Concomitant exposure to air pollution, green space, and noise and risk of stroke: a cohort study from Denmark

Aslak H. Poulsen,[a,*] Mette Sørensen,[a,b] Ulla A. Hvidtfeldt,[a] Jesper H. Christensen,[c,d] Jørgen Brandt,[c,d] Lise M. Frohn,[c,d] Matthias Ketzel,[c,e] Christopher Andersen,[c,g] Steen Solvang Jensen,[c,d] Thomas Münzel,[f] and Ole Raaschou-Nielsen[a,c]

[a]Environment and Cancer, Danish Cancer Society Research Center, Strandboulevarden 49, 2100, Copenhagen, Denmark
[b]Department of Natural Science and Environment, Roskilde University, Universitetsvej 1, 4000, Roskilde, Denmark
[c]Department of Environmental Science, Aarhus University, Frederiksborgvej 399, 4000, Roskilde, Denmark
[d]iClimate—Interdisciplinary Centre for Climate Change, Aarhus University, Frederiksborgvej 399, 4000, Roskilde, Denmark
[e]Global Centre for Clean Air Research (GCARE), Department of Civil and Environmental Engineering, University of Surrey, Guildford, UK
[f]University Medical Center Mainz of the Johannes Gutenberg University, Center for Cardiology, Cardiology I, Mainz, Germany
[g]Danish Big Data Centre for Environment and Health (BERTHA), Aarhus University, Roskilde, Denmark

The Lancet Regional Health - Europe 2023;31: 100655

Published Online xxx https://doi.org/10.1016/j.lanepe.2023.100655

Summary

Background Air pollution, road traffic noise, and green space are correlated factors, associated with risk of stroke. We investigated their independent relationship with stroke in multi-exposure analyses and estimated their cumulative stroke burden.

Methods For all persons, ≥50 years of age and living in Denmark from 2005 to 2017, we established complete address histories and estimated running 5-year mean exposure to fine particles ($PM_{2.5}$), ultrafine particles, elemental carbon, nitrogen dioxide (NO_2), and road traffic noise at the most, and least exposed façade. For air pollutants, we estimated total, and non-traffic contributions. Green space around the residence was estimated from land use maps. Hazard ratios (HR) and 95% confidence limits (CL) were estimated with Cox proportional hazards models and used to calculate cumulative risk indices (CRI). We adjusted for the individual and sociodemographic covariates available in our dataset (which did not include information about individual life styles and medical conditions).

Findings The cohort accumulated 18,344,976 years of follow-up and 94,256 cases of stroke. All exposures were associated with risk of stroke in single pollutant models. In multi-pollutant analyses, only $PM_{2.5}$ (HR: 1.058, 95% CI: 1.040–1.075) and noise at most exposed façade (HR: 1.033, 95% CI: 1.024–1.042) were independently associated with a higher risk of stroke. Both noise and air pollution contributed substantially to the CRI (1.103, 95% CI: 1.092–1.114) in the model with noise, green space, and total $PM_{2.5}$ concentrations.

Interpretation Environmental exposure to air pollution and noise were both independently associated with risk of stroke.

Funding Health Effects Institute (HEI) (Assistance Award No. R-82811201).

Keywords: Air pollution; Green space; Multi-pollutant; Road traffic noise; Stroke

Introduction

Stroke is a leading cause of morbidity and death in the world[1] Causes of stroke include genetic, lifestyle, and environmental factors. Air pollution exposure affects risk of stroke via vascular dysfunction, plaque formation, oxidative stress, and systemic inflammation.[2] In a recent meta-analysis, 5 $\mu g/m^3$ higher exposure to $PM_{2.5}$ was associated with a 6.3% higher risk of stroke.[3] Meta-analyses on NO_2 also indicate a positive association though the evidence was too weak to conclude a causal association.[4,5] Studies addressing elemental carbon (EC) or the closely related entities black carbon and $PM_{2.5}$ absorbance, generally indicate weak or no association with risk of stroke.[6–13] Ultrafine particles (UFP), the particulate matter fraction smaller than 0.1 μm, may penetrate beyond the respiratory tract and reach the

*Corresponding author. Environment and Cancer, Danish Cancer Society Research Center, Strandboulevarden 49, 2100, Copenhagen Ø, Denmark.
E-mail address: aslak@cancer.dk (A.H. Poulsen).

Research in context

Evidence before this study

We searched PubMed using the search string: ("stroke" OR "brain infarction" OR "cerebrovascular" OR "cerebral infarction") AND ("green space" OR "green area" OR "noise" OR "Air pollution" OR "traffic") and found recent meta-analyses on green space, noise, and air pollution. A meta-analysis from 2022 of studies on green space and cardiovascular disease (published until January 2022), found that green space around residence was associated with reduced incidence or prevalence of stroke. This was based on five studies. Most of them were of cross-sectional design and without individual data on green space pointing to the need for more and better studies. A meta-analysis from 2022 of 7 studies on noise and stroke (published until April 2022). An umbrella review from 2022, on air pollution and stroke included 22 meta-analyses (published until January 2022), found a consistent positive association with $PM_{2.5}$. The quality of evidence for NO_2 was insufficient and there was a lack of studies on air pollutants such as ultrafine particles or elemental carbon and few studies have addressed source-specific air pollution. The authors of the umbrella review called for multi-pollutant analyses to disentangle effects of individual air pollutants. Such studies lack for air pollutants but even more so for studies simultaneously including all the correlated exposure domains: air pollution, noise, and green space. We only identified one such study–a cross-sectional study where only $PM_{2.5}$ was associated with self-reported stroke. Studies simultaneously addressing all three domains both as confounders and exposures are necessary to resolve which components are actually contributing to the total environmental burden. Ascribing risk to individual factors is important as it will facilitate efficacious regulatory measures to reduce stroke incidence.

Added value of this study

To our knowledge, our study is the first large prospective study to simultaneously address air pollution, noise, and green areas as exposures and try to disentangle which factors are independent risk factors for stroke and how much they contribute to the total environmental burden. Our study confirms that $PM_{2.5}$ concentration and noise at residence are independent risk factors for stroke and both contribute to stroke risk. Green space appears to have little or no impact on stroke risk when noise and air pollution are sufficiently accounted for.

Implications of all the available evidence

Our findings suggest that epidemiological studies on noise or air pollution need to account for the other factor. Preventive measures targeting both noise and $PM_{2.5}$ air pollution seem merited.

brain.[14] They may thus be of particular relevance for risk of stroke. The few studies investigating long-term UFP exposure in relation to stroke have indicated a positive association.[11,13,15,16]

Most epidemiological studies do not subdivide air pollution by source, thereby disregarding potential differences in chemical particle composition and thus toxicity by emission source.[17–19] We have recently found that air pollution from non-traffic sources was associated with risk of stroke, whereas air pollution from traffic sources was largely unassociated with stroke risk.[13]

Noise is believed to affect cardiovascular health through multiple pathways including sleep disturbance and stress-induced activation of the hypothalamus-pituitary-adrenal axis.[20] Several recent studies have found a positive association between noise and stroke.[21–23] Access to green areas may reduce stress and facilitate physical activity.[24] Few studies have investigated green space in relation to stroke,[12,25–27] generally indicating a protective association.

Noise and air pollution are often correlated, due to shared sources. Also, the presence of green space might be correlated with air pollution and noise. We are, however, only aware of one previous multi-pollutant study simultaneously addressing associations between air pollution, noise, and green space in relation to risk of stroke, showing a cross-sectional association between $PM_{2.5}$ concentration only and self-reported stroke.[28]

We hypothesized that estimates of association between a single exposure and stroke might be affected by mutual confounding from other exposures within the environmental domains: air pollution, traffic noise, and green space. In the present nationwide cohort, we therefore aimed to unravel independent associations between air pollution with $PM_{2.5}$, NO_2, EC, and UFP, noise, and green space in relation to risk of stroke.

Methods

Study population

Since 1968, all Danish citizens have been issued a unique personal identification number at birth. This allows all citizens to be traced in health and administrative registers.[29] We obtained the complete address histories of all persons living in Denmark in 1979, including exact date of changing address. Address histories ended after >14 consecutive days of incomplete address data or when people emigrated from Denmark. From these persons we identified a cohort of all (n = 2,048,282) living in Denmark on 1st January 2005 and who were ≥50 years of age any time between this date and 31st December 2017,

when the study ended. Participants were required to be born after 1920, as educational data were not available for those born earlier.

By Danish law, entirely register-based studies do not require ethical approval.

Outcome

We used both the Danish register of death[30] and the Danish national patient register[31] to identify cases, defined as the first occurrence of stroke (*International Classification of Disease* (ICD) 8: 431–434, 436, from 1977 to 1993 and ICD10: I61–I64 from 1994) in either register recorded as primary cause of death or admission. To ensure we only included incident cases we excluded persons diagnosed with stroke between 1977 and study entry and censored people at first stroke after entry.

