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ABSTRACT

Ambient air pollution has been linked to stroke, but few studies have examined in detail stroke subtypes and confounding by road traffic noise, which was recently associated with stroke. Here we examined the association between long-term exposure to air pollution and incidence of stroke (overall, ischemic, hemorrhagic), adjusting for road traffic noise. In a nationwide Danish Nurse Cohort consisting of 23,423 nurses, recruited in 1993 or 1999, we identified 1,078 incident cases of stroke (944 ischemic and 134 hemorrhagic) up to December 31, 2014, defined as first-ever hospital contact. The full residential address histories since 1970 were obtained for each participant and the annual means of air pollutants (particulate matter with diameter < 2.5 μm and < 10 μm ($PM_{2.5}$ and PM_{10}), nitrogen dioxide (NO_2), nitrogen oxides (NOx)) and road traffic noise were determined using validated models. Time-varying Cox regression models were used to estimate hazard ratios (HR) (95% confidence intervals (CI)) for the associations of one-, three, and 23-year running mean of air pollutants with stroke adjusting for potential confounders and noise. In fully adjusted models, the HRs (95% CI) per interquartile range increase in one-year running mean of $PM_{2.5}$ and overall, ischemic, and hemorrhagic stroke were 1.12 (1.01–1.25), 1.13 (1.01–1.26), and 1.07 (0.80–1.44), respectively, and remained unchanged after adjustment for noise. Long-term exposure to ambient $PM_{2.5}$ was associated with the risk of stroke independent of road traffic noise.

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1. Introduction

More than 12 million new cases of stroke were reported worldwide in 2017, of which about half died, accounting for approximately 11% of all global deaths. Stroke poses a substantial burden in Denmark with approximately 10,000 new cases each year and 4000 deaths in 2017 corresponding to 7.5% of all deaths. Almost one million stroke deaths globally have been attributed to environmental risk factors in 2017, mainly ambient particulate matter with aerodynamic diameter $\leq$ 2.5 μm ($PM_{2.5}$) (GBD 2017 Causes of Death Collaborators 2018; Institute for Health Metrics and Evaluation (IHME, 2019). Association between air pollution and stroke has been confirmed in a number of both short-term and long-term exposure studies (Shah et al., 2015; Shamsipour et al., 1990; Stafoggia et al., 2014; Yuan et al., 2019). More recently, association between road traffic noise and stroke has been suggested (Sørensen et al., 2011). Air pollution and road traffic noise generally share major sources and could be highly correlated (Davies et al., 2009). Thus, road traffic noise might be a confounder of the association between air pollution and cardio- and cerebrovascular outcomes (Heritier et al., 2019; Sørensen et al., 2014).

Stroke is classified into two major subtypes, ischemic and hemorrhagic, which differ in etiology and risk-factors (Andersen et al., 2009; Price et al., 2018). While association between particulate matter (PM) and stroke is rather established, most studies had data on overall stroke only. A recent meta-analysis by Yuan et al. (2019) identified 13 studies examining the association of long-term exposure to $PM_{2.5}$ and incidence of stroke, of which only four had data on ischemic and hemorrhagic stroke, reporting mixed findings. Three of these studies found stronger associations of $PM_{2.5}$ with ischemic than hemorrhagic stroke (Cai et al., 2018; Kim et al., 2017; Qiu et al., 2017), while one found opposite (Puett et al., 2011). In Denmark, no studies have evaluated the effect of PM on stroke incidence and its subtypes, whereas two studies found association between NO_2 and ischemic stroke, and none with hemorrhagic (Sørensen et al., 2011, 2014; Andersen et al., 2012). Only three studies examined whether association between air pollution and stroke is confounded by road traffic noise, one on $PM_{2.5}$ and PM_{10} (Cai et al., 2018), two on NO_2 (Cai et al., 2018; Sørensen et al., 2014), and two on NO_x (Sørensen et al., 2011, 2014) and reported mixed results.

The objective of this study is to examine the association between long-term exposures to $PM_{2.5}$, PM with aerodynamic diameter < 10 μm (PM_{10}), NO_2, and nitrogen oxides (NO_x) for up to 23 years and incidence of stroke, separately for overall, ischemic and hemorrhagic stroke, while adjusting for road traffic noise.

2. Methods

2.1. The Danish Nurse cohort

The Danish Nurse Cohort (DNC) is a nationwide cohort initiated in 1993 by mailing a questionnaire to 23,170 female nurses who were > 44 years of age, of which 19,898 (86%) responded (Hundrup et al., 2011). In 1999, the cohort included additional 8,833 (69%) nurses. The questionnaires included detailed individual information on the lifestyle, body weight, hormone therapy, reproductive history, health perception, and psycho-social work environment. In this study, we used the data on 28,731 nurses from both 1993 and 1999 cohorts. Of the initial 28,731 nurses in our study, 151 had had a stroke prior to baseline and were excluded for further analyses. Due to unavailability of either exposure or relevant covariates in our dataset, we further excluded 5,175 subjects. This left us a total of 23,423 nurses for the final analyses. Using a unique identification number for each nurse, the DNC subjects were linked to the Civil Registration System (Pedersen, 2011), to obtain their full residential address history (since 1970 for exposure ascertainment) and vital status (since baseline entry) up to 31st December 2014.

