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Long-Term Exposure to Road Traffic Noise and Air Pollution, and Incident Atrial Fibrillation in the Danish Nurse Cohort

Zorana J. Andersen,[1] Johannah Cramer,[1] Jeanette T. Jørgensen,[1] Christian Dehlendorff,[2] Heresh Amini,[1] Amar Mehta,[3,4] Tom Cole-Hunter,[1,5,6] Laust H. Mortensen,[3,4] Rudi Westendorp,[4,7] Rina So,[1] Shuo Li,[1] Barbara Hoffmann,[8] Steffen Loft,[1] Elvira V. Bräuner,[9] Matthias Ketzel,[10,11] Ole Hertel,[10] Jørgen Brandt,[10,12] Steen Solvang Jensen,[10] Jesper H. Christensen,[10] Camilla Geels,[10] Lise M. Frohn,[10] Claus Backalarz,[13] Mette K. Simonsen,[14,15] and Youn-Hee Lim[1]

[1]Environmental Epidemiology Group, Section of Environmental Health, Department of Public Health, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[2]Statistics and Data Analysis, Danish Cancer Society Research Center, Copenhagen, Denmark
[3]Denmark Statistics, Copenhagen, Denmark
[4]Section of Epidemiology, Department of Public Health, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[5]Centre for Air Pollution, Energy, and Health Research, University of New South Wales, Sydney, New South Wales, Australia
[6]International Laboratory for Air Quality and Health, Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Queensland, Australia
[7]Center for Healthy Aging, University of Copenhagen, Copenhagen, Denmark
[8]Institute for Occupational, Social and Environmental Medicine; Centre for Health and Society, Medical Faculty, Heinrich-Heine-University of Düsseldorf, Düsseldorf, Germany
[9]Department of Growth and Reproduction, Rigshospitalet, University of Copenhagen, Denmark
[10]Department of Environmental Science, Aarhus University, Roskilde, Denmark
[11]Global Centre for Clean Air Research (GCARE), University of Surrey, United Kingdom
[12]iClimate, Aarhus University, Roskilde, Denmark
[13]DELTA Acoustics, Hørsholm, Denmark
[14]Diakonissestiftelsen, Frederiksberg, Denmark
[15]The Parker Institute, Bispebjerg and Frederiksberg Hospital, Copenhagen University Hospital, Copenhagen, Denmark

Background: Associations between long-term exposure to air pollution and road traffic noise have been established for ischemic heart disease, but findings have been mixed for atrial fibrillation (AF).

Objectives: The goal of the study was to examine associations of long-term exposure to road traffic noise and air pollution with AF.

Methods: Time-varying Cox regression models were used to estimate associations of 1-, 3-, and 23-y mean road traffic noise and air pollution exposures with AF incidence in 23,528 women enrolled in the Danish Nurse Cohort (age >44 y at baseline in 1993 or 1999). AF diagnoses were ascertained via the Danish National Patient Register. Annual mean weighted 24-h average road traffic noise levels (L_{den}) at the nurses' residences, since 1970, were estimated using the Nord2000 model, and annual mean levels of particulate matter with a diameter <2.5 μm ($PM_{2.5}$) and nitrogen dioxide (NO_2) were estimated using the DEHM/UBM/AirGIS model.

Results: Of 23,528 nurses with no prior AF diagnosis at the cohort baseline, 1,522 developed AF during follow-up. In a fully adjusted model (including $PM_{2.5}$), the estimated risk of AF was 18% higher [hazard ratio (HR); 95% confidence interval (CI): 1.18; 1.02, 1.36] in nurses with residential 3-y mean L_{den} levels >58 dB vs. <48 dB, with similar findings for 1-y mean exposures. A 3.9-$\mu g/m^3$ increase in 3-y mean $PM_{2.5}$ was associated with incident AF before and after adjustment for concurrent exposure to road traffic noise (HR 1.09; 95% CI: 1.00, 1.20 and 1.08; 95% CI: 0.97, 1.19, respectively). Associations with 1-y mean $PM_{2.5}$ exposures were positive but closer to the null and not significant. Associations with NO_2 were null for all time periods before and after adjustment for road traffic noise and inverse when adjusted for concurrent $PM_{2.5}$.