Air pollution

For all Danish addresses, we estimated total concentrations of $PM_{2.5}$, UFP, EC, and NO_2 at the front door and the contributions from traffic and non-traffic by means of the DEHM/UBM/AirGIS modelling system.[32,33] The system combines air pollution contributions modelled at three levels: 1) long-range transported regional background, from the Danish Eulerian Hemispheric Model,[34] 2) local background at 1 km × 1 km resolution, from the Urban Background Model with data on Danish air pollution emissions,[35,36] and 3) local street contributions, from the Operational Street Pollution Model, taking into account traffic intensity and composition, meteorology, emission factors, and street and building configurations.[32] Validation studies have found Pearson correlation coefficients between modelled and measured concentrations in the range 0.67–0.85 for $PM_{2.5}$, 0.77–0.79 for EC, and 0.60–0.80 for NO_2.[37,38] Estimation of particle number concentration has recently been integrated in the DEHM/UBM/AirGIS system and is used as a measure of UFP as these quantities are highly correlated. Modelled UFP correlated well with measurements; Pearson correlations ranged from 0.86 to 0.95. Further description and validation can be found elsewhere.[39,40] High-quality inventories of Danish emissions enabled us to model air pollution, both with and without the emissions from Danish road traffic, in the present paper denoted as "total air pollution", and "air pollution from non-traffic sources". The former includes contributions from all national and international sources and the latter excludes contributions emitted by Danish road traffic. Air pollution was modelled as hourly concentrations, aggregated as monthly averages (Figures S1–S4). These data were then linked to the person-specific address histories to provide time-varying exposure estimates for all participants reflecting exact time lived at each address.

Road traffic noise

For all residential addresses we modelled road traffic noise at the most (LdenMax) and least (LdenMin) exposed façades by means of the Nordic Prediction Method.[41] The model took into account address-specific geocodes and building floor, as well as information for all Danish road links on road type, annual average daily traffic load, travel speed, and light/heavy vehicle distribution. Screening effects from terrain, buildings, and noise barriers, and 1st and 2nd order reflections were also taken into account. Exposure was modelled for the years 2000, 2005, 2010, and 2015 and linear interpolation was used to quantify exposure for all other years between 2000 and 2017. Values <35 dB were set to 35 dB. Noise was calculated as the equivalent A-weighted sound pressure level for day, evening, and night, and expressed as L_{den} for all residential addresses (Figure S5). A validation of the Nordic Prediction Method in the Nordic countries found a mean difference of 0.3 dB between measured and estimated road LdenMax.[42] As for air pollution, the address specific noise levels were combined with the person-specific address histories to obtain time-varying exposure estimates for all participants.

Green space

Basemap uses 36 land-use classes to classify land use for all of Denmark in 2016 at a 10 m × 10 m resolution.[43] Using these data, we defined two green space variables: 1) to quantify green space close to home that might facilitate physical activity, we estimated the percentage of recreational areas, forests, and open nature areas within 1000 m of the residence. 2) To quantify potentially stress-reducing green space in close proximity to the residence, we estimated the percentage of "low built up" (as a proxy for household gardens, see Figure S6 and Table S1), "high built up" (as a proxy for green areas around multi-storage buildings, see Figure S6 and Table S1), agricultural areas, recreational areas, forests, and open nature areas within 150 m of the residence. We used 100% minus these green space indicators in the analysis and denoted the quantities as "NonGreen1000m" and "NonGreen150m" to describe the lack of green space within the two radii. For all participants the green space metrics followed their address histories and reflected the changing addresses.

Covariates

Annually updated data on *a priori* selected potential confounders were provided by Statistics Denmark on: civil status (married/cohabiting, other), highest attained educational level (mandatory, secondary/vocational, medium/long), occupational status (high-level white collar, low-level white collar, blue collar, unemployed, retired), country of origin ("Danish origin" or "Other"), personal income, and household income (sex and calendar-year specific quintiles).

The individual covariate data did not include medical conditions such as hypertension, diabetes, dyslipidemia,

atherosclerosis etc. nor did it include lifestyle factors such as BMI, physical activity and cigarette smoking.

We also obtained annually updated information for all Danish parishes (2160 parishes in 2017, mean area 16.2 km^2, median population 1032 persons) on the proportion of inhabitants with only basic education, with manual labour, with income in the lowest quartile, living in social housing, living in single-parent households, with a criminal record, and with non-Western background. We excluded persons with missing covariates.

Statistical analysis

Spearman correlations between 5-year averaged pollutants were calculated over the entire study period. Hazard ratios (HR) and 95% confidence intervals for 5-year TWA air pollution and stroke were calculated in Cox proportional hazards models with age as time scale.

Cohort members were followed from 50 years of age or 1 January 2005, whichever came last, until stroke, >14 consecutive days of unknown address, emigration, death or 31 December 2017, whichever came first. Associations were evaluated linearly per interquartile range (IQR) of exposure. We adjusted for age (by design), sex, and calendar year (in two-year categories), educational level, occupational status, civil status, country of origin, personal and household income, and area-level factors: proportion of parish inhabitants living in single-parent households, with only basic education, with manual labour, with income in the lowest quartile, with non-Western background, living in social housing, and with a criminal record. Except for sex and country of origin, all variables were time-dependent. For green space, only moving address changed exposure. That means that exposures and covariates changed over time and that at any point in time during follow-up reflected the conditions pertaining to that particular moment in time.

We undertook one-, two-, three-, and four-pollutant analyses for combinations of the air pollutants ($PM_{2.5}$, UFP, EC, and NO_2). Separate analyses were performed for total concentration and for the contribution from non-traffic sources. We undertook the non-traffic analyses because we have previously shown that this contribution was most important for stroke risk.[13] For green space (NonGreen1000m and NonGreen150m) and road traffic noise (LdenMax and LdenMin), respectively, we undertook one- and two-pollutant analysis. These analyses, within each of the three domains of environmental exposure were used to preselect pollutants for the final multi-pollutant models where we only included pollutants consistently associated with elevated risk in all domain-specific analyses. The resulting final multi-pollutant model with total air pollution concentration included $PM_{2.5}$, LdenMax, NonGreen1000m, and NonGreen150m. The final model with air pollution from non-traffic sources included $PM_{2.5}$, NO_2, LdenMax, NonGreen1000m, and NonGreen150m. Assuming additive effects of the combined exposures on risk of stroke, we calculated a cumulative risk index (CRI), per IQR of the exposures for all evaluated Cox models. CRI was defined as:

$$CRI = exp\left[\sum_{p=1}^{p} \widehat{\beta}_p x_p\right] \equiv exp(\widehat{\beta}' x')$$

where $\widehat{\beta}' = (\widehat{\beta}_1, \ldots \widehat{\beta}_p)$ are the log (HR) from a Cox model with p exposures estimated at x_p concentrations.[44] If the exposures are positively correlated, the CRI will be smaller than sum of single pollutant HRs indicating that a smaller number of exposures may be sufficient to describe the total effect of the pollutants.

We used natural cubic splines with three degrees of freedom (knots at 33rd and 67th percentiles) to evaluate the shape of the associations between exposures and stroke. Splines were fitted in single exposure models and in models including all eight exposures. We used visual inspection of the spline curves to evaluate if the shapes approximated linearity or another biological plausible association, and if the associations were robust to adjustment for other exposures.

As a sensitivity analysis, we analysed all single pollutant models with additional adjustment for population density as 1st and 2nd degree polynomials.

Statistical analysis was performed in SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

We excluded 54,416 persons with stroke before entry and 22,620 persons with missing information about covariates from the eligible 2,048,282, leaving a final cohort of 1,971,246 persons, with 18,344,976 years of follow-up and 94,256 cases of stroke, i.e. with a crude incidence rate of 514 cases per 100,000 person years.

Table 1 describes the cohort at baseline. For all pollutants, traffic contributed only a small fraction of total concentrations. The neighbourhood characteristics of the study population are detailed in Supplement Table S2. The Spearman correlations (Rs) between total pollutant concentrations and their non-traffic component ranged from 0.82 for NO_2 to 0.96 for $PM_{2.5}$ and UFP (Table 2). The correlations between total concentrations of the different air pollutants were in the range 0.71–0.93. Correlations ranged from 0.63 to 0.85 between the four non-traffic contributions. Correlations between air pollution and noise were weak to moderate ranging from 0.07 to 0.53. Green area <1000 m was only

weakly related to other factors (Rs: –0.08 to 0.05). Green areas <150 m was weakly correlated with noise and air pollution (Rs: 0.19–0.40).