2.2. Stroke definition

DNC participants were linked to The Danish National Patient Registry (DNPR) to obtain information on hospital contacts due to stroke, using International Classification of Diseases (ICD) codes 8: 431, 432, 433, 434, and 436, prior to 31st December 1993, and ICD-10 codes I61, I63, and I64 after 1st January 1994 (Schmidt et al., 2015). Stroke contact was defined as first-ever hospital contact (inpatient/hospital admission, outpatient, or emergency room contact) for stroke after cohort baseline (in 1993 or 1999) among nurses who didn't have contact for stroke before baseline. If the sub-type of the stroke was coded as "unknown" we assumed it to be an ischemic stroke, which is by far the most common subtype.

2.3. Exposure assessment

2.3.1. Residential air pollution

We modelled residential annual mean concentrations for $PM_{2.5}$, PM_{10}, NO_2, and NO_x with a multi-scale and high-resolution Danish air pollution modeling system, called DEHM/UBM/AirGIS. The model chain is driven by the meteorological model WRF (Weather Research and Forecast model version 3 (Skamarock et al., 2008)). The integrated air pollution modelling system has been developed with focus on air pollutants important for health and nature. The model chain consists of the chemistry-transport model, the Danish Eulerian Hemispheric Model (DEHM) (Brandt et al., 2012; Frohn et al., 2001), which calculates atmospheric transport, chemistry and deposition of 67 chemical species, based on national and international emission data. The model includes four domains with different spatial resolutions in order to calculate intercontinental and regional transport of air pollution, while maintaining a relative high resolution over Denmark. The four domains include a hemispheric domain covering the northern hemisphere with a 150 km × 150 km resolution, a European domain with 50 km × 50 km resolution, a northern European domain with a 16.7 km × 16.7 km resolution, and finally a domain covering Denmark with a 5.6 km × 5.6 km resolution. Emissions in the model include both global, European and Danish emission databases, including emissions of e.g. nitrogen-oxides (NOx), carbon-monoxide (CO), sulphur-oxides (SOx), and ammonia/ammonium (NHx), as well as volatile organic compounds (VOCs). In order to calculate the total $PM_{2.5}$ and PM_{10}, DEHM includes the following particle components; primary emitted particles, including black carbon (BC), organic carbon (OC), mineral dust and sea salt. The secondary inorganic aerosols (SIA) are ammonium (NH_4^+), nitrate (NO_3^-), and sulphate (SO_4^{2+}) and chemical interactions of these. Furthermore, DEHM has a scheme for natural VOC emissions (Zare et al., 2012) and a chemical scheme for formation of secondary organic aerosols (SOA) (Zare et al., 2014). In order to calculate PM_{10}, the model furthermore includes the coarse fraction of primary emitted particles, nitrate and sea salt. The DEHM model has been evaluated in numerous international studies, showing good performance (Solazzo et al., 2012, 2013). The Urban Background Model (UBM) (Brandt et al., 2001a, b, 2003; Brandt et al., 2001c) is a local scale model, covering Denmark with a 1 km × 1 km resolution. The UBM model obtains boundary conditions from the DEHM model and is applied to obtain high resolution over Denmark. The model is a plume-in-grid-model that calculates concentrations of chemical species, which have local emissions and impacts, including the primarily emitted particles of $PM_{2.5}$ and PM_{10}, as well as the gases NO_x, NO_2, CO and O_3. The model has been validated against all measurements in Denmark, showing good performance (Brandt et al., 2001a, b, 2003; Brandt et al., 2001c; Hvidtfeldt et al., 2018; Khan et al., 2019). Finally, the AirGIS model system is applied, to calculate air pollution levels at street address level, in streets with more than 500 vehicles per day. The AirGIS system includes the Operational Street Pollution Model (OSPM), which is incorporated into a GIS system that contains all the information needed to run the OSPM model, such as e.g. traffic density (divided into

different vehicle categories, such as cars, vans, trucks and buses and their emission factors), as well as street and building configurations, and background concentrations for all streets in Denmark. The system automatically calculates the input to the OSPM model, which then calculates the air pollution at the "front door" at all the street adresses in the nurse cohort. The AirGIS system is coupled to the DEHM/UBM models, where it receives background air pollution ceontration levels and meteorology from the WRF model in order to run the OSPM model. The AirGIS model is evaluated against all air pollution measurements in Denmark (Hvidtfeldt et al., 2018; Ketzel et al., 2012; Khan et al., 2019). Calculations at residential addresses in streets with more than 500 vehicles a day used the full model chain DEHM/UBM/AirGIS that includes a street pollution model and for residential addresses at streets with less than 500 vehicles a day, concentrations were calculated with the DEHM/UBM model system at a resolution of 1 km × 1 km. The modelled concentrations of $PM_{2.5}$ and PM_{10} were available from 1990 while the modelled concentrations of NO_2 and NO_x were available from 1970 until 2014. In the present study we considered both residential one year mean and three-year mean concentrations for all of the above-mentioned pollutants as air pollution exposure metrics. In addition, we analyzed 23-year mean residential concentrations for NO_2 and NO_x as the data for gases were available for longer periods.