Conclusion: Our analysis of prospective data from a cohort of Danish female nurses followed for up to 14 y provided suggestive evidence of independent associations between incident AF and 1- and 3-y exposures to road traffic noise and $PM_{2.5}$. https://doi.org/10.1289/EHP8090

Introduction

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia, characterized by abnormal electrophysiology of the heart's atria (Kirchhof et al. 2016). AF increases the risk of stroke, heart failure, myocardial infarction, dementia, and venous thromboembolism (Kirchhof et al. 2016; Staerk et al. 2017). An estimated 33.5 million people suffered from AF globally in 2010, and AF diagnoses are expected to increase with population aging and the use of improved diagnostic tools (Chugh et al. 2014; Kirchhof et al. 2016). Recognized risk factors for AF include obesity, smoking, and physical inactivity, whereas the roles of environmental factors, including air pollution and road traffic noise, are still unclear (Staerk et al. 2017).

Long-term exposures to road traffic noise (Babisch 2014) and air pollution (Lelieveld et al. 2019) have been associated with ischemic heart and metabolic disease, and AF is both a risk factor and potential consequence of cardiovascular disease and a risk factor for metabolic disease (Staerk et al. 2017). Despite this, few studies have examined road traffic noise and air pollution as risk factors for AF.

Short-term exposure to air pollution, over several days, has been associated with acute exacerbations of AF (Kwon et al. 2019; Dahlquist et al. 2020), though it is still unclear whether air pollution contributes to its pathogenesis. Seven cohort studies explored the association between long-term exposure to air pollutants such as particulate matter (PM) with an aerodynamic diameter ≤2.5 μm ($PM_{2.5}$), ≤10 μm (PM_{10}), nitrogen dioxide (NO_2), or nitrogen oxides (NO_x) and AF incidence, showing conflicting

Address correspondence to Zorana J. Andersen, Section of Environmental Health, Department of Public Health, University of Copenhagen, Øster Farimagsgade 5, Opgang B, Post Box 2099, 1014 Copenhagen, Denmark. Telephone: +45 20 74 04 62. Email: zorana.andersen@sund.ku.dk.

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results. Although some studies reported associations with $PM_{2.5}$ (Kim et al. 2019; Shin et al. 2019), PM_{10} (Kim et al. 2019), NO_2 (Kim et al. 2019; Monrad et al. 2017; Shin et al. 2019), or NO_x (Monrad et al. 2017), others exploring one or more of these pollutants have not (Atkinson et al. 2013; Carey et al. 2016; Kwon et al. 2019; Stockfelt et al. 2017). To our knowledge, only two studies have examined long-term exposure to road traffic noise with respect to AF. Carey et al. found no association between AF incidence and mean road traffic noise levels at night during the year before baseline in a cohort of >208,000 adult residents of the Greater London area who were followed for up to 7 y (Carey et al. 2016). Monrad et al. reported an association between incident AF and 5-y mean road traffic noise levels before diagnosis in a cohort of >50,000 Danish adults, with an average follow-up of 14.7 y (Monrad et al. 2016). However, the association attenuated to null after adjustment for traffic-related air pollution (NO_2 or NO_x), and AF was not associated with railway noise (Monrad et al. 2016). Finally, an association between long-term exposure to wind turbine noise and incident AF was recently reported for participants in the Danish Nurse Cohort (DNC) (Bräuner et al. 2019).

In this study, we examined the association between long-term exposure to both road traffic noise and air pollution and the incidence of AF.

