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Combined effects of road traffic noise and ambient air pollution in relation to risk for stroke?



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ABSTRACT

Exposure to road traffic noise and air pollution have both been associated with risk for stroke. The few studies including both exposures show inconsistent results. We aimed to investigate potential mutual confounding and combined effects between road traffic noise and air pollution in association with risk for stroke. In a population-based cohort of 57,053 people aged 50–64 years at enrollment, we identified 1999 incident stroke cases in national registries, followed by validation through medical records. Mean follow-up time was 11.2 years. Present and historical residential addresses from 1987 to 2009 were identified in national registers and road traffic noise and air pollution were modeled for all addresses. Analyses were done using Cox regression. A higher mean annual exposure at time of diagnosis of 10 $\mu\text{g}/\text{m}^3$ nitrogen dioxide (NO_2) and 10 dB road traffic noise at the residential address was associated with ischemic stroke with incidence rate ratios (IRR) of 1.11 (95% CI: 1.03, 1.20) and 1.16 (95% CI: 1.07, 1.24), respectively, in single exposure models. In two-exposure models road traffic noise (IRR: 1.15) and not NO_2 (IRR: 1.02) was associated with ischemic stroke. The strongest association was found for combination of high noise and high NO_2 (IRR = 1.28; 95% CI = 1.09–1.52). Fatal stroke was positively associated with air pollution and not with traffic noise. In conclusion, in mutually adjusted models road traffic noise and not air pollution was associated ischemic stroke, while only air pollution affected risk for fatal strokes. There were indications of combined effects.

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1. Introduction

Long-term exposure to road traffic noise and ambient air pollution are both suspected of increasing the risk for cerebrovascular events (Andersen et al., 2012; Floud et al., 2013; Maheswaran et al., 2012; Miller et al., 2007; Sorensen et al., 2011). However, as road traffic is an important source of both noise and ambient air pollution, the two exposures are correlated, raising questions about the extent of mutual confounding and combined effects.

A number of studies have investigated associations between short-term exposure to air pollution and stroke, and they generally report that elevated air pollution levels can trigger hospitalization and death from stroke within few days (Andersen et al., 2010; Oudin et al., 2010; Wellenius et al., 2012). Studies on long-term exposure to air pollution and incidence and mortality of stroke are less consistent, as some find or indicate positive associations (Andersen et al., 2012; Lipsett et al., 2011; Maheswaran et al., 2012; Miller et al., 2007; Raaschou-Nielsen et al., 2012) whereas others report no associations (Atkinson et al., 2013; Nafstad et al., 2004; Oudin et al., 2009). Only the Danish mortality study on air pollution adjusted analyses for road traffic noise, which lowered estimates slightly (Raaschou-Nielsen et al., 2012). Three studies have investigated the relationship between road traffic noise and cerebrovascular disease with inconsistent results. A Dutch cohort study reported no associations between road traffic noise and cerebrovascular mortality neither before nor after adjustment for

Abbreviations: NO_2 , nitrogen dioxide; NO_x , nitrogen oxides; IRR, incidence rate ratios; L_{den} , noise level day–evening–night; SES, socioeconomic status; MET, metabolic equivalent

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air pollution (Beelen et al., 2009); we previously reported a significant association between road traffic noise and incident stroke, both before and after adjustment for air pollution in a Danish cohort (Sørensen et al., 2011); and a recent cross-sectional multi-center study using a joint category of self-reported heart disease and stroke, indicated that road traffic noise increase risk only before adjustment for air pollution (Floud et al., 2013). Two recent studies found aircraft noise to be positively associated with risk for stroke hospitalization (Correia et al., 2013; Hansell et al., 2013). One of these studies adjusted for air pollution, which did not confound the results (Correia et al., 2013), potentially because aircraft noise is only weakly to moderately correlated with air pollution (Clark et al., 2012; Floud et al., 2013), indicating an association between aircraft noise and risk for stroke independent of air pollution.

Some of the overall biological mechanisms believed to link exposure to risk for stroke are similar for road traffic noise and ambient air pollution, including effects on the vascular system such as endothelial dysfunction, increased blood pressure and atherosclerosis (Auchincloss et al., 2008; Briet et al., 2007; Kalsch et al., 2013; Schmidt et al., 2013; Schneider et al., 2008; van Kempen and Babisch, 2012; Wellenius et al., 2013). Both exposures are also suspected of increasing oxidative stress and affecting the immune system (Miller et al., 2012; Prasher, 2009; Schmidt et al., 2013). However, the pathways through which the two exposures act are very different; particulate air pollution through inhalation and translocation to the blood, whereas traffic noise exerts more indirect effects through stress and disturbance of sleep (Donaldson et al., 2005; Miedema and Vos, 2007; Selander et al., 2009a).

