution mixture as exposure. Traini et al. evaluated the causal effect of a mixture of air pollutants on mortality in a large cohort in the Netherlands using a multivariate generalised propensity score model. The authors report positive associations between air pollution mixtures and all-cause mortality, with $PM_{2.5}$ being the main driver of the associations (Traini et al., 2022). Other authors explored two- or multi-pollutant models as part of their analyses. In the ELAPSE study, effect estimates for NO_2 and BC were robust to $PM_{2.5}$ adjustment, whereas $PM_{2.5}$ estimates decreased on adjustment for NO_2 and BC. In a large Canadian study, associations for $PM_{2.5}$ and incidence of stroke were positive, independent of co-exposure to NO_2 and O_3, and also robust in multi-pollutant models that adjusted for both NO_2 and O_3 (Olaniyan et al., 2022).

Exposure to ambient air pollution has been linked to cardiovascular disease and stroke through a number of mechanisms. Suggested pathways comprise oxidative stress and inflammation, autonomic nervous imbalance, and direct particle translocation. These pathways may activate secondary pathways such as endothelial dysfunction, thrombotic pathways, activation of a hypothalamic and pituitary-adrenal axis (HPA), and epigenomic changes (de Bont et al., 2022). Furthermore, impaired clotting and arterial fibrillation may be important additional risks for stroke incidence that have also been linked to particulate matter air pollution exposures. Long-term exposure to environmental PM in particular has been shown to be associated with accelerated progression of atherosclerosis through reactive oxygen species formation and systemic inflammation (Brook, 2008). These mechanisms may also lead to or increase obesity or diabetes after prolonged exposure, which in the long term can enhance the risk of ischaemic stroke. In addition, chronic exposure to PM and gaseous pollutants might damage the brain, indirectly through the activation of autonomic respiratory reflex arcs, and/or directly through local inflammation in the brain, caused by an influx of nanoparticles and gaseous pollutants through the blood– brain barrier (Hahad et al., 2020, Peters, 2023).

4.2. Greenness, grey and blue spaces

Increased number of studies have found protective effects of green spaces on cardiovascular mortality, but less studies have focused on stroke. A recent meta-analysis included only three studies and showed that a 0.1 increase in NDVI was significantly associated with lower odds of stroke incidence (OR: 0.98, 95 % CI: 0.96–0.99) which was very similar to our meta-analytic results from the administrative cohort (HR per 0.1 unit = 0.99 (95 %CI, 0.98; 0.99)] (Liu et al., 2022). A similar study in the same area of Rome found a stronger protective effect of NDVI on stroke incidence compared to our study (Orioli et al., 2019). The difference estimate might be explained by different time periods and/or different buffer sizes. Another study in the same region of Catalonia with similar data also found protective effects (Avellaneda-Gomez et al., 2022). The lack of natural environment has been less studied, and to our knowledge, this is the first study observing a positive association between impervious surface and stroke incidence. Consistent with the single exposure models, the combination of both, higher levels of greenness and lower levels of impervious surfaces, was captured in our PCA analyses, and was found to be protective against stroke incidence across cohorts.

The evidence of the effect of blue spaces on human health is still limited and the few published studies on mental health and mortality show mixed results (Smith et al., 2021, Kasdagli et al., 2023). Even in our study, in most cohorts we did not find associations between blue spaces and stroke incidence, except that we observed an increased risk in stroke incidence when participants lived further away from blue spaces in the traditional adult cohorts. One explanation might be that in cities, such as CEANS and KORA, living closer to the water is related to some socioeconomic factors (White et al., 2020). In the administrative cohorts, where we combine urban with rural areas, other unknown factors might explain the protective effects of living further away from the water. It is also possible that distance to the nearest water body is not a good indicator as it does not include any information on the amount and/or quality of this water, so the % of water in a certain buffer around the home address might be better. Another explanation of no associations that we observed in the sensitivity analyses is the nonlinear effects that might be present in these associations. More studies regarding the effects of blue spaces on health are required for further elucidation.

Several mechanisms have been proposed to explain the positive impact of higher levels of green and blue spaces, and less grey areas, on cardiovascular health. In short, they comprise a) promotion of physical activity through access to green/blue spaces, b) decreased stress and anxiety, c) better social interaction and d) contribution to a healthier environment including e.g. less air pollution and a reduction of heat island effects (Markevych et al., 2017, White et al., 2020, Georgiou et al., 2021). Some of the mechanisms such as increased physical activity and reduced stress levels are well-known protective effects for stroke (O'Donnell et al., 2016).

4.3. Temperature

Similar to previous studies, we considered seasonal temperature in our analyses, hypothesising that higher average summer temperatures as well as lower average winter temperatures might increase the risk of stroke. We captured temperature variability by looking at the seasonal (summer and winter) standard deviation of temperature. Only for the administrative cohorts are our results in line with previous studies regarding the positive association between higher summer temperatures and stroke. It is conceivable that the large grid cells (11kmx11km), for which temperature data is available in our study, might not be small-scaled enough to detect an urban heat island effect, the phenomenon that some city areas are typically warmer than the surrounding suburban/rural areas (Grimmond, 2007, Grilo et al., 2020). Similarly, the variation in annual mean temperature might be too small for the smaller cohorts to detect any effects, due to the small area they cover. For the average winter temperature, we did not see any association for the traditional adult cohorts and a small positive association for the administrative cohorts, which was mainly driven by the Catalonia cohort. This finding was unexpected as we anticipated that a milder winter would lead to less stroke cases. Future studies would need to incorporate higher resolution exposure assessment to account for long-term heat island effects, and larger temporality to disentangle in more detail the association between long-term temperatures and stroke incidence.