Methods

The DNC

The DNC includes nurses from the Danish Nurse Organization, which includes 95% of the Danish nursing workforce (Hundrup et al. 2012). In 1993, 23,170 female nurses (age >44 y) were mailed initial questionnaires, of which 19,898 (86%) responded. In 1999, 8,833 additional nurses were recruited (489 reinvited nonresponders from 1993 and 8,344 nurses who had reached 45 years of age), giving a total of 28,731 nurses recruited in 1993 or 1999. Questionnaires completed at baseline in 1993 or 1999 gathered information on working conditions, lifestyle factors (dietary, physical activity, smoking, and alcohol consumption), self-reported health (including hypertension, diabetes, and myocardial infarction), height and weight, and reproductive health. The DNC study was approved by the Danish scientific ethics committee, and written informed consent was obtained from all the participants. The present study was approved by the Danish Data Protection Agency (Case number: 514-0518/20-3,000).

AF Definitions

AF diagnoses were ascertained through linkage to the Danish National Patient Registry, which includes information from all Danish hospitals on in-patient hospitalizations since 1977, and information from outpatient clinic contacts and emergency room visits since 1995. Incident AF was defined as the first hospital contact for AF [International Classification of Diseases (ICD) codes: ICD-8: 427.93, 427.94 and ICD-10: I48 (AF and flutter)] after baseline in 1993 or 1999. Women who had a hospital contact for AF prior to baseline were excluded. Use of the Danish National Patient Registry for AF ascertainment is supported by a review of medical records for 300 incident AF cases identified based on hospital discharge diagnoses in the Danish National Patient Registry that reported a positive predicted value (PPV) of 92.6% (Rix et al. 2012), and by a more recent medical records review of 100 incident cases of AF identified through the Danish National Patient Registry that reported a PPV of 95% (Sundbøll et al. 2016). Hospitals do not receive financial reimbursement unless services and discharge diagnoses are reported to the Registry; therefore, ascertainment of AF diagnoses should be close to100%. Apart from inclusion of outpatient visits in 1995, there were no changes in the AF incidence registration system in the Danish National Patient Registry for the rest of the study during the study period.

Exposure Assignment

The geographical coordinates of each residential address between 1970 and 31 December 2014 were identified for each participant through the Danish Address Register and were used to estimate residential road traffic noise and air pollution exposures.

Assessment of Residential Road Traffic Noise

Residential road traffic noise at each residential address was calculated using the Nord2000 method (DELTA 2002; DELTA 2006), which uses following input variables: the address geocode; the height of apartments above street level; information on nearby roads, including annual average daily traffic, traffic composition and speed, road type and properties (e.g., motorway, rural highway, road wider than 6 m, and other roads); building polygons for all surrounding buildings; and meteorology, including wind speed and direction, air temperature, and cloud cover. The propagation model is based on geometrical ray theory computing the one-third octave band sound attenuation along the path from the source to the receiver, which accounts for properties of the terrain (shape and ground type, including impedance and roughness) and variations in weather conditions. Annual mean road traffic noise contributed by roads within a 3-km radius were estimated for each residential address during 1970–2015 as the equivalent continuous A-weighted sound pressure level (LA_{eq}) at the most exposed façade of the dwelling during the day (L_d; 07:00–19:00 hours), evening (L_e; 19:00–22:00 hours), and night (L_n; 22:00–07:00 hours). These data were used to derive L_{den}, the annual weighted 24-h average noise levels during the day, evening, and night, after adding 5- and 10-dB penalties to the estimated evening and night noise levels, respectively. Validation of the Nord2000 model was done by comparing the model predictions with outdoor noise measurements at 544 different sites, which showed, on average, small differences, with higher predicted noise levels than measurements, in the order of 0.5 dB on average and 1 dB at the worst (DELTA Acoustics & Electronics 2006).