2.3.2. Road traffic noise

Residential road traffic noise levels from 1970 and onwards were modelled using the Nord2000 model (Kragh et al., 2001). The Nord2000 model is the state-of-the-art traffic noise propagation model. The predictors of the model are geocodes of the location, building polygons for all surrounding buildings and the height of apartments above street level, traffic composition and speed, road lines with information on yearly average daily traffic, road type and properties (e.g. rural highway, motorway, road wider than 6 m, and other roads), and meteorology (air temperature, cloud cover, wind speed, and wind direction). The traffic noise contribution is calculated for four weather classes, which typically occur in Denmark. The frequency of weather classes in the calculations are included with a frequency as they occur in an average Danish meteorological year. The propagation model is based on geometrical ray theory computing the 1/3 octave band sound attenuation along the path from the source to the receiver, accounting for the properties of the terrain (shape, ground type, including impedance and roughness) and variations in weather conditions, appropriate when estimating yearly average noise levels. Various weather conditions have been predefined and respective noise levels computed. The long-term noise levels, as the yearly average noise contributions, are then determined by weighting the occurrence of the different weather conditions obtained from weather statistics. The Nord2000 model has been validated by more than 500 propagation cases, 9 of them involving residential road traffic noise (DELTA Acoustics & Electronics, 2006), and validation of the model has furthermore been conducted for noise originating from higher sources, e.g. wind turbines (DELTA Acoustics, 2009). The noise levels in this study were expressed as the annual mean of a weighted 24 h average (L_{den}), adding a 5 dB penalty to the evening noise levels and a 10 dB penalty to the nighttime noise levels.

2.4. Statistical analyses

Cox proportional hazards regression models with age as underlying time scale were used to estimate the association between air pollution and the incidence of overall, ischemic, and hemorrhagic stroke, adjusted for time of entry to the study (1993 or 1999). As most pollutant concentrations decreased from 1993 to 2014, we additionally adjusted for calendar year by a restricted cubic spline (to account for potential non-linearity). We used Directed Acyclic Graph (DAG) to identify the minimum set of covariates including potential confounders (Textor et al., 2016). Our argument for including only a limited set of covariates

is that while many other risk factors for stroke exist, these were not deemed to affect (or be caused by other causes of) the exposure to PM and/or noise. According to the DAG, adjustment for age, socioeconomic status (SES), and urbanicity is the minimal sufficient adjustment set (Fig. S1, Supplemental Information (SI)). Since the DNC is a cohort of Danish nurses, we believe the SES by design is very similar for majority of subjects. However, as the SES of their parents, economics of their marital partners, or other factors may play a role, we adjusted our models for residential municipality-level average income in the baseline year. For urbanicity, we used the residential degree of urbanicity, which is defined by the European Union, and is categorized into rural (thinly populated areas), sub-urban (towns and suburbs - intermediate density areas), and urban areas (cities - densely populated areas). We further adjusted for leisure-time physical activity (low, medium, high), alcohol drinking (none (0 drinks/week), moderate (1–15 drinks/week), and heavy (> 15 drinks/week)), smoking (never, previous, or current smoker), marital status (married, separated, divorced, single, and widow), and fruit consumption (daily, weekly, rarely). Finally, the models additionally adjusted for road traffic noise. Hazard ratios (HRs) and 95% confidence intervals (CIs) were reported per interquartile range (IQR) of the exposure.

To evaluate proportional hazards assumption, we performed graphical diagnostics based on the scaled Schoenfeld residuals, and conduced a trend test of scaled Schoenfeld residuals.

We evaluated the shapes of the exposure–response functions by (1) plots of the restricted cubic splines and (2) a likelihood ratio test of the significance of the non-linear part of the pollutant measure where low *p*-values indicate statistically significant deviations from linearity. If a plateau was obvious from the plot of the restricted cubic spline, the exposure values were truncated corresponding to a piecewise linear relationship with two segments, the first having a slope and the other forced to be flat, and the association was re-investigated.

In addition, we explored the effect modification of the association between $PM_{2.5}$ and ischemic stroke by L_{den}, smoking status, obesity, hypertension, myocardial infarction, diabetes, physical activity, degree of urbanicity, use of hormone replacement therapy, and work status.

All statistical analyses were performed in R version 3.6.1 (R Core Team, 2013), using the following packages: knitr (Xie, 2019), tableone (Yoshida 2019), rms (Harrell, 2019), epi (Carstensen et al., 2019), and survival (Therneau, 2015). The exposure maps for each pollutant at cohort baseline were created using ArcGIS® software by ESRI.

3. Results

During a median follow-up time of 19.45 years, 1,078 (4.6%) developed stroke, resulting in an incidence rate of 248.5 per 100,000 person-years (Table 1). Mean age (SD) at cohort baseline was 52.6 years (7.7) [59.1 (9.1)/52.2 (7.5): stroke/stroke free] (Table 1).