The aim of the present study was to investigate mutual confounding and combined associations between residential exposure to road traffic noise and ambient air pollution in relation to risk for incident stroke in a large prospective cohort. We used NO_x and NO_2 as indicators of air pollution, because they have been shown to be good markers of traffic-related air pollution and correlate closely with particulate matter. We also aimed to investigate associations between the two exposures and fatal incident stroke and subtypes of strokes: subarachnoid hemorrhage, intracerebral hemorrhage and cerebral infarction.

2. Methods

2.1. Study population

The study was based on the Danish Diet, Cancer and Health cohort (Tjønneland et al., 2007). In total, 57,053 of 160,725 residents of Copenhagen or Aarhus aged 50–64 years without a history of cancer were enrolled into the cohort between 1993 and 1997. Participants had to be born in Denmark. At enrollment, each participant completed self-administered, interviewer-checked, questionnaires covering food intake, lifestyle habits including detailed information on present and previous smoking and physical activity, health status, and social factors. Participants reported frequency of daily smoking of four types of tobacco as well as previous smoking. The average amount of tobacco smoked each day (smoking intensity) was calculated by equating a cigarette to 1 g, a cheroot or a pipe to 3 g, and a cigar to 5 g of tobacco. Information on physical activity was based on 12 questions covering average number of hours per week spent in the past year on different types of leisure time physical activity. The total energy per week spent on leisure time physical activity was evaluated using the MET-score. In a food frequency questionnaire participants were asked how often on average they had consumed different types of foods during the preceding 12 months. A mean daily intake of foods (g/day) was calculated by multiplying the frequencies of intake by a gender specific portion size using the software Foodcalc version 1.3 (Lauritsen, 2004). Participants also reported their average amount of alcohol consumption as the intake of specific amounts of each beverage type: light, normal, and fortified beer; red, white, and fortified wine; and spirits, which were converted into number of standard drinks (12 g alcohol) and added to yield a measure of average g alcohol per day. Coffee consumption was defined in four categories: ≤ 1 , 2–3, 4–5 and ≥ 6 cups of coffee per day. Height and weight were measured by trained staff members according to standardized protocols, from which BMI was calculated (kg/m^2).

The study was conducted in accordance with the Helsinki Declaration, approved by local ethical committees (Copenhagen and Frederiksberg) and all participants provided written informed consent.

2.2. Identification of outcome

The endpoint was incident stroke (International Classification of Disease (ICD) 10: I60, I61, I63 and I64), and potential cases were identified by linkage to the nationwide Danish National Hospital Registry and the Danish Causes of Death Registry. We considered both primary and secondary discharge stroke diagnosis as possible stroke cases. All these potential cases were validated by direct review of medical records by a physician with neurological experience. Stroke cases were defined as rapid onset of focal or global neurological deficit of vascular origin that persisted beyond 24 h, leading to either death or confirmed by CT or MRI scan. Based on CT, MRI, autopsy records and lumbar punctures, we subsequently categorized strokes in following sub-diagnoses: subarachnoid hemorrhage, intracerebral hemorrhage and ischemic stroke (cerebral infarction) as well as fatal strokes, defined as death within 30 days of hospitalization for stroke.

2.3. Exposure assessment

2.3.1. Road traffic noise

Road traffic noise exposure was calculated for the years 1990, 1995, 2000, 2005 and 2010 using SoundPLAN (version 6.5, <http://www.soundplan.dk/>) for all residential addresses at which cohort members had lived between 1987 and diagnosis/censoring. This noise calculation program is based on the Nordic prediction method for road traffic noise (Bendtsen, 1999). The input variables for the noise model were: point for noise estimation (geographical coordinates and height); road links with information on annual average daily traffic, vehicle distribution (of light and heavy vehicles), travel speed, and road type (motorway, express road, road wider than 6 m, road less than 6 m and more than 3 m, and other road); and building polygons for all buildings. We obtained traffic data for all Danish roads with more than 1000 vehicles per day from a national road and traffic database (Jensen et al., 2009), based on different traffic data sources, including: (1) data from the 140 Danish municipalities with most residents, covering 97.5% of the addresses included in the present study; (2) a central database covering all the major state and county roads and (3) database on all major roads in the Greater Copenhagen Area. We assumed a flat terrain, which is a reasonable assumption in Denmark, and that urban areas, roads, and areas with water were hard surfaces, whereas all other areas were acoustically porous. No information was available on noise barriers or road surfaces. Road traffic noise was calculated as the equivalent continuous A-weighted sound pressure level (L_{Aeq}) at the most exposed facade of the dwelling at each address for day (L_{d} ; 07:00–19:00 h), evening (L_{e} ; 19:00–22:00 h) and night (L_n ; 22:00–07:00 h), and expressed as L_{den} (den=day, evening, night) by applying a 5-dB penalty for the evening and a 10-dB penalty for the night as follows:

$$L_{den} = 10 \times \log \left(\frac{1}{24} \times (12 \times \exp(L_d/10) + 3 \times \exp((L_e + 5)/10) + 9 \times \exp((L_n + 10)/10)) \right)$$

Similar to a previous study, all values below 42 dB was considered as a lower limit of ambient noise and set to 42 dB (Selander et al., 2009b).