The Danish air pollution modeling system DEHM/UBM/AirGIS (http://au.dk/AirGIS) (Khan et al. 2019) was used to estimate annual average NO_2 exposures for 1970–2014, and annual average $PM_{2.5}$ exposures for 1990–2014. The system comprises three air pollution models: the Danish Eulerian Hemispheric Model, which is used to assess the long-range transport components; the Danish Urban Background Model, to estimate the local background on a 1-km^2 resolution grid overlaying Denmark; and the Operational Street Pollution Model (OSPM), to estimate front-door concentrations at each residential address. When compared with routine measurements from the Danish monitoring program (comprising 17 stations across the country), R^2 values for DEHM/UBM/AirGIS ranged from 0.7 to 0.9, depending on the site, pollutant, and averaging period; $PM_{2.5}$ concentrations were underestimated by 7%–13% (Hvidtfeldt et al. 2018; Ellermann et al. 2020). In this study we estimated associations between AF and 1-, 3-, and 23-y moving average NO_2 and L_{den} exposures (prior to the end of follow-up for each participant), and associations with 1- and 3-y moving average $PM_{2.5}$ exposures. The 1-y mean exposures represented recent exposures, whereas the longer-term 3- and 23-y time windows were selected because they represented the longest possible exposure windows from the first year with annual average data (1970 for NO_2 and L_{den}, and 1990 for $PM_{2.5}$) through 1992, the year before follow-up began

among women enrolled in 1993. Data were split by year, from 1970 until the end of follow-up for each person, from which we constructed three exposure periods for $PM_{2.5}$, NO_2, and L_{den}.

Statistical Analyses

Associations between L_{den}, $PM_{2.5}$, and NO_2, and incident AF were estimated using time-varying Cox regression models, with attained age as the underlying time scale. Age at cohort entry (as of 1 April 1993 or 1 April 1999) was the start of follow-up, whereas end of follow-up was the date of incident AF ascertainment (event), the date of death or emigration, or 31 July 2015, whichever occurred first. All exposure data were time-varying. Women with missing exposure data for the cohort baseline year (1993 or 1999) were excluded from analyses ($n = 2{,}163$). When exposure data were missing for other years due to gaps in residential address information, the missing data were replaced with the average value for all years with available data in the 3- or 23-year time window. The proportion of missing exposure data across all years was 0.40% for $PM_{2.5}$ and NO_2 and 0.39% for L_{den}, and <2% of participants had missing exposure data.

Single- and two-pollutant models were used to estimate the effects of exposure to 1-, and 3-y running means of each pollutant (L_{den}, $PM_{2.5}$, and NO_2), and 23-y running means of L_{den} and NO_2, modeled continuously (per 10 dB for L_{den} and per interquartile range (IQR) increase for the air pollutants).

Associations were investigated with increasing adjustment for confounders, in three steps: Model 1, adjusted for age (underlying time scale) and baseline year (1993 or 1999, to control for possible differences between the two cohort rounds); Model 2, further adjusted for AF risk factors including smoking status (never, previous, or current), fruit consumption (rarely, a few times per week, daily, or several times per day), alcohol consumption (none, moderate: 1–14 drinks/wk, or heavy: ≥15 drinks/wk), typical leisure time physical activity level (low: reading or watching TV or doing other mainly sedentary activities; medium: walking, biking, or other types of light physical activity at least four times a week, including weekend walks, light gardening, and cycling/walking to and from work; or high: exercising regularly, participation in organized sports or heavy gardening at least four times a week, high intensity training or participating in professional sports at least four times a week), marital status (married, separated, divorced, single, or widowed), and level of urbanization (rural: <180 persons/km^2, provincial: 180–5,220 persons/km^2, or urban >5,220 persons/km^2), all assessed at the cohort baseline in 1993 or 1999. In addition, models included a spline term of calendar year with 3 degrees of freedom to control for long-term temporal trends in air pollution, road traffic noise, and AF incidence. Women with missing data for any of the Model 2 covariates were excluded from the analysis.

We assessed potential deviations from linearity by modeling each exposure (adjusted for Model 2 covaries) using restricted cubic splines, and we used likelihood ratio tests to compare the fit of the spline models to models with continuous (linear) exposure variables. We checked for violations of the proportional hazards assumption using Schoenfeld residuals. In two-pollutant models, we further adjusted Model 2 for mean $PM_{2.5}$, NO_2, or L_{den} exposures during the same time window.