In single pollutant models, all air pollutants were associated with higher risk of stroke, with the highest HR for $PM_{2.5}$, as previously reported.[13] Unadjusted HRs differed little from the fully adjusted estimates (Supplement Table S3). In multi-pollutant models, $PM_{2.5}$ was the most robust air pollutant, showing increased HRs in all two-, three-, and four pollutant models. HRs for UFP, NO_2, and EC were all reduced to below 1.00 in one or more multi-pollutant combinations (Table 3). For air pollution concentrations from non-traffic sources, HRs for both $PM_{2.5}$ and NO_2 were consistently above 1.00, whereas UFP and EC showed HRs below 1.00 in several multi-pollution models (Table 4). For both total air pollutants and for non-traffic contributions, CRI analyses indicated $PM_{2.5}$ as the primary exposure with only small additional effect on the CRI from including other pollutants (Table 3, Table 4, Fig. 1a, and Figure S7).

Noise, both at the least and most exposed façade, was associated with risk of stroke in single pollutant models, whereas only LdenMax had an increased HR in a model including both (Table 5). The CRI for the model with both noise measures was near identical to the single pollutant LdenMax HR (Table 5 and Fig. 1b).

Non-green space within 1000 m and within 150 m of residence, were both associated with a higher risk of stroke in single pollutant models and when included in the same model (Table 5). The CRI for the model including both non-green space measures was similar to the sum of the two single pollutant estimates (Table 5 and Fig. 1c).

In the multi-pollutant model including total $PM_{2.5}$, LdenMax, and non-green space within 150 m and 1000 m, the HRs for the two latter were reduced to just slightly above 1.00, whereas the association for noise and $PM_{2.5}$ persisted, with only minor reductions (Fig. 2a, Supplement Table S4). The CRI of the four-pollutant model was 1.108 (95% CI: 1.097–1.120).

In the multi-pollutant model with non-traffic contributions of $PM_{2.5}$, NO_2, LdenMax, and non-green space within 150 m and 1000 m, both green space metrics were associated with HRs only slightly above 1.00 (Fig. 2b, Supplement Table S5). The HR for LdenMax was virtually unchanged compared to the single pollutant model. Both $PM_{2.5}$ and NO_2 from non-traffic sources were associated with an elevated risk of stroke, although the HRs were reduced compared with the single pollutant models. The CRI of this model was 1.150 (95% CI: 1.144–1.157).

In the spline models, $PM_{2.5}$ demonstrated a slightly sigmoid positive association with stroke, which

Baseline characteristics	Percent	Median (5–95 percentile)
Women	52	
Age (years), median		58 (50–79)
Country of origin		
Denmark	98	
Other	2	
Civil status		
Married/Cohabiting	73	
Other	27	
Education		
Mandatory	36	
Secondary or vocational	45	
Medium or long	19	
Occupational status		
White collar, high level	10	
White collar, low level	15	
Blue collar	30	
Unemployed	4	
Retired	41	
Personal income, quintiles		
1st (low)	25	
2nd–4th	55	
5th (high)	20	
Household income, quintiles		
1st (low)	21	
2nd–4th	55	
5th (high)	25	
Air pollution levels (5-year mean)		
$PM_{2.5}$ ($\mu g/m^3$)		
Total		11.2 (8.7–12.6)
Non-traffic		10.9 (8.52–11.7)
UFP ($particles/cm^3$)		
Total		11,099 (7212–17,232)
Non-traffic		9755 (6821–13,061)
EC ($\mu g/m^3$)		
Total		0.7 (0.4–1.1)
Non-traffic		0.5 (0.4–0.7)
NO_2 ($\mu g/m^3$)		
Total		15.2 (9.3–27.3)
Non-traffic		11.2 (7.8–14.1)
Road traffic noise (dB)		
Most exposed facade (LdenMax)		55 (40–68)
Least exposed facade (LdenMin)		44 (33–56)
Surrounding green space (%)		
Green space within 150 m[a]		58.8 (17.9–87.5)
Publicly accessible green space within 1000 m[b]		13.1 (2.9–36.3)

[a](Green150m) Percentage of areas within 150 m of the residential address, not classified as agricultural areas, household gardens, recreational areas, forests and open nature areas. For analysis the complementary quantity NonGreen150m = 100–Green150m was used. [b](Green1000m) Percentage of areas within 1000 m of the residential address that are not publicly accessible green areas (i.e. not classified as recreational areas, forests and open nature areas). For analysis the complementary quantity NonGreen1000m = 100–Green1000m was used.

Table 1: **Baseline individual-level sociodemographic characteristics and 5-year exposure levels among the study population of 1,971,246 persons.**

	Total $PM_{2.5}$	Total UFP	Total EC	Total NO_2	Non-traffic $PM_{2.5}$	Non-traffic UFP	Non-traffic EC	Non-traffic NO_2	$Lden_{max}$[a]	$Lden_{min}$[b]	NonGreen150m[c]	NonGreen1000[d]
Total $PM_{2.5}$	1	0.77	0.71	0.76	0.96	0.77	0.69	0.80	0.20	0.26	0.23	0.02
Total UFP	0.77	1	0.91	0.92	0.67	0.96	0.86	0.82	0.25	0.44	0.37	−0.06
Total EC	0.71	0.91	1	0.93	0.56	0.80	0.9	0.69	0.34	0.51	0.40	−0.07
Total NO_2	0.76	0.92	0.93	1	0.61	0.80	0.78	0.82	0.39	0.53	0.40	−0.05
Non-traffic $PM_{2.5}$	0.96	0.67	0.56	0.61	1	0.72	0.63	0.77	0.07	0.16	0.13	0.03
Non-traffic UFP	0.77	0.96	0.8	0.80	0.72	1	0.85	0.84	0.12	0.32	0.29	−0.05
Non-traffic EC	0.69	0.86	0.90	0.78	0.63	0.85	1	0.71	0.13	0.37	0.29	−0.07
Non-traffic NO_2	0.80	0.82	0.69	0.82	0.77	0.84	0.71	1	0.15	0.31	0.26	−0.00
LdenMax[a]	0.20	0.25	0.34	0.39	0.07	0.12	0.13	0.15	1	0.48	0.19	0.05
LdenMin[b]	0.26	0.44	0.51	0.53	0.16	0.32	0.37	0.31	0.48	1	0.34	−0.08
NonGreen150[c]	0.23	0.37	0.40	0.40	0.13	0.29	0.29	0.26	0.19	0.34	1	0.01
NonGreen1000[d]	0.02	−0.06	−0.07	−0.05	0.03	−0.05	−0.07	−0.00	0.05	−0.08	0.01	1

[a]$Lden_{max}$: Traffic noise at most exposed facade. [b]$Lden_{min}$: Traffic noise at least exposed facade. [c]NonGreen150m: Percentage of areas within 150 m of the residential address, not classified as agricultural areas, household gardens, recreational areas, forests and open nature areas. [d]NonGreen1000m: Percentage of areas within 1000 m of the residential address that are not publicly accessible green areas (i.e. not classified as recreational areas, forests and open nature areas).

***Table 2*: Spearman rank correlations between 5-year time weighted average residential air pollution concentrations, road traffic noise and surrounding green space at residences of all cohort members, Denmark, 2005–2017.**

approached linearity when disregarding upper and lower 5% of the exposure range, or when adjusted for other exposures (Fig. 3). UFP was also positively associated with stroke and the association was near-linear in the single pollutant model, whereas adjustment for other exposures introduced more uncertainty for low exposures. EC and NO_2 curves with and without adjustment for other exposure differed substantially. Noise at most and least exposed façade were both positively and linearly associated with stroke in single pollutant models; only noise at most exposed face was robust to adjustment for other exposures (Fig. 4). Greenspace within 1000 m showed a weak, positive, and near-linear association with risk of stroke in the single exposure model; the