2.3.2. Air pollution

Ambient concentrations of NO_x and NO_2 were calculated with the Danish AirGIS dispersion modeling system for each year (1987–2009) at each address at which the cohort members had lived, including the Operational Street Pollution Model (OSPM). AirGIS allows calculation of air pollution at a location as the sum of: local air pollution from traffic in the streets; the urban background contribution; and a regional background contribution (Berkowicz et al., 2008). Input data for the AirGIS system included traffic data for individual road links (same input data as described for the noise modeling), emission factors for the Danish car fleet, street and building geometry, building height and meteorological data (Jensen et al., 2001). The AirGIS system and the OSPM model have been successfully validated and applied in several studies (Ketzel et al., 2011, 2012; Raaschou-Nielsen et al., 2011). As an example, AirGIS modeled and measured 1-month mean concentrations of NO_x and NO_2 over an 8-year period (1998–2005) in a busy street in Copenhagen (Jagtvej, 25,000 vehicles/day, street canyon) showed a correlation coefficient of 0.88 and 0.67, respectively (Ketzel et al., 2011).

2.4. Statistical analyses

Analyses were based on Cox proportional hazards model with age as underlying time, ensuring comparison of individuals of the same age. We used left truncation at age at 1st July 1997 (to ensure at least 10 years of exposure history for all cohort participants), and followed participants until age of stroke, death, emigration, or 30 November 2009, whichever came first. Exposure to road traffic noise and air pollution were modeled as exposure at the address at the time of diagnosis, exposure at the address at the time of enrolment into the cohort, and as time-weighted averages for the 1-, 5- and 10- year periods preceding the diagnosis, taking all present and historical addresses in that period into account. The time-

dependent exposure windows (diagnosis and 1-, 5- and 10-years) were entered as time-dependent variables into the statistical risk model, thus for each incident stroke recalculating exposure for all cohort members at exactly the same age as the case at the time of diagnosis and at risk at the time of the stroke. As an example, if a case was diagnosed with stroke at age 65.6 years, we for all cohort members at risk at age 65.6 years recalculated all time-dependent exposures: yearly exposure at the present address at age 65.6 years (referred to as 'time of diagnosis') as well as 1-, 5- and 10-years' time-weighted averages preceding age 65.6 years, taking all present and historical addresses of the cohort members in that period into account.

Incidence rate ratios (IRRs) for stroke (all stroke, subtypes of stroke and fatal strokes) in association with road traffic noise (L_{den}) and air pollution (NO_x and NO_2) were calculated crude and adjusted for sex, length of school attendance as an individual marker for socioeconomic status (≤ 7 , 8–10, > 10 years), area level socioeconomic status (SES) of baseline municipalities or district for Copenhagen municipality (in total 10 districts) in four groups (low, medium low, medium high and high SES) based on municipality/district information on education, work market affiliation and income, smoking status (never, former, current) and intensity (g/day), intake of fruits (g/day), vegetables (g/day), alcohol (g/day) and coffee (≤ 1 , 2–3, 4–5, and ≥ 6 cups of coffee per day), physical activity (metabolic equivalent (MET) score), body mass index (BMI, kg/m²) and calendar-year (time-dependent in 5 years intervals).

Analyses were performed in two steps. First, we investigated independent associations of road traffic noise and air pollution exposure at the diagnosis address in relation to following outcomes: all strokes, fatal strokes and subtypes of strokes (ischemic strokes, intracerebral hemorrhage and subarachnoid hemorrhage). As we found strongest association of all exposures on ischemic stroke, we subsequently investigated associations of road traffic noise (L_{den}) and air pollution (NO_x and NO_2) using five exposure windows (diagnosis, enrollment, 1 year, 5 years and 10 years) in models with both exposures fitted simultaneously in relation to risk for ischemic stroke.

Potential combined effects between road traffic noise and air pollution (NO_2) in relation to ischemic stroke were investigated by combining tertiles of the two exposures (at time of diagnoses) into nine categories, using the category of low noise and low air pollution as reference group (categorical analysis). We also tested whether the linear association between noise and ischemic stroke differed among tertiles of NO_2 and vice versa, by introducing interaction terms into the model and tested by the Wald test.