Of the 1,078 S cases 944 (87.6%) were ischemic and 134 (12.4%) hemorrhagic. Nurses with ischemic stroke were more likely to be current smokers, rarely consume fruits, live in urban areas, and have low physical activity as compared to stroke free nurses. Nurses with hemorrhagic strokes had similar prevalence of the mentioned risk factors as nurses with ischemic stroke but had slightly higher body mass index than nurses who did not develop hemorrhagic stroke (Table 1).

Nurses who had a stroke were exposed to higher levels of all air pollutants than those who did not develop stroke (Table 1). The mean concentrations of $PM_{2.5}$, PM_{10}, NO_2, and NO_x at baseline for stroke/stroke free were 21.2/19.6, 25.1/23.4, 14.1/12.5, and 22.8/18.9 μg/m^3, respectively, and 53.6/52.7 dB for road traffic noise level.

The spatial variability of pollutants revealed higher levels of $PM_{2.5}$ in South Eastern Denmark, partly due to secondary pollution from central Europe. Whilst the Danish west coast had higher levels of PM_{10}, likely influenced by sea-spray. The NO_2, NO_x, and noise levels were mostly higher in the urban populated areas including Copenhagen, Aarhus, Odense and Aalborg (SI, Fig. S2). The correlation of $PM_{2.5}$ and

Table 1
Descriptive statistics at the cohort baseline (1993 or 1999) among 23,423 female nurses from the Danish Nurse Cohort by stroke types at the end of follow up.

	Total (n = 23,423)	All stroke (n = 1,078)	Ischemic (n = 944)	Hemorrhagic (n = 134)	No stroke (n = 22,345)
Age at baseline, mean (SD)	52.6 (7.7)	59.1 (9.1)	59.4 (9.1)	57.3 (8.3)	52.2 (7.5)
Year of cohort enrollment, n (%)					
1993	14,939 (63.8)	956 (88.7)	846 (89.6)	110 (82.1)	13,983 (62.6)
1999	8484 (36.2)	122 (11.3)	98 (10.4)	24 (17.9)	8362 (37.4)
Leisure time physical activity, n (%)					
Low	1533 (6.5)	93 (8.6)	86 (9.1)	7 (5.2)	1440 (6.4)
Medium	15,617 (66.7)	741 (68.7)	650 (68.9)	91 (67.9)	14,876 (66.6)
High	6273 (26.8)	244 (22.6)	208 (22.0)	36 (26.9)	6029 (27.0)
Alcohol drinking, n (%)					
None (0 drinks/week)	3555 (15.2)	213 (19.8)	199 (21.1)	14 (10.4)	3342 (15.0)
Moderate (1–15 drinks/week)	14,440 (61.6)	630 (58.4)	543 (57.5)	87 (64.9)	13,810 (61.8)
Heavy (> 15 drinks/week)	5428 (23.2)	235 (21.8)	202 (21.4)	33 (24.6)	5193 (23.2)
Smoking status, n (%)					
Never	8142 (34.8)	309 (28.7)	270 (28.6)	39 (29.1)	7833 (35.1)
Previous	7098 (30.3)	310 (28.8)	269 (28.5)	41 (30.6)	6788 (30.4)
Current	8183 (34.9)	459 (42.6)	405 (42.9)	54 (40.3)	7724 (34.6)
Marital status, n (%)					
Married	16,497 (70.4)	640 (59.4)	560 (59.3)	80 (59.7)	15,857 (71.0)
Separated	417 (1.8)	22 (2.0)	21 (2.2)	1 (0.7)	395 (1.8)
Divorced	2761 (11.8)	153 (14.2)	130 (13.8)	23 (17.2)	2608 (11.7)
Single	2331 (10.0)	138 (12.8)	118 (12.5)	20 (14.9)	2193 (9.8)
Widow	1417 (6.0)	125 (11.6)	115 (12.2)	10 (7.5)	1292 (5.8)
Fruit intake, n (%)					
Daily	861 (3.7)	44 (4.1)	36 (3.8)	8 (6.0)	817 (3.7)
Weekly	6695 (28.6)	296 (27.5)	255 (27.0)	41 (30.6)	6399 (28.6)
Rarely	15,867 (67.7)	738 (68.5)	653 (69.2)	85 (63.4)	15,129 (67.7)
Body mass index (BMI) (kg/m^2), mean (SD)	23.69 (3.51)	23.76 (3.52)	23.71 (3.49)	24.06 (3.69)	23.69 (3.51)
Hypertension, n (%)					
Yes	20,342 (87.6)	826 (77.6)	720 (77.3)	106 (79.9)	19,516 (88.1)
No	2883 (12.4)	239 (22.4)	212 (22.7)	27 (20.3)	2644 (11.9)
Myocardial infarction, n (%)					
No	23,075 (99.4)	1041 (97.7)	909 (97.5)	132 (99.2)	22,034 (99.4)
Yes	150 (0.6)	24 (2.3)	23 (2.5)	1 (0.8)	126 (0.6)
Diabetes, n (%)					
No	22,946 (98.8)	1039 (97.6)	908 (97.4)	131 (98.5)	21,907 (98.9)
Yes	279 (1.2)	26 (2.4)	24 (2.6)	2 (1.5)	253 (1.1)
Degree of urbanicity					
Urban	7204 (30.8)	363 (33.7)	319 (33.8)	44 (32.8)	6841 (30.6)
suburban	5381 (23.0)	239 (22.2)	203 (21.5)	36 (26.9)	5142 (23.0)
rural	10,832 (46.2)	476 (44.2)	422 (44.7)	54 (40.3)	10,356 (46.3)
Income[1], mean (SD)	164.4 (24.7)	163.5 (24.3)	163.4 (24.0)	164.8 (26.6)	164.4 (24.7)
Air pollutants, 1-year mean (SD)					
PM$_{2.5}$ (µg/m^3)	19.7 (3.6)	21.2 (3.3)	21.2 (3.3)	20.9 (3.6)	19.6 (3.6)
PM$_{10}$ (µg/m^3)	23.5 (3.9)	25.1 (3.5)	25.1 (3.5)	25.0 (4.3)	23.4 (3.9)
NO$_2$ (µg/m^3)	12.6 (8.0)	14.1 (9.2)	13.5 (8.5)	14.2 (9.0)	12.5 (8.0)
NO$_x$ (µg/m^3)	19.1 (23.9)	22.8 (29.2)	22.8 (26.2)	25.2 (29.8)	18.9 (23.9)
L$_{den}$ (dB)	52.7 (8.1)	53.6 (7.6)	53.5 (7.6)	53.1 (7.9)	52.7 (8.1)