Associations with road traffic noise were further modeled using a categorical L_{den} variable with cut points at the 25th and 75th percentiles of the exposure distribution (<48, 48–58, or >58 dB). We also explored potential threshold effects of L_{den} by estimating associations with L_{den} in subgroups of the study population with average exposures >53 and >58 dB, which represent maximum road traffic noise levels recommended by the World Health Organization and the Danish government, respectively (Ministry of the Environment of Denmark 2007; WHO Regional Office for Europe 2018). In addition, we estimated associations with $PM_{2.5}$ in subgroups exposed to <10, <20, and <25 $\mu g/m^3$ to explore associations with AF at low levels of exposure.

We examined effect modification of associations between AF and 3-y running average exposures to L_{den} and $PM_{2.5}$ by factors that may increase susceptibility through effects on overall health, including obesity [body mass index (BMI) ≥ 30 kg/m^3, yes/no], physical activity (low, medium, or high), and level of urbanization (rural, provincial, or urban), and by increasing the risk of cardiovascular disease, including hormone replacement therapy (never, previous, or current), and comorbid conditions (self-reported diagnosis or medication use), including hypertension (yes/no), diabetes (yes/no), and a history of myocardial infarction (yes/no). For associations between AF and road traffic noise, we also examined potential effect modification by night shift work (night shift only vs. day, evening, or rotating shifts) which is related to sleep disturbance (similar to noise exposure at night) and may increase the risk of cardiovascular disease, and potential modification by concurrent exposures to $PM_{2.5}$ (<19.5, 19.5–23.2, or >23.2 $\mu g/m^3$) and NO_2 (<7.5, 7.5–15.7, or >15.7 $\mu g/m^3$). For associations between $PM_{2.5}$ and AF we also examined potential effect modification by L_{den} (<48, 48–58, or >58 dB) and smoking status (never, previous, or current), because effect mechanisms may be similar for tobacco and air pollution. All potential modifiers were defined at baseline. Interactions were modeled by including interaction terms between the main exposure (L_{den} or $PM_{2.5}$) and indicator terms for categories of the potential modifier, and interaction *p*-values were derived using likelihood ratio tests.

We performed additional sensitivity analyses to examine the effect of adjusting Model 2 for area-level socioeconomic status (SES) using municipality mean family income in Danish crowns at the year of cohort recruitment, 1993 or 1999, available from Danish national registers on personal income, and the cluster option for municipality to account for correlations among women living in the same municipalities. Statistical analyses were performed with R (version 3.6.1; R Development Core Team), and exposure maps for each pollutant at cohort baseline were created using features of the Spatial Analyst extension to ESRI's ArcMap 10.7.1 GIS.

Results

Of the 28,731 nurses, 105 were excluded due to a preexisting AF diagnosis at baseline, and 5,098 due to missing exposure or covariate data, leaving a total of 23,528 for the final analyses. Over mean follow-up of 18.4 y (minimum–maximum; 16 d–22.4 y) and 432,384 person-years, 1,522 (6.5%) nurses developed AF. The mean age [mean ± standard deviation (SD)] at baseline was 52.6 ± 7.7 y (Table 1). At baseline, mean (mean ± SD) residential exposure to road traffic noise was 52.7 ± 8.2 dB, whereas mean exposure levels for $PM_{2.5}$, and NO_2 were 19.7 ± 3.6 and 12.6 ± 8.1 $\mu g/m^3$, respectively (Table 1). Median levels (IQR) of L_{den} (9.5), $PM_{2.5}$ (5.2), and NO_2 (8.2) were 53.1 dB, 19.7 $\mu g/m^3$, and 10.2 $\mu g/m^3$, respectively (Supplementary Table S1). Nurses included in the analyses were younger; smoked less; drank more alcohol; were more physically active; had lower prevalence of hypertension, diabetes, and myocardial infarction; and had lower incidence of AF in the study period from cohort entry in 1993 or 1991 until 2015, than nurses excluded from analyses (Supplementary Table S2). There were 275 municipalities in Denmark at the cohort recruitment in 1993 or 1999, with mean number of women living in municipality 86 (median 41), with minimum of 3 and maximum of 1,554 women per municipality.