The assumption of linearity of road traffic noise and air pollution in relation to risk for stroke was evaluated visually and by formal testing with linear spline models with boundaries placed at deciles for cases. We found no statistically significant deviations from linearity for either L_{den} , NO_x or NO_2 . The procedure PHREG in SAS version 9.1 (SAS Institute, North Carolina, USA) was used for the statistical analyses.

3. Results

3.1. Study base

Among the 57,053 cohort participants we excluded 572 participants with a diagnosis of cancer before enrollment, 572 participants with a discharge diagnosis of stroke in the Danish National Patient Registry before enrollment, 162 participants for whom we could not locate the medical record, 3047 participants with incomplete residential address history in the period from July 1987 to the event or censoring date, and 427 censored before July 1997, and 704 participants with missing data for one or more covariates, leaving a study cohort of 51,569 participants. Among these, 1999 participants were diagnosed with stroke validated by medical records during a mean follow-up of 11.2 years. Cases were more likely to be men, have fewer years of school attendance, smoked more and eat less fruit and vegetables, as compared with the whole cohort (Table 1). The correlation (R_{Pearson}) between exposure of L_{den} and air pollution at the enrolment address was 0.66 for NO_2 and 0.62 for NO_x ($P < 0.0001$). The correlation between NO_x and NO_2 was 0.92 ($P < 0.0001$).

3.2. Single exposures and subtypes of stroke

Table 2 shows associations between yearly exposure at the diagnosis address to road traffic noise and air pollution in single exposure models in relation to all strokes and subtypes of strokes. Exposure to road traffic noise and NO_2 was significantly associated with risk for all strokes, whereas for NO_x there was no clear relationship. With regard to the different subtypes of stroke, both

Table 1

Baseline characteristics of the Diet, Cancer and Health cohort by stroke status at follow-up.

Characteristic at enrollment	Total cohort (n=51,569)	All strokes (n=1999)
Men (%)	47.0	59.0
Age (years)	56.2 (50.7–64.2)	58.8 (51.7–64.7)
Years of school attendance (%)		
≤ 7	33.1	40.0
8–10	46.4	42.3
> 10	20.5	17.7
Social economic status (%) ^a		
Low	14.5	17.8
Medium low	45.7	46.3
Medium high	18.8	18.4
High	21.0	17.5
Smoking status (%)		
Never	35.9	24.4
Former	28.1	25.3
Current	36.0	50.3
Smoking intensity (g/day)	15 (4–35)	18 (5–39)
Intake of fruit (g/day)	170 (27.0–524)	149 (22.5–496)
Intake of vegetables (g/day)	161 (49.1–367)	143 (42.6–348)
Drink alcohol (%)	98.8	97.0
Alcohol intake (g/day)	13.2 (1.11–64.5)	15.1 (1.00–79.4)
Intake of coffee (cups/day) (%)		
≤ 1	16.9	19.3
2–3	26.9	24.5
4–5	28.2	26.1
≥ 6	28.0	30.1
Physical activity (MET score)	56.5 (18.0–149)	55.5 (15.0–160)
BMI (kg/m ²)	25.5 (20.5–33.4)	26.1 (20.5–34.5)
Road traffic noise, L_{den} (dB)	56.5 (48.9–70.1)	57.1 (48.7–70.6)
Air pollution, NO_x ($\mu\text{g}/\text{m}^3$)	20.8 (14.4–88.8)	20.8 (14.4–98.5)
Air pollution, NO_2 ($\mu\text{g}/\text{m}^3$)	16.6 (12.0–33.1)	17.1 (12.2–34.9)

Values are medians (5–95 percentiles) unless otherwise stated.

^a Socioeconomic status of municipalities based on municipality information on education, work market affiliation and income.

Table 2

Associations between risk for stroke and subtypes of stroke and yearly exposure to road traffic noise (L_{den}) and air pollution (NO_x and NO_2) at the diagnosis address in single exposure models.