[1]Average income in municipality (per 1000 Danish krone (DKK)).

Table 2
Spearman correlation between air pollutants and road traffic noise exposures at baseline.

	L$_{den}$ (dB)	PM$_{2.5}$	PM$_{10}$	NO$_2$	NOx
L$_{den}$	1				
PM$_{2.5}$	0.36	1			
PM$_{10}$	0.24	0.85	1		
NO$_2$	0.60	0.65	0.51	1	
NOx	0.50	0.57	0.54	0.92	1

other air pollutants at cohort baseline was moderate to high (0.85 with PM$_{10}$, 0.65 with NO$_2$, and 0.57 with NOx) and low with road traffic noise (0.36) (Table 2). The correlation of PM$_{10}$ with gases and noise was even lower and ranged from 0.24 to 0.54. The correlation between one-year, three-year, and 23-year mean exposure windows was high (0.99 for PM$_{2.5}$ and PM$_{10}$, ranged from 0.84 to 0.98 for NO$_2$, and from 0.79 to 0.98 for NOx) (SI, Table S1).

We found statistically significant associations for one-year mean PM$_{2.5}$ and incidence of overall stroke in the fully adjusted model where

the HR (95% CI) per IQR increase of 3.9 µg/m^3 was 1.12 (1.01–1.25). The estimates were similar after adjusting for noise (HR 1.13, 95% CI, 1.01–1.25). In the fully adjusted models, the HR (95% CI) for one-year mean of PM$_{10}$, NO$_2$, and NOx were, respectively, 1.05 (0.97–1.13), 1.05 (0.97–1.13), 1.02 (0.99–1.06) per IQR increase of 3.3, 8.0, and 11.0 µg/m^3, which remained unchanged after adjustment for noise (Table 3). Results were similar with three-year mean (all pollutants) or 23-year mean (NO$_2$ and NO$_x$ only).

The association for the one-year mean PM$_{2.5}$ was stronger with ischemic than hemorrhagic stroke (HR (95% CI): 1.13 (1.01–1.26) vs 1.07 (0.08–1.44) per IQR increase of 3.9 µg/m^3). Whilst a stronger but non-significant association was found for the one-year mean NO$_2$ and ischemic when compared to hemorrhagic stroke, the same was not true for PM$_{10}$ and NO$_x$ (Table 3). All results were robust to adjustment for noise. The HRs remained similar with three- and 23-year mean exposure windows for ischemic stroke; however, for hemorrhagic stroke the three-year mean PM$_{2.5}$ and PM$_{10}$ resulted in stronger HRs than one-year mean (1.16 vs 1.07 for PM$_{2.5}$ and 1.13 vs 1.09 for PM$_{10}$) (Table 3).