Total concentration of air pollutants	$PM_{2.5}$ total HR (95% CI)[a] per IQR: 1.85 µg/m^3	Ultrafine Particles total HR (95% CI)[a] per IQR: 4248 #/cm^3	Elemental carbon total HR (95% CI)[a] per IQR: 0.28 µg/m^3	NO_2 total HR (95% CI)[a] per IQR: 7.15 µg/m^3	Cumulative risk index CRI (95% CI)[a]
Single pollutant models					
$PM_{2.5}$	1.077 (1.061–1.094)				1.077 (1.061–1.094)
UFP		1.039 (1.026–1.052)			1.039 (1.026–1.052)
EC			1.009 (1.001–1.018)		1.009 (1.001–1.018)
NO_2				1.028 (1.017–1.04)	1.028 (1.017–1.040)
Two pollutant models					
$PM_{2.5}$ + UFP	1.084 (1.063–1.107)	0.992 (0.975–1.009)			1.075 (1.055–1.095)
$PM_{2.5}$ + EC	1.119 (1.097–1.142)		0.966 (0.953–0.978)		1.081 (1.063–1.099)
$PM_{2.5}$ + NO_2	1.100 (1.078–1.123)			0.978 (0.963–0.993)	1.076 (1.057–1.096)
UFP + EC		1.063 (1.043–1.084)	0.979 (0.966–0.992)		1.041 (1.024–1.058)
UFP + NO_2		1.034 (1.015–1.053)		1.006 (0.990–1.023)	1.040 (1.022–1.058)
EC + NO_2			0.987 (0.972–1.002)	1.040 (1.022–1.059)	1.026 (1.009–1.043)
Three pollutant models					
$PM_{2.5}$ + UFP + EC	1.109 (1.085–1.133)	1.029 (1.008–1.050)	0.954 (0.939–0.970)		1.089 (1.078–1.100)
$PM_{2.5}$ + UFP + NO_2	1.098 (1.074–1.123)	1.005 (0.985–1.024)		0.976 (0.959–0.993)	1.077 (1.066–1.088)
$PM_{2.5}$ + EC + NO_2	1.120 (1.095–1.145)		0.966 (0.950–0.982)	0.999 (0.980–1.019)	1.081 (1.070–1.092)
UFP + EC + NO_2		1.053 (1.031–1.076)	0.971 (0.955–0.988)	1.021 (1.001–1.041)	1.044 (1.034–1.054)
Four pollutant model					
$PM_{2.5}$ + UFP + EC + NO_2	1.113 (1.088–1.138)	1.032 (1.010–1.055)	0.958 (0.941–0.975)	0.990 (0.970–1.011)	1.089 (1.067–1.112)

IQR: interquartile range; HR: hazard ratio; CI: confidence interval. [a]All estimates are given per interquartile increase in exposure and adjusted for age, sex, calendar-year, civil status, individual and family income, country of origin, occupational status, education, and neighborhood-level percentage of population with low income, with only basic education, who are unemployed, with manual labor, with non-Western background, with criminal record, who are sole-provider, and who live in social housing.

***Table 3*: Hazard ratios (HR) and cumulative risk index (CRI) for single-, two-, three- and four-pollutant models of the total concentration of the air pollutants $PM_{2.5}$, ultrafine particles, NO_2 and elemental carbon in relation to risk of stroke.**

Non-Traffic contribution to air pollutants	$PM_{2.5}$ Non-traffic HR (95% CI)[a] per IQR: 1.63 μg/m^3	Ultrafine particles Non-traffic HR (95% CI)[a] per IQR: 2769 #/cm^3	Elemental carbon Non-traffic HR (95% CI)[a] per IQR: 0.12 μg/m^3	NO_2 Non-traffic HR (95% CI)[a] per IQR: 2.68 μg/m^3	Cumulative risk index (CRI, 95% CI)[a]
Single pollutant models					
$PM_{2.5}$	1.091 (1.074–1.108)				1.091 (1.074–1.108)
UFP		1.038 (1.028–1.049)			1.038 (1.028–1.049)
EC			1.005 (1.000–1.009)		1.005 (1.000–1.009)
NO_2				1.077 (1.065–1.089)	1.077 (1.065–1.089)
Two pollutant models					
$PM_{2.5}$ + UFP	1.083 (1.063–1.104)	1.008 (0.996–1.021)			1.092 (1.075–1.109)
$PM_{2.5}$ + EC	1.106 (1.086–1.126)		0.991 (0.984–0.997)		1.096 (1.082–1.110)
$PM_{2.5}$ + NO_2	1.043 (1.023–1.064)			1.058 (1.043–1.072)	1.103 (1.084–1.122)
UFP + EC		1.049 (1.036–1.062)	0.992 (0.986–0.999)		1.041 (1.031–1.051)
UFP + NO_2		0.985 (0.971–1.000)		1.088 (1.072–1.105)	1.072 (1.056–1.088)
EC + NO_2			0.997 (0.991–1.003)	1.078 (1.066–1.091)	1.075 (1.065–1.085)
Three pollutant models					
$PM_{2.5}$ + UFP + EC	1.093 (1.072–1.114)	1.023 (1.009–1.038)	0.985 (0.978–0.993)		1.101 (1.093–1.109)
$PM_{2.5}$ + UFP + NO_2	1.051 (1.030–1.073)	0.977 (0.963–0.992)		1.072 (1.054–1.090)	1.101 (1.091–1.111)
$PM_{2.5}$ + EC + NO_2	1.056 (1.034–1.079)		0.990 (0.983–0.998)	1.057 (1.042–1.072)	1.105 (1.097–1.113)
UFP + EC + NO_2		0.984 (0.967–1.002)	1.001 (0.993–1.008)	1.089 (1.071–1.106)	1.073 (1.065–1.081)
Four pollutant model					
$PM_{2.5}$ + UFP + EC + NO_2	1.056 (1.034–1.079)	0.984 (0.967–1.002)	0.994 (0.986–1.002)	1.067 (1.049–1.086)	1.102 (1.068–1.137)

IQR: interquartile range; HR: hazard ratio; CI: confidence interval. [a]All estimates are given per interquartile increase in exposure and adjusted for age, sex, calendar-year, civil status, individual and family income, country of origin, occupational status, education, and neighborhood-level percentage of population with low income, with only basic education, who are unemployed, with manual labor, with non-Western background, with criminal record, who are sole-provider, and who live in social housing.

Table 4: **Hazard ratios (HR) and cumulative risk index (CRI) for single-, two-, three- and four-pollutant models of the non-traffic contribution of $PM_{2.5}$, ultrafine particles, NO_2 and elemental carbon in relation to risk of stroke.**

association vanished after adjustment for other exposures (Fig. 4). For green space coverage <150 m from house, both models showed a maximum for HRs around 50% green space coverage.

$PM_{2.5}$ from non-traffic sources was positively associated with stroke in the single-pollutant model although less so after adjustment for other exposures (Supplement Figure S8). Non-traffic NO_2 was associated with stroke in only the middle part of the exposure range in single exposure models and the association was attenuated and more linear after adjustment for other exposures.

In sensitivity analysis additional adjustment for population density produced no conspicuous changes in linear HRs (Supplement Table S6).

Discussion

In this nationwide cohort study with 94,256 cases of stroke, $PM_{2.5}$, NO_2, UFP, EC, noise, and lack of green space at the residence were all associated with a higher risk of stroke in single pollutant models. In multi-pollutant analyses, only air pollution with $PM_{2.5}$ and noise at most exposed façade were independently associated with a higher risk of stroke, with both contributing substantially to the CRI. In a multi-pollutant analysis restricting air pollution to the contribution from non-traffic sources, also NO_2 was independently associated with higher risk and contributed substantially to the CRI. Except for non-green space <150 m, the exposures associated with stroke in our final linear multi-pollutant model were the same as those robustly associated with stroke in the non-linear analysis and they were compatible with a linear representation, at least for the 5–95th percentile exposure range.

Air pollution

The linear associations between $PM_{2.5}$, NO_2, UFP, and EC, and risk of stroke in the single pollutant models of our study agree with the existing literature.[6–12] The existing evidence for single pollutant studies is strongest for $PM_{2.5}$ and our two- and multi-pollutant models as well as our spline analyses suggested $PM_{2.5}$ as the primary causative agent. A Dutch study on cerebrovascular disease (1238 cases) showed associations with UFP, NO_2, $PM_{2.5}$, and $PM_{2.5}$ absorbance in single pollutant models,[11] albeit with confidence intervals spanning the null. In two pollutant models, UFP was the most robust pollutant, which is in contrast to our results. The population of the Dutch study was mostly urban, which could lead to a different composition and possibly higher levels of UFP air pollution than in our nationwide study. Furthermore, in the Dutch study, UFP was modelled differently from the other pollutants; if UFP was modelled more precisely than the other pollutants, that could be the reason why UFP was most robust in multi-pollutant models. Since all confidence intervals spanned the null, the observed associations could also