Yearly exposure at the diagnosis address	N cases	Crude	Adjusted ^a
		IRR (95% CI) ^b	IRR (95% CI) ^b
All strokes			
L_{den} (per 10 dB)	1999	1.14 (1.07–1.21)	1.11 (1.04–1.19)
NO_x (per 20 $\mu\text{g}/\text{m}^3$)	1999	1.06 (1.02–1.10)	1.02 (0.98–1.07)
NO_2 (per 10 $\mu\text{g}/\text{m}^3$)	1999	1.13 (1.06–1.21)	1.08 (1.01–1.16)
Subtypes of stroke:			
Ischemic strokes			
L_{den} (per 10 dB)	1637	1.19 (1.11–1.28)	1.16 (1.07–1.24)
NO_x (per 20 $\mu\text{g}/\text{m}^3$)	1637	1.07 (1.03–1.12)	1.04 (0.99–1.08)
NO_2 (per 10 $\mu\text{g}/\text{m}^3$)	1637	1.16 (1.05–1.21)	1.11 (1.03–1.20)
Intracerebral hemorrhage			
L_{den} (per 10 dB)	248	0.99 (0.82–1.19)	0.99 (0.81–1.20)
NO_x (per 20 $\mu\text{g}/\text{m}^3$)	248	1.01 (0.89–1.14)	0.98 (0.86–1.11)
NO_2 (per 10 $\mu\text{g}/\text{m}^3$)	248	1.05 (0.87–1.26)	1.00 (0.80–1.24)
Subarachnoid hemorrhage			
L_{den} (per 10 dB)	105	0.77 (0.57–1.03)	0.79 (0.58–1.08)
NO_x (per 20 $\mu\text{g}/\text{m}^3$)	105	0.93 (0.75–1.14)	0.96 (0.77–1.19)
NO_2 (per 10 $\mu\text{g}/\text{m}^3$)	105	0.83 (0.59–1.16)	0.90 (0.62–1.30)

^a IRR, incidence rate ratio; CI, confidence interval.

^b Adjusted for age, sex, length of school attendance, municipality SES, smoking status and intensity, intake of fruits, vegetables, alcohol and coffee, physical activity (MET score), BMI and calendar-year.

Table 3
Associations between risk for ischemic strokes ($N=1637$) and different time-windows of exposure to road traffic noise (L_{den}) and air pollution (NO_x and NO_2) in single and two-exposure models.

Exposure	Single exposure model	Two-exposure model (L_{den} and NO_x)	Two-exposure model (L_{den} and NO_2)
	IRR (95% CI) ^{a,b}	IRR (95% CI) ^{a,b}	IRR (95% CI) ^{a,b}
Diagnosis exposure^c			
L_{den} (per 10 dB)	1.16 (1.07–1.24)	1.19 (1.08–1.30)	1.15 (1.04–1.26)
NO_x (per 20 $\mu\text{g}/\text{m}^3$)	1.04 (0.99–1.08)	0.97 (0.92–1.03)	–
NO_2 (per 10 $\mu\text{g}/\text{m}^3$)	1.11 (1.03–1.20)	–	1.02 (0.92–1.12)
1-year exposure^d			
L_{den} (per 10 dB)	1.16 (1.07–1.24)	1.21 (1.10–1.33)	1.19 (1.09–1.31)
NO_x (per 20 $\mu\text{g}/\text{m}^3$)	1.02 (0.98–1.07)	0.95 (0.90–1.01)	–
NO_2 (per 10 $\mu\text{g}/\text{m}^3$)	1.06 (0.98–1.15)	–	0.95 (0.85–1.05)
5-years exposure^d			
L_{den} (per 10 dB)	1.14 (1.06–1.23)	1.19 (1.09–1.31)	1.18 (1.08–1.30)
NO_x (per 20 $\mu\text{g}/\text{m}^3$)	1.02 (0.97–1.06)	0.96 (0.91–1.01)	–
NO_2 (per 10 $\mu\text{g}/\text{m}^3$)	1.04 (0.96–1.13)	–	0.93 (0.84–1.04)
10-years exposure^d			
L_{den} (per 10 dB)	1.12 (1.03–1.21)	1.16 (1.06–1.28)	1.17 (1.06–1.29)
NO_x (per 20 $\mu\text{g}/\text{m}^3$)	1.01 (0.97–1.05)	0.96 (0.91–1.01)	–
NO_2 (per 10 $\mu\text{g}/\text{m}^3$)	1.02 (0.93–1.11)	–	0.91 (0.82–1.02)
Enrolment exposure^e			
L_{den} (per 10 dB)	1.09 (1.01–1.17)	1.13 (1.03–1.23)	1.14 (1.03–1.25)
NO_x (per 20 $\mu\text{g}/\text{m}^3$)	1.01 (0.97–1.04)	0.98 (0.93–1.02)	–
NO_2 (per 10 $\mu\text{g}/\text{m}^3$)	1.01 (0.93–1.09)	–	0.93 (0.84–1.03)

^a IRR, incidence rate ratio; CI, confidence interval.

^b Adjusted for age, sex, length of school attendance, municipality SES, smoking status and intensity, intake of fruits, vegetables, alcohol and coffee, physical activity (MET score), BMI and calendar-year.

^c Yearly exposure at the residential address at the time of diagnosis.

^d Time-weighted average exposure preceding the diagnosis of stroke, taking all addresses in that period into account (1-, 5- or 10-years).

^e Yearly exposure at the residential address at the time of enrolment.

Table 4

Combined effects of road traffic noise (L_{den}) and air pollution (NO_2) at diagnosis address^a in relation to risk of ischemic stroke.