The graphical diagnostics based on the scaled Schoenfeld residuals for overall stroke and all pollutants showed no violation of the

Table 3
Associations between air pollutants (one-year mean, three-year mean, and 23-year mean) and incidence of ischemic and hemorrhagic stroke in the Danish Nurse Cohort.[d]

	Exposure window	IQR[a]	Overall stroke			Ischemic stroke			Hemorrhagic stroke		
			Model 1[b]	Model 2[c]	Model 3[d]	Model 1[b]	Model 2[c]	Model 3[d]	Model 1[b]	Model 2[c]	Model 3[d]
$PM_{2.5}$	1-year	3.9	1.15 (1.05–1.25)	1.12 (1.01–1.25)	1.13 (1.01–1.25)	1.16 (1.06–1.27)	1.13 (1.01–1.26)	1.14 (1.01–1.27)	1.06 (0.82–1.36)	1.07 (0.80–1.44)	1.06 (0.78–1.43)
$PM_{2.5}$	3-year	3.9	1.14 (1.03–1.25)	1.12 (0.99–1.26)	1.12 (0.98–1.27)	1.14 (1.03–1.26)	1.11 (0.98–1.27)	1.11 (0.97–1.27)	1.13(0.86–1.50)	1.16 (0.82–1.64)	1.17 (0.82–1.68)
PM_{10}	1-year	3.3	1.06 (0.99–1.13)	1.05 (0.97–1.13)	1.05 (0.97–1.13)	1.06 (0.99–1.13)	1.04 (0.96–1.13)	1.04 (0.96–1.13)	1.06 (0.88–1.29)	1.09 (0.89–1.34)	1.09 (0.88–1.34)
PM_{10}	3-year	3.3	1.05 (0.97–1.13)	1.04 (0.96–1.13)	1.04 (0.95–1.13)	1.04 (0.96–1.12)	1.03 (0.94–1.12)	1.02 (0.93–1.12)	1.11 (0.90–1.37)	1.13 (0.90–1.42)	1.14 (0.90–1.44)
NO_2	1-year	8.0	1.07 (1.01–1.13)	1.05 (0.97–1.15)	1.05 (0.97–1.15)	1.08 (1.02–1.14)	1.06 (0.98–1.14)	1.07 (0.98–1.17)	1.02 (0.86–1.22)	0.97 (0.77–1.22)	0.93 (0.71–1.22)
NO_2	3-year	8.0	1.07 (1.01–1.13)	1.04 (0.97–1.12)	1.04 (0.95–1.13)	1.07 (1.01–1.14)	1.05 (0.97–1.14)	1.05 (0.96–1.15)	1.03 (0.87–1.22)	0.97 (0.77–1.22)	0.95 (0.73–1.24)
NO_2	23-year	8.0	1.06 (1.01–1.12)	1.02 (0.94–1.10)	1.02 (0.93–1.11)	1.06 (1.00–1.13)	1.02 (0.94–1.11)	1.01 (0.92–1.11)	1.05 (0.89–1.24)	0.97 (0.76–1.23)	1.05 (0.81–1.36)
NOx	1-year	11.0	1.03 (1.00–1.06)	1.02 (0.99–1.06)	1.03 (0.99–1.06)	1.03 (1.00–1.06)	1.02 (0.99–1.06)	1.02 (0.99–1.07)	1.04 (0.97–1.13)	1.04 (0.94–1.14)	1.03 (0.93–1.15)
NOx	3-year	11.0	1.03 (1.00–1.06)	1.02 (0.99–1.06)	1.02 (0.99–1.06)	1.03 (1.00–1.06)	1.02 (0.99–1.06)	1.02 (0.98–1.06)	1.04 (0.97–1.13)	1.03 (0.94–1.13)	1.03 (0.93–1.14)
NOx	23-year	11.0	1.03 (1.00–1.05)	1.01 (0.98–1.04)	1.01 (0.98–1.04)	1.02 (1.00–1.05)	1.01 (0.97–1.04)	1.00 (0.97–1.04)	1.05 (0.98–1.12)	1.03 (0.95–1.12)	1.06 (0.97–1.15)

[a] The IQR units are in μg/m³. [b] Model 1 = adjusted for age as underlying timeline, year of entry to cohort (1993 or 1999), and calendar year. [c] Model 2 = Model 1 + income, degree of urbanicity, physical activity, alcohol drinking, smoking, marital status, and fruit consumption. [d] Model 3 = Model 2 + noise.

proportional hazard assumption (SI, Figure S3), and the trend test of scaled Schoenfeld residuals was not significant (SI, Table S2).

We observed linear dose–response relationship and an indication of a threshold above which the effect was not observed any more for $PM_{2.5}$ and PM_{10} around 20 μg/m³, 10 for NO_2, and 30 for NOx (for overall stroke), with limited number of observations and wide confidence intervals above these threshold values (SI, Figure S4). The likelihood ratio test of non-linearity showed no significant violation of linearity for any pollutant and exposure period (SI, Table S3). Truncation of the values above the thresholds resulted in higher HRs for all pollutants over all exposure windows, especially for NO_2 (SI, Table S4-S6). The dose–response curves were very similar for all exposure windows (SI, Figure S4).

Finally, we found no effect modification of the association between ischemic stroke and $PM_{2.5}$ by noise, smoking status, obesity, hypertension, myocardial infarction, diabetes, physical activity, degree of urbanicity, use of hormone replacement therapy, and work status (*p*-value > 0.05) (SI, Table S7).

4. Discussion

In this nationwide cohort study of Danish female nurses, we found positive associations between long-term exposure to air pollution and incidence of stroke. Associations were strongest for $PM_{2.5}$ and ischemic stroke and were not confounded by road traffic noise.