4.4. Potential bias and limitations

Our exposure levels were based on different years for the different exposures, which might have led to misclassification. However, it has been shown that the spatial variation of air pollution levels using land use regression models remains stable over periods of 10 years (Eeftens et al., 2011). In addition, a previous study in a similar setting showed in sensitivity analyses with back-extrapolated and time-varying exposures that associations were mostly similar to those in the main analysis (Wolf et al., 2021). Likewise, we do not expect large changes in the built environment over time. We therefore expect the models to be comparatively stable over the years and the specific year to be of minor significance. Regarding long term air temperature, however, we would presume that the spatial variation is less stable, and hence expect a larger bias for this exposure. In addition, the low-resolution temperature maps lead to reduced exposure variability which might be too small to detect associations, specifically for the smaller cities.

To draw valid conclusions, it is also essential to accurately model the exposure variables as errors in exposure assessment can introduce biases into the study findings. Measurement error is inherent in the estimation of exposures in environmental epidemiology and includes both classical and Berkson –type errors. Several simulations have shown the measurement error (Butland et al., 2019, Bergen et al, 2016, Samoli et al., 2020) will generally lead to bias of the effects towards the null in air pollution epidemiology. In a multi-exposure setting Bergen et al (2016) have shown that a pollutant with less measurement error may pick up parts of the effect from a pollutant measured with greater error in a multi exposure model. Unfortunately, we lack validation data to assess the impact of measurement error on our effect estimates, but the stability of the estimates between various approaches and adjustments adds credibility to the results.

A limitation of our study is that we cannot directly compare traditional adult cohorts with detailed individual information on risk factors and the administrative cohorts. Some differences we find in the associations between the study types may be due to the design of the study as much as to their location and cannot be disentangled within these data. While the traditional adult cohorts were located in the north and middle of Europe, most of the administrative cohorts come from southern Europe. However, even between the two Swedish cohorts, the traditional adult CEANS study which was conducted Stockholm county and the nation-wide Swedish cohort, we find differences in the PCA loadings as well as in the associations with stroke. Moreover, while the confounder adjustment was the same for the traditional adult cohorts, the administrative cohorts differed from the traditional adult cohorts and also between the cohorts. Nevertheless, adjusting for area-based SES variables in administrative cohorts seemed to change the effect estimates in line with most of the association found in the adult cohorts, pointing out the importance of these variables in this kind of setting. Following the concept of triangulation, concordant associations from different studies, study types and across different climatic conditions, generally support the plausibility of detected associations (Steenland et al., 2020).

In our data we could not differentiate between ischaemic stroke and haemorrhagic stroke. As the underlying mechanisms for these different types of stroke may differ, the impact of any environmental exposure might also be different. Chen 2022, for example found a statistically significant positive association between the exposure to $PM_{2.5}$ and ischemic stroke, while there was no association for haemorrhagic stroke (Chen et al., 2022).

5. Conclusion

In these exposome analyses we took multiple environmental exposures into account and highlight that single and complex mixtures of air pollution and the urban built environment can be risk and protective factors for incident stroke. To pinpoint the key aspects in the formation of healthier, liveable environments, these adverse and protective effects are already actionable today. Further research should address combined effects of more exposures, as noise and light at night and related interactions as they may play a role in the relationship between urban living and the development of CVD. This information will help policymakers and urban planners to create healthier cities thereby reducing the health burden for stroke.

Funding

Project funded by the European Union's Horizon 2020 research and innovation programme (No 874627). Jeroen de Bont is funded by the Svenska Forskningsrådet Formas (2022-00468) and Ulla Hamberg Angeby and Lennart Angeby Foundation 2022 (2022-02870).

CRediT authorship contribution statement

Jeroen de Bont: Conceptualization, Investigation, Methodology, Data curation, Formal analysis, Validation, Visualization, Writing – original draft, Writing – review & editing. **Regina Pickford:** Conceptualization, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **Christopher Åström:** Data curation, Formal analysis, Writing – review & editing. **Fabian Colomar:** Data curation, Formal analysis, Writing – review & editing. **Konstantina Dimakopoulou:** Data curation, Formal analysis, Writing – review & editing. **Kees de Hoogh:** Conceptualization, Methodology, Funding acquisition, Validation, Writing – review & editing. **Dorina Ibi:** Data curation, Formal analysis, Writing – review & editing.

Klea Katsouyanni: Conceptualization, Methodology, Writing – review & editing. **Erik Melén:** Conceptualization, Methodology, Funding acquisition, Writing – review & editing. **Federica Nobile:** Data curation, Formal analysis, Writing – review & editing. **Göran Pershagen:** Conceptualization, Writing – review & editing. **Åsa Persson:** Data curation, Writing – review & editing. **Evangelia Samoli:** Conceptualization, Validation, Methodology, Writing – review & editing. **Massimo Stafoggia:** Conceptualization, Validation, Methodology, Writing – review & editing. **Cathryn Tonne:** Conceptualization, Validation, Funding acquisition, Methodology, Writing – review & editing. **Jelle Vlaanderen:** Conceptualization, Validation, Methodology, Project administration, Funding acquisition, Resources, Writing – review & editing. **Kathrin Wolf:** Data curation, Formal analysis, Writing – review & editing. **Roel Vermeulen:** Conceptualization, Validation, Methodology, Project administration, Funding acquisition, Resources, Writing – review & editing. **Annette Peters:** Conceptualization, Methodology, Supervision, Writing – original draft, Funding acquisition, Writing – review & editing. **Petter Ljungman:** Conceptualization, Methodology, Supervision, Writing – original draft, 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.

Data availability

The authors do not have permission to share data.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2023.108136.

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