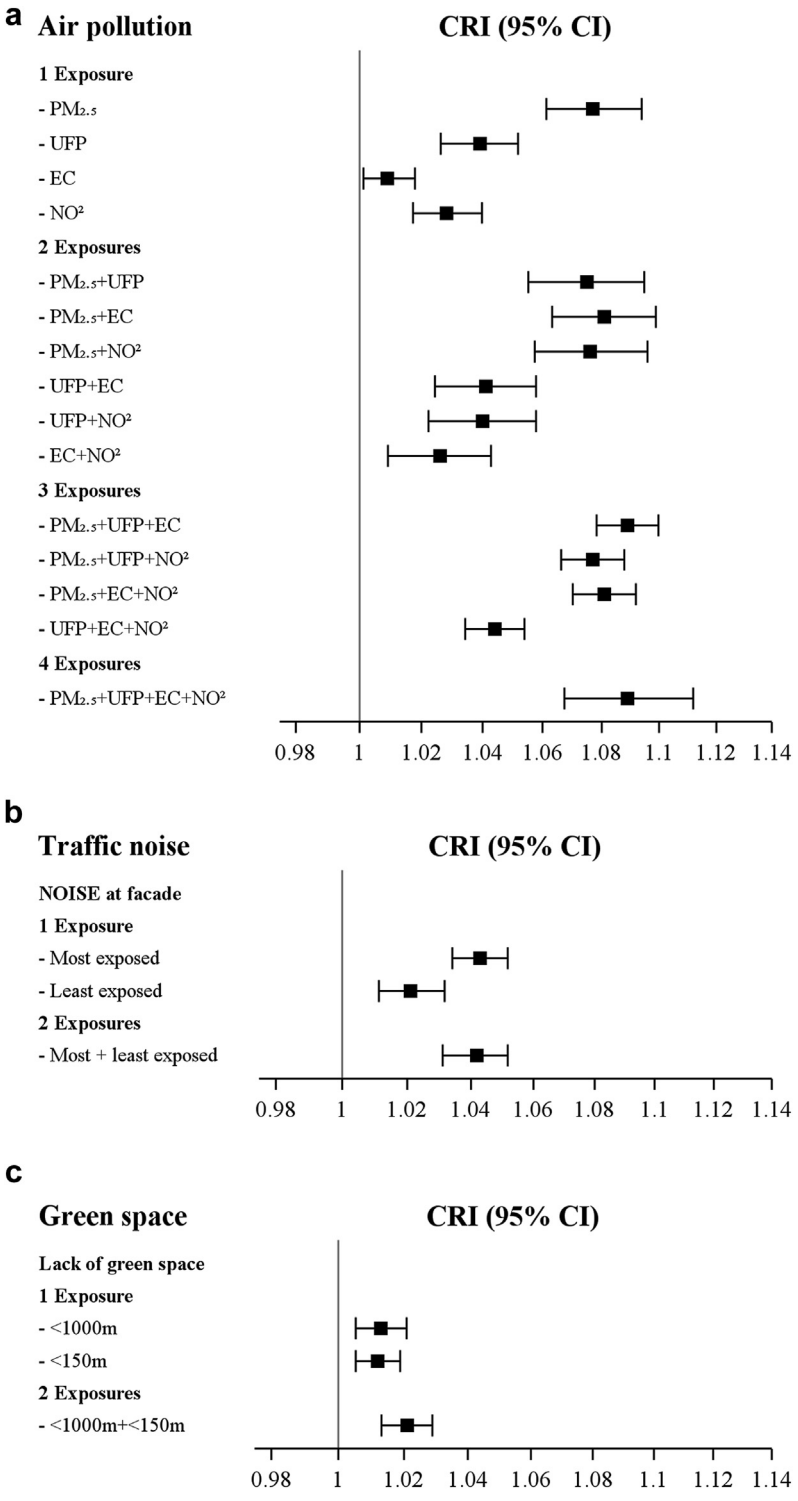

Fig. 1: Cumulative risk index (CRI) with 95% confidence intervals (CI) for stroke from fully adjusted[a] single-, two-, three- and four-pollutant models of $PM_{2.5}$, ultrafine particles (UFP), NO_2 and elemental carbon (EC) (a), noise at most and least exposed façade (b) and lack of green space within 150 and 1000 m of the residence (c). [a]All estimates are given per interquartile increase in exposure and adjusted for age, sex, calendar-year, civil status, individual and family income, country of origin, occupational status, education, and neighborhood-level percentage of population with low income, with only basic education, who are unemployed, with manual labor, with non-Western background, with criminal record, who are sole-provider, and who live in social housing.

	Noise, most exposed façade (LdenMax) HR (95% CI)[a] per IQR: 10.6 dB	Noise, least exposed façade (LdenMin) HR (95% CI)[a] per IQR: 9.5 dB	Cumulative risk index (CRI, 95% CI)[a]
Single pollutant models			
LdenMax[b]	1.043 (1.034–1.052)		1.043 (1.034–1.052)
LdenMin[c]		1.021 (1.011–1.032)	1.021 (1.011–1.032)
Two pollutant model			
LdenMax + LdenMin	1.044 (1.033–1.054)	0.998 (0.986–1.009)	1.042 (1.031–1.052)
	NonGreen1000m[c] HR (95% CI)[a] per IQR: 12.6%	**NonGreen150m[b] HR (95% CI)[a] per IQR: 18.1%**	
Single pollutant models			
NonGreen1000m[d]	1.014 (1.005–1.022)		1.014 (1.005–1.021)
NonGreen150m[e]		1.012 (1.005–1.019)	1.012 (1.005–1.019)
Two pollutant model			
NonGreen150m + NonGreen1000m	1.011 (1.003–1.020)	1.010 (1.003–1.017)	1.021 (1.013–1.029)

IQR: interquartile range; HR: hazard ratio; CI: confidence interval. [a]All estimates are given per interquartile increase in exposure and adjusted for age, sex, calendar-year, civil status, individual and family income, country of origin, occupational status, education, and neighborhood-level percentage of population with low income, with only basic education, who are unemployed, with manual labor, with non-Western background, with criminal record, who are sole-provider, and who live in social housing. [b]$Lden_{max}$: Traffic noise at most exposed facade. [c]$Lden_{min}$: Traffic noise at least exposed facade. [d]NonGreen1000m: Percentage of areas within 1000 m of the residential address that are not publicly accessible green areas (i.e. not classified as recreational areas, forests and open nature areas). [e]NonGreen150m: Percentage of areas within 150 m of the residential address, not classified as agricultural areas, household gardens, recreational areas, forests and open nature areas.

Table 5: **Hazard ratios (HR) and cumulative risk index (CRI) for single- and two-pollutant models of road traffic noise and lack of green space in relation to risk of stroke.**

be a result of chance. Other studies investigating multiple air pollutants in relation to stroke/cerebrovascular disease have generally found the strongest association with $PM_{2.5}$, but have not investigated UFP. In the European ELAPSE project, a pooled cohort with 6950 stroke cases, NO_2, $PM_{2.5}$, and BC were associated with stroke in single pollution models and NO_2 dominated in two pollution models.[6] In a recent Spanish study, based on 10,865 stroke cases, NO_2 was also most robust in models including also $PM_{2.5}$, BC or green space.[12] Similar methodological factors as listed for the Dutch study may have affected these studies. In the present study, $PM_{2.5}$ was the dominant agent in models of total air pollution, whereas the non-traffic models found an association with both $PM_{2.5}$ and NO_2. In the same cohort as used in the present study, we have previously demonstrated that the stroke risk from a 10 $\mu g/m^3$ higher NO_2 level differed between traffic (HR: 1.001, 95% CI: 0.983–1.020) and non-traffic sources (HR: 1.317, 95% CI: 1.261–1.373) indicating that NO_2 acts as a proxy for correlated exposures rather than being a causative agent by itself.[13] This could also be a possible explanation for the observed non-linear association of NO_2 and stroke that was highly vulnerable to adjustment for other air pollutants. Altogether, our linear and spline multi-pollutant results suggest that $PM_{2.5}$ might be the most important air pollutant (among those included) in relation to risk of stroke. The CRI was higher than the HR for any single pollutant, indicating that the risk of stroke in association with environmental exposures cannot be adequately described with any single pollutant.

Few previous studies on long-term risk of stroke have separated air pollution by source. In a Swedish cohort study with 1391 stroke cases, associations with stroke did not differ substantially between air pollution from different sources, such as traffic, residential heating, shipping and industry.[9] In a German study, the risk of stroke was much stronger associated with $PM_{2.5}$ from traffic than with $PM_{2.5}$ from industry.[16] The difference between these results and the results of our study may relate to a different composition of PM in different countries or regions. In Denmark, the primary national non-traffic emissions source of $PM_{2.5}$ are non-industrial combustion, with residential heating as the main contributor. We have recently, in the same cohort as in the present study, found that traffic-related air pollution was associated with diabetes but not with stroke, and that air pollution from non-traffic sources was associated with stroke but not with diabetes.[13,45] It should be investigated if these results showing endpoint-specific importance of different air pollution sources also apply to populations at other locations than Denmark.