	N cases	N cases	N cases
	IRR (95% CI) ^{a,b}	IRR (95% CI) ^{b,c}	IRR (95% CI) ^{b,c}
Road traffic noise (L_{den})^c			
NO_2^d	≤ 55.2 dB	55.2–62.1 dB	> 62.1 dB
≤ 11.3 $\mu\text{g}/\text{m}^3$	319 1.00 (ref)	163 1.05 (0.87–1.27)	58 1.14 (0.86–1.50)
11.3–15.7 $\mu\text{g}/\text{m}^3$	190 0.93 (0.78–1.12)	231 1.04 (0.88–1.24)	130 1.21 (0.98–1.49)
> 15.7 $\mu\text{g}/\text{m}^3$	36 0.88 (0.61–1.26)	152 1.10 (0.89–1.35)	358 1.28 (1.09–1.52)

^a Yearly exposure at the residential address at the time of diagnosis.

^b IRR, incidence rate ratio; CI, confidence interval.

^c Adjusted for age, sex, length of school attendance, municipality SES, smoking status and intensity, intake of fruits, vegetables, alcohol and coffee, physical activity (MET score), BMI and calendar-year.

^d Exposure categories in tertiles among cases.

yearly mean of exposure to road traffic noise and air pollution at the diagnosis address were associated with a higher risk for ischemic stroke, significantly for noise (IRR=1.16; 95% CI=1.07–1.24) and NO_2 (IRR=1.11; 95% CI=1.03–1.20) and borderline significant for NO_x (IRR=1.04; 95% CI=0.99–1.08). Neither road traffic noise nor air pollution were associated with risk for the two other subtypes of stroke: intracerebral hemorrhage and subarachnoid hemorrhage.

3.3. Two pollutant models and ischemic stroke

Table 3 shows associations between exposure and ischemic stroke for both single and two-exposure models for five different

exposure time-windows. For all exposure windows, road traffic noise was significantly associated with higher risk for ischemic stroke both before and after adjustment for air pollution. The associations between noise and stroke were strongest in the most recent exposure time windows (the year of diagnosis and 1-year mean exposure). For single exposure model of NO_2 only the most recent exposure window (yearly mean exposure at the diagnosis address) was significantly associated with ischemic stroke and borderline significant for the 1-year mean exposure, whereas the other exposure windows estimates were insignificant and lower for longer exposure periods. After adjustment for road traffic noise there was no association between NO_2 and stroke. NO_x was weakly associated with ischemic stroke in the most recent exposure

windows (diagnosis and 1-y), but as for NO₂ the association was not present after adjustment for road traffic noise.

3.4. Combined exposure

Table 4 shows the combined association between exposure to road traffic noise (L_{den}) and NO₂ in relation to risk of ischemic stroke. The results showed exposure–response relationship between road traffic noise and ischemic stroke within all three tertiles of exposure to NO₂, whereas for NO₂ we found a dose–response relationship only in the highest noise tertile (> 62.1 dB). The strongest association was found for the combination of the highest exposure to both noise and NO₂ (IRR=1.28; 95% CI=1.09–1.52). In linear analyses of interactions between noise and air pollution, a 10 dB higher traffic noise at diagnosis was associated with IRR's of 1.09 (95% CI: 1.93–1.28), 1.20 (95% CI: 1.04–1.40) and 1.14 (95% CI: 0.99–1.31) among low, medium and high tertile of NO₂, respectively (P for interaction=0.67), and a 10 $\mu\text{g}/\text{m}^3$ higher NO₂ at diagnosis was associated with IRR's of 0.81 (95% CI: 0.58–1.13), 1.04 (95% CI: 0.81–1.32) and 1.04 (95% CI: 0.95–1.15) among low, medium and high tertile of traffic noise, respectively (P for interaction=0.34).

3.5. Fatal stroke

Both air pollution proxies were significantly associated with risk for fatal stroke for all four exposure windows, both before and after adjustment for road traffic noise (Table 5). Exposure to road traffic noise was not significantly associated with risk for a fatal stroke, neither before nor after adjustment for air pollution. Out of a total of 1637 ischemic strokes, 56 were fatal.

4. Discussion

In this study exposure to road traffic noise and air pollution (NO₂) was associated with higher risk for ischemic stroke in single exposure models. However, in mutually adjusted models only road

traffic noise was associated with higher risk for ischemic stroke. The strongest association with ischemic stroke was seen for the combined exposure of high road traffic noise and high NO₂. For fatal strokes, air pollution seemed associated with a higher risk whereas for road traffic noise no association was found.