This is the first Danish study that has evaluated the effect of ambient particles on stroke incidence, and results are in line with the existing evidence. A meta-analysis found 13 cohorts on the association of long-term exposure to $PM_{2.5}$ and incidence of stroke, with pooled HR (95% CI) for overall stroke of 1.11 (1.05, 1.17) per 5 μg/m³ increment in $PM_{2.5}$. The HR (95% CI) in our study for overall stroke was 1.16 (95% CI: 1.01, 1.33) per 5 μg/m³ increment in one-year mean exposure to $PM_{2.5}$. A recent large study included > 11 million people of the southeast United States, and evaluated annual mean exposure to $PM_{2.5}$ and its association with first hospital admission for stroke . They reported a HR (95% CI) of 1.16 (1.16, 1.17) per 5 μg/m³ increment, which is comparable to our estimates. On the other hand, our exposure range for $PM_{2.5}$ was in the lower end of these studies and we found some indication of no increase in risk above 20 μg/m³. A study from China with interquartile range of $PM_{2.5}$ exposure from 31 to 97 μg/m³ found linear exposure response relationships with HR of 1.12 (1.02–1.23) per 10 μg/m³ in both men and women (Huang et al., 2019).

Strokes can either be ischemic, i.e. an occlusion of a blood vessel, or hemorrhagic, i.e. a rupture of a blood vessel. The main risk factor for both types of stroke are hypertension and smoking. Obesity, pre-existing diabetes, myocardial infarction, atrial fibrillation, are all more strongly associated with ischemic than hemorrhagic strokes, while lifestyle, such as smoking and alcohol consumption are more consistently associated with hemorrhagic strokes (Andersen et al., 2009; Price et al., 2018). Air pollution has been established as a risk factor for hypertension (Giorginia et al., 2016), cardiovascular disease (Rajagopalan et al., 2018), and diabetes (Yang et al., 2020), and possibly obesity. Furthermore, atherosclerosis, which has been associated with air pollution (Rajagopalan et al., 2018), is one of the main mechanism behind development of ischemic stroke. Thus, it is plausible that air pollution, also increases risk of ischemic strokes more convincingly by increasing risk of a number of cardio-metabolic diseases, than for hemorrhagic strokes, which seem to be more driven by lifestyle and hypertension. Our findings and other epidemiological evidence to date support these causal pathways (Yuan et al., 2019). The abovementioned *meta*-analysis included four studies evaluating the association of PM with stroke subtypes where the HR (95% CI) was 1.62 (0.88, 2.97) for ischemic and 1.20 (0.79, 1.80) for hemorrhagic stroke, both per 5 μg/m³ increment of $PM_{2.5}$ (Yuan et al., 2019). In our study, these values were 1.17 (1.01, 1.34) and 1.09 (0.75, 1.56), respectively, per 5 μg/m³ increment of one-year mean $PM_{2.5}$. Our results are well in line with the

findings of Cai et al. (2018), Qiu et al. (2017), and Kim et al. (2017) where they all found positive associations between $PM_{2.5}$ and ischemic stroke. However, it was not in compliance with Cai et al. (2018), and Qiu et al. (2017) findings for hemorrhagic stroke where they reported negative association for $PM_{2.5}$. Differences in study populations, cohort characteristics, exposure estimation methods, adjustment set of covariates in the models and analysis methods could contribute to differences in estimates.

Our study results are well supported by mechanistic and animal studies that link air pollution with cerebrovascular diseases. The Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air) has found that endothelial function was significantly decreased with long-term exposure to ambient $PM_{2.5}$ (Krishnan et al., 2012). Another analysis from MESA Air has also reported that increased intima-medial thickness has been associated with higher long-term $PM_{2.5}$ exposure (Adar et al., 2013). Other studies have suggested that exposure to particles in the ambient air may increase peripheral thrombosis and atherosclerotic lesion formation through a concert of pathways (Bhatnagar, 2006).

The epidemiological and toxicological research on the association of stroke and ambient gases, especially on nitrogen oxides, is more limited than for particles. To date, two Danish studies have investigated the association of ambient nitrogen oxides on stroke incidence and mortality. Andersen et al. (2012) using the data from Danish Diet, Cancer and Health (DCH) cohort, which comprised 50,000 men and women (50–65 years of age) in Copenhagen and Aarhus areas, have studied the association of a 22-year mean NO_2 exposure with incidence of overall, ischemic, and hemorrhagic stroke, and reported HRs (95% CI) of, respectively, 1.09 (0.98–1.20), 1.10 (0.94–1.28), and 0.91 (0.75–1.09) per 10 $\mu g/m^3$ increment in ambient NO_2 (Andersen et al., 2012). These values in our study were 1.02 (0.92–1.13), 1.02 (0.92–1.14), and 0.96 (0.71–1.29) per 10 $\mu g/m^3$ increment in 23-year mean NO_2, respectively. Sørensen et al. (2014) also used the DCH cohort and reported similar results (Sørensen et al., 2014). Overall, our results for NO_2 using DNC data are in line with previous findings of DCH investigators in Denmark. In a national study of almost 75,000 Italians, Gandini et al. (2018) found an association between ambient annual mean NO_2 and first hospital admission for stroke with HR (95% CI) of 1.14 (1.10–1.19) per 10 $\mu g/m^3$ increment (Gandini et al., 2018). Cai et al. (2018) have studied three cohorts in Norway and UK, and reported HR (95% CI) of 1.04 (0.90, 1.19) for ischemic stroke, and 0.98 (0.84, 1.16) for hemorrhagic stroke per 10 $\mu g/m^3$ increment in annual mean ambient NO_2. Toxicology literature suggests that NO_2 can react with constituents of the airway surface fluids and thereby produce highly reactive protein and lipid oxidation products. Subsequently, this could damage the epithelial cells and cause inflammation through secondary reactions (Gamon and Wille, 2016).