Noise

Noise exposure at the most exposed façade was associated with risk of stroke in both linear and spline models and adjusting for air pollution and green areas only altered the risk estimates slightly. These results concord with a recent meta-analysis and subsequent studies.[22,23,46] There are, however, also studies not detecting any association with noise or where the association was only apparent prior to adjustment for air pollution.[47] Noise is believed to affect cardiovascular health through multiple pathways including sleep disturbance and stress-induced activation of the hypothalamus-pituitary-adrenal axis.[20] Assuming that people in noisy environments will sleep on the quiet side of their house, the fact that we found no association between noise at least exposed façade and risk of stroke suggest that sleep

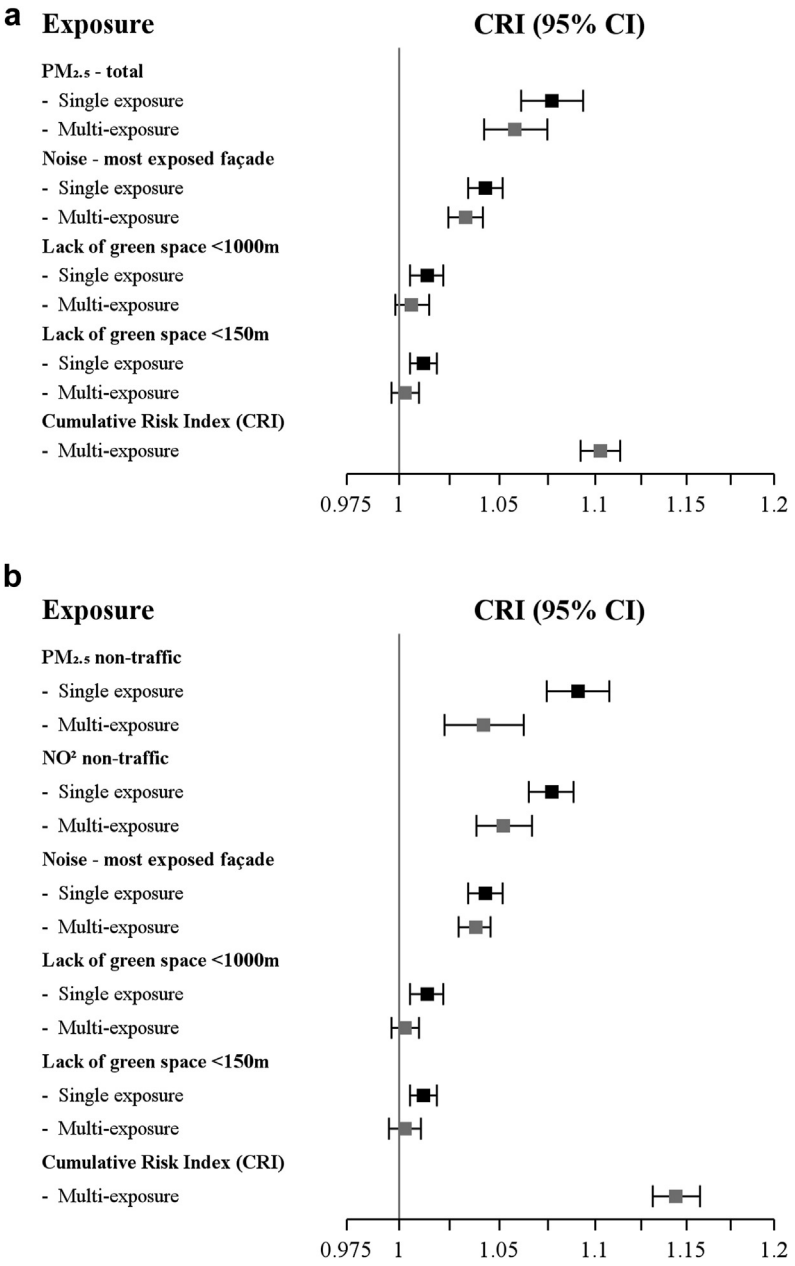

Fig. 2: Hazard ratios (HR) for stroke in association with interquartile range increase in road traffic noise and lack of green space. a) total concentration of air pollution. b) Contribution to air pollution from non-traffic sources. Single- (black) and multi-exposure (grey) models.

disturbances is not a primary pathway with regard to stroke. This was also indicated by a large Swiss cohort, where ischemic stroke mortality was strongest associated with daytime noise.[48]

Green space

Green space at the residence is hypothesized to affect risk of stroke via several pathways, including reduced stress, increased physical activity and altered composition or reduced levels of noise and air pollution.[24] We applied two metrics of green space assuming that seeing and being in green space within 150 m of the residence could potentially reduce stress, whereas green space within 1000 m of the residence could rather indicate areas facilitating and motivating physical activity.

Both metrics were associated with a slightly reduced risk of stroke in models including no other pollutants,

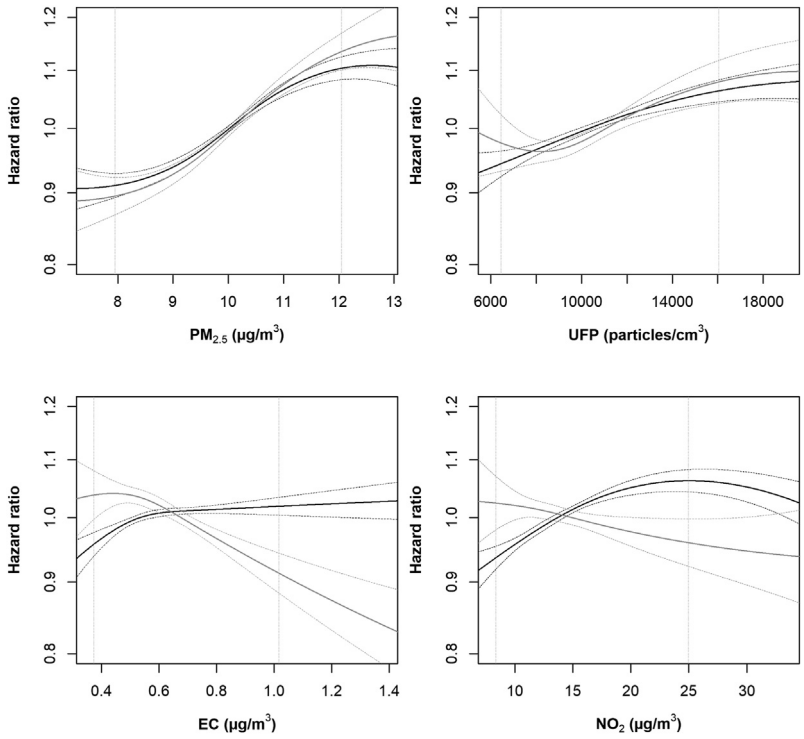

Fig. 3: Splines for relationships of pollutants with stroke. Single exposure models (grey) and models including also splines for the other seven exposures (air pollutants, green space <150 m and <100 m, and noise at most and least exposed façade) (black). All models adjusted for age (by design), sex, calendar-year, civil status, individual and family income, country of origin, occupational status, education, and neighborhood-level percentage of population with low income, basic education, being unemployed, with manual labor, with non-Western background, with criminal record, who are sole-provider, and living in social housing. The plots display the exposure range from 1st to 99th percentile. Vertical lines show 5th and 95th percentiles.

which is in accordance to the findings of some previous studies.[12,25,28] In the present study, no discernible association remained after accounting for air pollution and noise. In agreement with our results, other studies considering both green space and air pollution have not found an association with green space[28] or found a lower risk estimate after adjusting for air pollution.[12] Thus, it appears that it is important to consider confounding from other environmental exposures when analysing associations between green space near the residence and the risk of stroke. This may also have influenced our counterintuitive results for green space within 150 m of home where the risk of stroke was strongest at around 50% green space coverage. Further studies will be needed to understand this observation.