In the present cohort we have previously reported positive associations between air pollution and incident stroke without including adjustment for road traffic noise (Andersen et al., 2012), cerebrovascular mortality with adjustment for road traffic noise (Raaschou-Nielsen et al., 2012) as well as between road traffic noise and incident stroke adjusted by air pollution (Sorensen et al., 2011). In the present study we focus on mutual confounding and combined associations of air pollution and road traffic noise, using a longer follow-up period than previously as well as a stroke diagnosis validated by examination of medical records, including detailed information on type of stroke.

We found that air pollution and road traffic noise both seemed associated with a higher risk for stroke in single exposure models. For air pollution this agrees with some (Lipsett et al., 2011; Maheswaran et al., 2012; Miller et al., 2007), but not all studies (Atkinson et al., 2013; Oudin et al., 2009), and for road traffic noise there is only one study on stroke hospitalization beside ours, which agrees with this finding (Floud et al., 2013). For both exposures we found only association with ischemic and not with hemorrhagic strokes, in accordance with one long-term air pollution study (Maheswaran et al., 2012) and various short-term air pollution studies (Chan et al., 2006; Wellenius et al., 2005, 2012).

In mutually adjusted linear analyses we found road traffic noise to be associated with risk for ischemic stroke, whereas there were no associations with either of the two air pollution proxies. This indicates that the association between air pollution and incident stroke seen in single exposure linear models might be mainly caused by confounding from road traffic noise, though artificial findings due to high correlation between two exposures and collinearity cannot be excluded. In disagreement with this are the findings on short-term exposure to air pollution, that consistently have found that elevated air pollution levels in the days preceding an event can trigger a stroke (Andersen et al., 2010;

Table 5

Associations between risk for fatal strokes ($N=171$) and exposure to road traffic noise (L_{den}) and air pollution (NO_x and NO₂) in single exposure models applying different exposure windows.

Exposure	Single exposure model	Two-exposure model (L_{den} and NO _x)	Two-exposure model (L_{den} and NO ₂)
	IRR (95% CI) ^{a,b}	IRR (95% CI) ^{a,b}	IRR (95% CI) ^{a,b}
Diagnosis exposure^c			
L_{den} (per 10 dB)	1.02 (0.81–1.28)	0.79 (0.60–1.04)	0.67 (0.50–0.90)
NO _x (per 20 $\mu\text{g}/\text{m}^3$)	1.17 (1.05–1.31)	1.26 (1.10–1.44)	–
NO ₂ (per 10 $\mu\text{g}/\text{m}^3$)	1.47 (1.21–1.80)	–	1.90 (1.45–2.47)
1-year exposure^d			
L_{den} (per 10 dB)	1.03 (0.81–1.29)	0.82 (0.62–1.08)	0.78 (0.58–1.05)
NO _x (per 20 $\mu\text{g}/\text{m}^3$)	1.15 (1.03–1.29)	1.23 (1.07–1.40)	–
NO ₂ (per 10 $\mu\text{g}/\text{m}^3$)	1.32 (1.06–1.63)	–	1.54 (1.16–2.05)
5-years exposure^d			
L_{den} (per 10 dB)	1.14 (0.90–1.43)	0.92 (0.70–1.23)	0.92 (0.68–1.25)
NO _x (per 20 $\mu\text{g}/\text{m}^3$)	1.16 (1.05–1.28)	1.18 (1.04–1.34)	–
NO ₂ (per 10 $\mu\text{g}/\text{m}^3$)	1.32 (1.06–1.64)	–	1.39 (1.04–1.86)
10-years exposure^d			
L_{den} (per 10 dB)	1.15 (0.91–1.46)	0.94 (0.71–1.26)	0.93 (0.68–1.26)
NO _x (per 20 $\mu\text{g}/\text{m}^3$)	1.15 (1.04–1.26)	1.16 (1.03–1.31)	–
NO ₂ (per 10 $\mu\text{g}/\text{m}^3$)	1.34 (1.08–1.68)	–	1.41 (1.05–1.89)

^a IRR, incidence rate ratio; CI, confidence interval.

^b Adjusted for age, sex, length of school attendance, municipality SES, smoking status and intensity, intake of fruits, vegetables, alcohol and coffee, physical activity (MET score), BMI and calendar-year.

^c Yearly exposure at the residential address at the time of diagnosis.

^d Time-weighted average exposure preceding the diagnosis of a fatal stroke, taking all addresses in that period into account (1-, 5- or 10-years).