We found that road traffic noise did not confound the associations between air pollutants and stroke. Only three previous studies on air pollution and stroke had data on road traffic noise, and only one study which examined PM and stroke. Sørensen et al. (2011) found that overall stroke was not associated with NO_x neither before nor after adjustment for traffic noise (Sørensen et al., 2011). Sørensen et al. (2014) found that road traffic noise and not NO_2 was associated with ischemic stroke while fatal stroke was positively associated with NO_2 and not with noise (Sørensen et al., 2014). In agreement with our findings, Cai et al (2018) found that noise did not confound the associations between stroke subtypes and NO_2, PM_{10}, and $PM_{2.5}$ (Cai et al., 2018).

We found unchanged estimates between air pollutants and stroke when using different averaging exposure periods, which suggests the exposure estimates are temporally stable. Not many studies have evaluated the sensitivity of air pollution-stroke association to the temporal scale of exposure assessment. Stockfelt et al. (2017) have studied one-year, two-year, and five-year mean exposure to $PM_{2.5}$ and PM_{10} in Gothenburg, Sweden, and the incidence of stroke in two cohorts (Stockfelt et al., 2017). They found that longer exposure periods (five-

year mean vs one-year mean) resulted in stronger associations for both $PM_{2.5}$ and PM_{10}.

Finally, we did not find strong evidence of effect modification by noise, smoking status, obesity, hypertension, myocardial infarction, diabetes, physical activity, degree of urbanicity, use of hormone replacement therapy, and work status. The HRs (95% CI) of an association between one-year mean of $PM_{2.5}$ and ischemic stroke for rural, suburban, and urban areas were 1.19 (1.08, 1.32), 1.08 (0.93, 1.24), and 1.19 (1.08, 1.32), respectively.

The strength of this study is that it was a longitudinal analysis with nationwide participants, detailed individual information, and high quality data. Since we only included middle-age female nurses, we have reduced confounding by SES to a great extent, though we also adjusted for municipality-level income data. We benefitted from Danish registers for defining stroke incidence cases by sub-types and had access to full residential address histories of all study participants since 1970. On the other hand, the generalizability of our findings to other age-groups and males may be limited.

In conclusion, in a nationwide cohort of Danish nurses aged 44 years and older, we found an increased risk of stroke incidence with higher long-term exposure to air pollution. The associations were strongest with $PM_{2.5}$ and ischemic than hemorrhagic stroke. They remained unchanged when adjusted for road traffic noise and stayed stable with different exposure periods.

CRediT authorship contribution statement

Heresh Amini: Methodology, Visualization, Writing - original draft. **Christian Dehlendorff:** Data curation, Formal analysis, Methodology, Software, Validation, Visualization, Writing - review & editing. **Youn-Hee Lim:** Methodology, Writing - review & editing. **Amar Mehta:** Methodology, Writing - review & editing. **Jeanette T. Jørgensen:** Methodology, Resources, Data curation, Writing - review & editing. **Laust H. Mortensen:** Methodology, Writing - review & editing. **Rudi Westendorp:** Methodology, Writing - review & editing. **Barbara Hoffmann:** Methodology, Writing - review & editing. **Steffen Loft:** Methodology, Writing - review & editing. **Tom Cole-Hunter:** Writing - review & editing. **Elvira V. Bräuner:** Methodology, Writing - review & editing. **Matthias Ketzel:** Methodology, Resources, Writing - review & editing. **Ole Hertel:** Methodology, Resources, Writing - review & editing. **Jørgen Brandt:** Methodology, Resources, Writing - review & editing. **Steen Solvang Jensen:** Methodology, Resources, Writing - review & editing. **Jesper H. Christensen:** Methodology, Resources, Writing - review & editing. **Camilla Geels:** Methodology, Resources, Writing - review & editing. **Lise M. Frohn:** Methodology, Resources, Writing - review & editing. **Claus Backalarz:** Methodology, Resources, Writing - review & editing. **Mette K. Simonsen:** Resources, Writing - review & editing. **Zorana J. Andersen:** Conceptualization, Methodology, Validation, Investigation, Resources, Writing - review & editing, Supervision, Project administration, Funding acquisition.

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Appendix A. Supplementary material

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