Strengths and limitations

A major strength of this study was the nationwide prospective cohort design. We also benefited from the comprehensive Danish registers providing detailed information on residential history, stroke diagnoses, and a comprehensive set of covariates at individual and area level.[29–31,49] The detailed address histories combined with validated state-of-the-art models with address level resolution, allowed us to model air pollution total concentrations and contribution from traffic and non-traffic sources, and noise at both the least and most exposed façade.[32,43] It was a strength of the present study that we analysed simultaneously multiple air pollutants and several measures of green space and noise. We are only aware of one other study to do so.[28] It was an additional strength that we modelled these exposures time-varying and with a similar spatial resolution and applied both linear and spline models. We estimated green space from a 10 × 10 m resolution map of Denmark and used validated state-of-the-art models with address level resolution to model air pollution and noise.[32,43] Any exposure modelling, even of the highest quality, will entail some degree of uncertainty. We would expect such uncertainty to introduce non-differential exposure misclassification in our study, which may affect the size and precision of risk estimates due to a mixture of classical and Berkson error. Even though we applied high-quality modelling to all exposures, it is a general concern of multi-pollutant models that the most precisely estimated pollutant may tend to dominate. Additionally, high correlations between exposures, as seen for air pollutants in the present study, may render

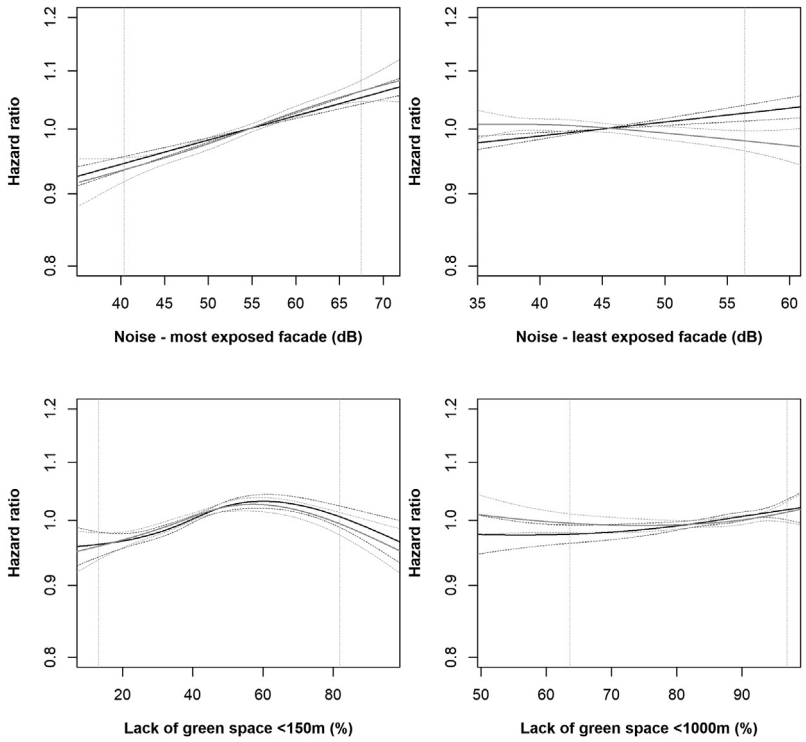

Fig. 4: Splines for relationship of noise and green space with stroke. Single exposure models (grey) and models including also splines for all air pollutants, green space <150 m and <100 m, and noise at most and least exposed facade (black). All models adjusted for age (by design), sex, calendar-year, civil status, individual and family income, country of origin, occupational status, education, and neighborhood-level percentage of population with low income, basic education, being unemployed, with manual labor, with non-Western background, with criminal record, who are sole-provider, and living in social housing. The plots display the exposure range from 1st to 99th percentile. Vertical lines show 5th and 95th percentiles.

results of multi-pollution models statistically unstable and difficult to interpret.[50] We applied a preselection of exposure variables within each of the three environmental exposure domains, where only pollutants consistently associated with stroke in two, three, and four pollution models were entered into our final multi-pollution model. Nevertheless, we cannot rule out that correlations between exposures may have affected our multi-pollutant results. Also, even though we included the pollutants most consistently associated with stroke and we endeavoured to measure them to equal standards we cannot entirely rule out that unmeasured air pollutants may be associated with risk of stroke. This could mean that the risk ascribed to $PM_{2.5}$ may in part be due to other correlated but unmeasured aspects of air pollution. It could also mean that the CRI underestimates the total health burden of air pollution, noise and lack of green space. We did not have information on occupational or non-residential exposure. Also, we had no information on lifestyle factors such as smoking, BMI or physical activity. This is a potential limitation of our study. We have, however, in a random sub-sample of the Danish population with the same covariates as in the present study, demonstrated that the association with air pollution was largely unaffected by further adjustment for smoking diet, physical activity, and BMI.[51] Even though the sub-sample population may not be entirely representative of our cohort, this indicates that the potential for residual confounding from lifestyle factors is limited.

Medical conditions such as hypertension and diabetes might be on the pathway between environmental exposures and stroke, and simple adjustment for intermediate factors could mask part of the association between environmental exposures and stroke. Formal analysis of possible mediation and effect modification is beyond the scope of the present study.

For inpatients, the positive predictive value of a stroke diagnosis based on the Danish National Patient Register is high (83.5%).[52] The data does, however, not allow reliable identification of stroke subtypes. This was a limitation of our study, as some previous studies have suggested stronger associations with air pollution for ischemic stroke.[53]

We excluded 1% of the cohort members due to missing data on covariates, primarily education. Those excluded did not differ in terms of exposure (Table S6). We believe that it is unlikely that the exclusion of only

1%, with a representative exposure, have had substantial impact on the results. Our population was a Western, largely Caucasian population, aged 50 or older. Differences in composition and levels of air pollution and noise, as well as potentially different implications of green areas in other climatic conditions, should be considered if generalizing our results to other populations.

Conclusion

This multi-pollutant nationwide cohort study showed that $PM_{2.5}$ air pollution and traffic noise at the residence were independently associated with risk of stroke. Green space at the residence showed no association with risk of stroke after adjustment for air pollution and noise. Both air pollution and noise contributed substantially to the CRI, suggesting that the cumulative burden of environmental exposures cannot be quantified adequately by any single pollutant.

Contributors

A.H.P., M.S., and O.R.N. contributed to the study concept and design. A.H.P., M.S., U.A.H., J.H.C., J.B., L.M.F, M.K., C.A., S.S. obtained, generated and/or cleaned data. A.H.*P. and* M.S. verified data. A.H.P. did the statistical analyses and drafted the paper. All authors contributed to a critical revision of the manuscript and final approval of the version to be published.

Data sharing statement

The data supporting the findings of this study are available at a secure server at Statistics Denmark at Statistics Denmark. Access to data requires permission from Statistics Denmark and the Danish Cancer Society.

Declaration of interests

The authors declare no conflicting interests.

Acknowledgements

Funding: This work was supported by the Health Effects Institute (HEI) (Assistance Award No. R-82811201). HEI is an organization jointly funded by the United States Environmental Protection Agency (EPA) and certain motor vehicle and engine manufacturers. The contents of this article do not necessarily reflect the views of HEI or its sponsors, nor do they necessarily reflect the views and policies of the EPA or motor vehicle and engine manufacturers.

The study funder was not involved in the design of the study; the collection, analysis and interpretation of the data; writing the paper; and did not impose any restrictions regarding the publication of the paper.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2023.100655.