Oudin et al., 2010; Wellenius et al., 2012). We cannot rule out that the road traffic noise model predicts noise levels more precisely than the dispersion model predicts air pollution levels, which could potentially explain the apparent more robust association with noise. We used NO_x and NO_2 as indicators of air pollution, because they have been shown to be good markers of traffic-related air pollution and correlate closely with particulate matter, including ultrafine particles and PM_{10} in Danish streets (Ketzel et al., 2003). It is possible that other proxies of traffic related air pollution, such as ultrafine particles or $\text{PM}_{2.5}$, might result in different trends than observed for NO_x and NO_2 in the present study. However, we have previously reported positive associations between the air pollution proxies used in the present study and risk for diseases where particles are thought to be the main hazardous component of air pollution, including lung cancer (Raaschou-Nielsen et al., 2011) and COPD (Andersen et al., 2011); these associations are unlikely to be confounded by road traffic noise, which indicates that our modeled air pollution proxies also capture exposure to particles well.

Noise and air pollution are correlated in the present study reflecting that road traffic is a source of both exposures, and therefore input variable for both noise and air pollution models. However, the correlation is only moderate with an R^2 of around 0.40, and thus approximately 60% variation that cannot be explained by the other exposure. Reasons for that includes that the air pollution model uses information on regional and urban background contribution which is not relevant for noise modeling, and also differences in dispersion of the two exposures, as the air pollution model includes information on street configuration (street canyons), wind in street canyons and chemistry, whereas the noise model includes information on reflection and absorption of sound by both façade and ground.

The results indicated a combined effect of the two exposures in relation to ischemic stroke in the highest exposure categories in the categorical analyses. For road traffic noise there was an exposure-dependent increase in risk at both low, medium and high levels of air pollution, whereas for air pollution we only found an exposure-dependent increase in risk in the highest noise level category. This suggests that only at high noise levels the body is sensitive to the hazardous effects of air pollution in relation to ischemic stroke. However, analyses of linear associations of noise among categories of air pollution and vice versa indicated no effect modification, and more studies in this area are needed.

Only one previous study on stroke hospitalization (besides the study conducted using the present cohort (Sorensen et al., 2011)) have included both exposures (Floud et al., 2013). In contrast to the present study they found that in a single exposure model road traffic noise was associated with 'heart disease and stroke', but after adjustment for NO_2 there was no association. However, the study used a joint outcome category containing self-reported 'heart disease and stroke', making it impossible to distinguish between the two outcomes. Two studies on incident myocardial infarction have included both exposures, and both found that road traffic noise increased the risk both before and after adjustment for air pollution (Selander et al., 2009b; Sorensen et al., 2012).

Interestingly, we found that only air pollution was associated with risk for fatal strokes, whereas there was no or only weak, insignificant associations with road traffic noise. This agrees with the only previous study on road traffic noise and cerebrovascular mortality, which also found no associations with noise (Beelen et al., 2009), as well as most (Jerrett et al., 2013; Lipsett et al., 2011; Miller et al., 2007; Yorifuji et al., 2010) but not all studies on long-term air pollution and cerebrovascular mortality (Nafstad et al., 2004). This indicates that both exposures are associated with risk for stroke: road traffic noise seems to be strongest associated with risk for incident ischemic stroke whereas air pollution seems associated with risk for

severe strokes with fatal outcome. This result might suggest different biological pathways of action of two exposures, where noise affects milder ischemic, non-fatal strokes, while air pollution might cause more severe outcomes, leading to death.

The strengths of our study include the prospective design, the large number of cases, the strict validation of the diagnosis of stroke using nationwide registers and review of medical records, which made it possible to investigate associations with specific types of stroke. Other strengths include access to residential address histories and that we considered only the first hospitalization for stroke.

The present study also has some limitations. The estimations of air pollution and road traffic noise were based on models. Although the AirGIS dispersion model and the Nordic prediction method for road traffic noise are both standard methods used for many years, estimation of the exposures is inevitably associated with some degree of uncertainty. One reason is inaccurate input data, which would result in exposure misclassification. As the exposure model does not distinguish between cases and the cohort, such misclassification is likely to be non-differential, which would in most situations influence the risk estimate towards the neutral value. We also lacked information on individual factors that might influence exposure to noise or air pollution, such as information on time spend at home, workplace addresses, bedroom location, indoor exposures etc., which might result in exposure misclassification and an underestimation of the association (Selander et al., 2009b). However, again such misclassifications are most likely non-differential, and influence the risk estimate towards the neutral value. Finally, there might be confounding from risk factors not accounted for in the analyses, although we already adjusted for many important risk factors. Also, we have information on potential lifestyle confounders at only one point in time (baseline). However, we adjusted for calendar-year, thereby taking follow-up time into account as all participants were included during a relatively short period (Oct 1993–May 1997).

5. Conclusions

In conclusion, the present study suggests that road traffic noise are more strongly associated with incident ischemic stroke than air pollution, whereas for fatal strokes only air pollution seems associated with a higher risk. This could indicate different biological pathways of noise and air pollution, related to mild and severe strokes, respectively. There were indications of combined effects.

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