At baseline, correlations between 1-y average air pollutants and L_{den} were low to moderate, with Spearman's rank correlation coefficients (ρ) of 0.36 and 0.61 for $PM_{2.5}$ and NO_2, respectively,

Table 1. Descriptive statistics at the cohort baseline in 1993 or 1999 for 23,528 Danish Nurse Cohort study participants by AF incidence status at the end of follow-up on 31 July 2015.

	Total $n = 23,528$	AF $n = 1,522$	No AF $n = 22,006$
Cohort year or entry [*n* (%)]			
1993	15,035 (63.9)	1,264 (83.0)	13,771 (62.6)
1999	8,493 (36.1)	258 (17.0)	8,253 (37.4)
Age, mean ± SD	52.6 ± 7.7	57.0 ± 8.6	52.3 ± 7.5
Body mass index (kg/m^2), mean ± SD	23.7 ± 3.5	24.5 ± 4.0	23.6 ± 3.5
Body mass index (kg/m^2) [*n* (%)]			
Underweight (<18.5 kg/m^2)	576 (2.5)	37 (2.5)	539 (2.5)
Normal weight (18.5 – 25 kg/m^2)	16,137 (69.3)	907 (60.6)	15,230 (69.9)
Overweight (25 – 30 kg/m^2)	5,271 (22.6)	411 (27.5)	4,860 (22.3)
Obese (≥30 kg/m^2)	1,301 (5.6)	141 (9.4)	1,160 (5.3)
Missing (*n*)	358	40	318
Smoking status [*n* (%)]			
Never	8,166 (34.7)	464 (30.5)	7,702 (35.0)
Previous	7,145 (30.4)	489 (32.1)	6,656 (30.2)
Current	8,217 (34.9)	569 (37.4)	7,648 (34.8)
Missing (*n*)	962	84	878
Alcohol consumption [*n* (%)]			
None (0 drinks/wk)	3,579 (15.2)	279 (18.3)	3,300 (15.0)
Moderate (1–15 drinks/wk)	14,499 (61.6)	913 (60.0)	13,586 (61.7)
Heavy (>15 drinks/wk)	5,450 (23.2)	330 (21.7)	5,120 (23.3)
Missing (*n*)	861	77	784
Physical activity[a] [*n* (%)]			
Low	1,561 (6.6)	118 (7.8)	1,443 (6.6)
Medium	15,676 (66.6)	1,019 (67.0)	14,657 (66.6)
High	6,291 (26.7)	385 (25.3)	5,906 (26.8)
Missing (*n*)	356	32	324
Fruit consumption [*n* (%)]			
Rarely	864 (3.7)	58 (3.8)	806 (3.7)
Few times per week	6,724 (28.6)	402 (26.4)	6,322 (28.7)
Daily or several times per day	15,940 (67.7)	1,062 (69.8)	14,878 (67.6)
Missing (*n*)	454	50	404
Hypertension [*n* (%)]			
No	20,553 (87.5)	1,197 (78.8)	19,356 (88.1)
Yes	2,945 (12.5)	323 (21.2)	2,622 (11.9)
Missing (*n*)	44	3	41
Diabetes[b] [*n* (%)]			
No	23,066 (98.8)	1,486 (98.2)	21,580 (98.8)
Yes	284 (1.2)	27 (1.8)	257 (1.2)
Missing (*n*)	260	16	244
Myocardial infarction[b] [*n* (%)]			
No	23,254 (99.3)	1,495 (98.7)	21,759 (99.4)
Yes	156 (0.7)	20 (1.3)	136 (0.6)
Missing (*n*)	189	13	176
Employment shift type[c] [*n* (%)]			
Day	11,683 (62.4)	602 (61.2)	11081 (62.5)
Evening	1,860 (9.9)	116 (11.8)	1,744 (9.8)
Night	1,019 (5.4)	71 (7.2)	948 (5.3)
Rotating	4,163 (22.2)	195 (19.8)	3,968 (22.4)
Missing (*n*)	7,290	835	6,455