References

1 Collaborators GBDS. Global, regional, and national burden of stroke, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2019;18(5):439–458.
2 Shkirkova K, Lamorie-Foote K, Connor M, et al. Effects of ambient particulate matter on vascular tissue: a review. *J Toxicol Environ Health B Crit Rev*. 2020;23(7):319–350.
3 Alexeeff SE, Liao NS, Liu X, Van Den Eeden SK, Sidney S. Long-term $PM_{2.5}$ exposure and risks of ischemic heart disease and stroke events: review and meta-analysis. *J Am Heart Assoc*. 2021;10(1):e016890.
4 Stieb DM, Berjawi R, Emode M, et al. Systematic review and meta-analysis of cohort studies of long term outdoor nitrogen dioxide exposure and mortality. *PLoS One*. 2021;16(2):e0246451.
5 Olaniyan T, Pinault L, Li C, et al. Ambient air pollution and the risk of acute myocardial infarction and stroke: a national cohort study. *Environ Res*. 2021;204(Pt A):111975.
6 Wolf K, Hoffmann B, andersen ZJ, et al. 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 Health*. 2021;5(9):e620–e632.
7 Ljungman PLS, andersson N, Stockfelt L, et al. Long-term exposure to particulate air pollution, black carbon, and their source components in relation to ischemic heart disease and stroke. *Environ Health Perspect*. 2019;127(10):107012.
8 Stafoggia M, Cesaroni G, Peters A, et al. Long-term exposure to ambient air pollution and incidence of cerebrovascular events: results from 11 European cohorts within the ESCAPE project. *Environ Health Perspect*. 2014;122(9):919–925.
9 Stockfelt L, andersson EM, Molnar P, et al. Long-term effects of total and source-specific particulate air pollution on incident cardiovascular disease in Gothenburg, Sweden. *Environ Res*. 2017;158:61–71.
10 Beelen R, Stafoggia M, Raaschou-Nielsen O, et al. Long-term exposure to air pollution and cardiovascular mortality: an analysis of 22 European cohorts. *Epidemiology*. 2014;25(3):368–378.
11 Downward GS, van Nunen E, Kerckhoffs J, et al. Long-term exposure to ultrafine particles and incidence of cardiovascular and cerebrovascular disease in a prospective study of a Dutch cohort. *Environ Health Perspect*. 2018;126(12):127007.
12 Avellaneda-Gomez C, Vivanco-Hidalgo RM, Olmos S, et al. Air pollution and surrounding greenness in relation to ischemic stroke: a population-based cohort study. *Environ Int*. 2022;161:107147.
13 Poulsen A, Sørensen M, Hvidtfeldt U, et al. Source specific air pollution and risk of stroke in Denmark. *Environ Health Perspect*. 2023. In press. https://doi.org/10.1289/EHP10556.
14 Qi Y, Wei S, Xin T, et al. Passage of exogeneous fine particles from the lung into the brain in humans and animals. *Proc Natl Acad Sci U S A*. 2022;119(26):e2117083119.
15 Li Y, Lane KJ, Corlin L, et al. Association of long-term near-highway exposure to ultrafine particles with cardiovascular diseases, diabetes and hypertension. *Int J Environ Res Public Health*. 2017;14(5):461.
16 Rodins V, Lucht S, Ohlwein S, et al. Long-term exposure to ambient source-specific particulate matter and its components and incidence of cardiovascular events–the Heinz Nixdorf Recall study. *Environ Int*. 2020;142:105854.
17 Sun X, Wei H, Young DE, et al. Differential pulmonary effects of wintertime California and China particulate matter in healthy young mice. *Toxicol Lett*. 2017;278:1–8.
18 Fushimi A, Nakajima D, Furuyama A, et al. Source contributions to multiple toxic potentials of atmospheric organic aerosols. *Sci Total Environ*. 2021;773:145614.
19 Chen XC, Chuang HC, Ward TJ, et al. Toxicological effects of personal exposure to fine particles in adult residents of Hong Kong. *Environ Pollut*. 2021;275:116633.
20 Munzel T, Sorensen M, Gori T, et al. Environmental stressors and cardio-metabolic disease: part I-epidemiologic evidence supporting a role for noise and air pollution and effects of mitigation strategies. *Eur Heart J*. 2017;38(8):550–556.
21 Sorensen M, Poulsen AH, Hvidtfeldt UA, et al. Transportation noise and risk of stroke: a nationwide prospective cohort study covering Denmark. *Int J Epidemiol*. 2021;50(4):1147–1156.
22 Roswall N, Pyko A, Ogren M, et al. Long-term exposure to transportation noise and risk of incident stroke: a pooled study of nine scandinavian cohorts. *Environ Health Perspect*. 2021;129(10):107002.
23 Vienneau D, Saucy A, Schaffer B, et al. Transportation noise exposure and cardiovascular mortality: 15-years of follow-up in a nationwide prospective cohort in Switzerland. *Environ Int*. 2022;158:106974.
24 Nieuwenhuijsen MJ, Khreis H, Triguero-Mas M, Gascon M, Dadvand P. Fifty shades of green: pathway to healthy urban living. *Epidemiology*. 2017;28(1):63–71.
25 Orioli R, Antonucci C, Scortichini M, et al. Exposure to residential greenness as a predictor of cause-specific mortality and stroke incidence in the Rome longitudinal study. *Environ Health Perspect*. 2019;127(2):27002.
26 Pereira G, Foster S, Martin K, et al. The association between neighborhood greenness and cardiovascular disease: an observational study. *BMC Public Health*. 2012;12:466.
27 Tamosiunas A, Grazuleviciene R, Luksiene D, et al. Accessibility and use of urban green spaces, and cardiovascular health: findings from a Kaunas cohort study. *Environ Health*. 2014;13(1):20.

28 Klompmaker JO, Janssen NAH, Bloemsma LD, et al. Associations of combined exposures to surrounding green, air pollution, and road traffic noise with cardiometabolic diseases. *Environ Health Perspect*. 2019;127(8):87003.
29 Schmidt M, Pedersen L, Sorensen HT. The Danish civil registration system as a tool in epidemiology. *Eur J Epidemiol*. 2014;29(8):541–549.
30 Helweg-Larsen K. The Danish register of causes of death. *Scand J Public Health*. 2011;39(7 Suppl):26–29.
31 Lynge E, Sandegaard JL, Rebolj M. The Danish national patient register. *Scand J Public Health*. 2011;39(7 Suppl):30–33.
32 Khan J, Kakosimos KE, Raaschou-Nielsen O, et al. Development and performance evaluation of new AirGIS—a GIS based air pollution and human exposure modelling system. *Atmos Environ*. 2019;198:102–121.
33 Jensen SSKM, Becker T, Christensen J, et al. High resolution multi-scale air quality modelling for all streets in Denmark. *Transp Res D Transp Environ*. 2017;52:322–339.
34 Brandt J, Silver JD, Frohn LM, et al. An integrated model study for Europe and North America using the Danish Eulerian Hemispheric Model with focus on intercontinental transport of air pollution. *Atmos Environ*. 2012;53:156–176.
35 Brandt J, Christensen JH, Frohn LM, Berkowicz R. Air pollution forecasting from regional to urban street scale–implementation and validation for two cities in Denmark. *Phys Chem Earth*. 2003;28:335–344.
36 Frohn L, Geels C, andersen C, et al. Evaluation of multidecadal high-resolution atmospheric chemistry transport modelling for exposure assessments in the continental Nordic countries. *Atmos Environ*. 2022;290:119334.
37 Hvidtfeldt UA, Ketzel M, Sorensen M, et al. Evaluation of the Danish AirGIS air pollution modeling system against measured concentrations of $PM_{2.5}$, PM10, and black carbon. *Environ Epidemiol*. 2018;2:e014.
38 Ketzel M, Berkowicz R, Hvidberg M, Jensen SS, Raaschou-Nielsen O. Evaluation of AirGIS: a GIS-based air pollution and human exposure modelling system. *Int J Environ Pollut*. 2011;47:226–238.
39 Frohn LM, Ketzel M, Christensen JH, et al. Modelling ultrafine particle number concentrations at address resolution in Denmark from 1979-2018—Part 1: regional and urban scale modelling and evaluation. *Atmos Environ*. 2021;264:17.
40 Ketzel M, Frohn LM, Christensen JH, et al. Modelling ultrafine particle number concentrations at address resolution in Denmark from 1979 to 2018–Part 2: local and street scale modelling and evaluation. *Atmos Environ*. 2021;264:16.
41 Bendtsen H. The Nordic prediction method for road traffic noise. *Sci Total Environ*. 1999;235:331–338.
42 Ström T. *Road traffic noise–an estimate of prediction uncertainty (in Swedish)*. Swedish National Testing and Research Institute; 1997;24.
43 Levin G, Iosub CI, Jepsen MR. *Basemap02. Technical documentation of a model for elaboration of a land-use and land-cover map for Denmark*. Aarhus University, Danish Centre for Environment and Energy; 2017. Technical Report from DCE No. 95.
44 Crouse DL, Peters PA, Hystad P, et al. Ambient $PM_{2.5}$, O(3), and NO(2) exposures and associations with mortality over 16 Years of follow-up in the Canadian census health and environment cohort (CanCHEC). *Environ Health Perspect*. 2015;123(11):1180–1186.
45 Sorensen M, Poulsen AH, Hvidtfeldt UA, et al. Exposure to source-specific air pollution and risk for type 2 diabetes: a nationwide study covering Denmark. *Int J Epidemiol*. 2022;51(4):1219–1229.
46 Hao G, Zuo L, Weng X, et al. Associations of road traffic noise with cardiovascular diseases and mortality: longitudinal results from UK Biobank and meta-analysis. *Environ Res*. 2022;212(Pt A):113129.
47 Cole-Hunter T, So R, Amini H, et al. Long-term exposure to road traffic noise and all-cause and cause-specific mortality: a Danish Nurse Cohort study. *Sci Total Environ*. 2022;820:153057.
48 Heritier H, Vienneau D, Foraster M, et al. Diurnal variability of transportation noise exposure and cardiovascular mortality: a nationwide cohort study from Switzerland. *Int J Hyg Environ Health*. 2018;221(3):556–563.
49 Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449–490.
50 Stafoggia M, Breitner S, Hampel R, Basagana X. Statistical approaches to address multi-pollutant mixtures and multiple exposures: the state of the science. *Curr Environ Health Rep*. 2017;4(4):481–490.
51 Sorensen M, Hvidtfeldt UA, Poulsen AH, et al. The effect of adjustment to register-based and questionnaire-based covariates on the association between air pollution and cardiometabolic disease. *Environ Res*. 2022;203:111886.
52 Luhdorf P, Overvad K, Schmidt EB, Johnsen SP, Bach FW. Predictive value of stroke discharge diagnoses in the Danish National Patient Register. *Scand J Public Health*. 2017;45(6):630–636.
53 Verhoeven JI, Allach Y, Vaartjes ICH, Klijn CJM, de Leeuw FE. Ambient air pollution and the risk of ischaemic and haemorrhagic stroke. *Lancet Planet Health*. 2021;5(8):e542–e552.