Marital status [*n* (%)]			
Married	16,557 (70.4)	973 (63.9)	15,584 (70.8)
Separated	421 (1.8)	26 (1.7)	395 (1.8)
Divorced	2,786 (11.8)	181 (11.9)	2,605 (11.8)
Single	2,329 (9.9)	190 (12.5)	2,139 (9.7)
Widowed	1,435 (6.1)	152 (10.0)	1,283 (5.8)
Missing [*n* (%)]	247	18	229
Hormone-replacement therapy [*n* (%)]			
Never	16,973 (73.3)	967 (64.5)	16,006 (73.9)
Previous	2,238 (9.7)	229 (15.3)	2,009 (9.3)
Current	3,945 (17.0)	303 (20.2)	3,642 (16.8)
Missing (*n*)	505	30	475
Urbanization level [*n* (%)]			
Rural	9,716 (41.3)	657 (43.2)	9,059 (41.2)
Provincial	10,262 (43.6)	631 (41.5)	9,631 (43.8)
Urban	3,550 (15.1)	234 (15.4)	3,316 (15.1)
Missing (*n*)	840	80	760
Annual air pollution exposure levels at cohort baseline			
$PM_{2.5}$ levels ($\mu g/m^3$), mean ± SD	19.7 ± 3.6	20.7 ± 3.3	19.6 ± 3.6
$PM_{2.5}$ levels ($\mu g/m^3$) [*n* (%)]			
Low (<19.5)	11,762 (50.0)	535 (35.2)	11,227 (51.0)
Medium (19.5–23.2)	8,343 (35.5)	668 (43.9)	7,675 (34.9)
High (>23.2)	3,423 (14.5)	319 (21.0)	3,104 (14.1)
Missing (*n*)	2,917	304	2,613
NO_2 levels ($\mu g/m^3$), mean ± SD	12.6 ± 8.1	13.2 ± 8.4	12.6 ± 8.1
NO_2 levels ($\mu g/m^3$) [*n* (%)]			
Low (<7.5)	5,869 (24.9)	322 (21.2)	5,547 (25.5)
Medium (7.5-15.7)	11,833 (50.3)	766 (50.3)	11,067 (50.3)
High (>15.7)	5,826 (24.8)	434 (28.5)	5,392 (24.5)
Missing (*n*)	2,917	304	2,613
Annual road traffic noise exposure levels at cohort baseline			
L_{den} (dB), mean ± SD	52.7 ± 8.2	53.2 ± 7.8	52.7 ± 8.2
L_{den} (dB), *n* (%)			
Low (<48)	5,281 (22.4)	308 (20.2)	4,973 (22.6)
Medium (48–58)	12,316 (52.3)	800 (52.6)	11,516 (52.3)
High (>58)	5,931 (25.2)	414 (27.2)	5,517 (25.1)
Missing (*n*)	2,917	304	2,613

Note: Data are complete, unless otherwise indicated. "Missing" represents data that were excluded from analyses. AF, atrial fibrillation; dB, decibel; L_{den}, annual mean 24-h road traffic noise levels; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with an aerodynamic diameter of <2.5 $\mu g/m^3$; SD, standard deviation.

[a]Physical activity defined: low (typically reading or watching television in leisure time or doing other mainly sedentary leisure time activities)/medium (walking, biking, or other types of light physical activity at least 4 times a week, including weekend walks, light gardening, and cycling/walking to and from work)/high (exercising regularly/participation in organized sports and/or heavy gardening at least 4 times a week; high-intensity training or participating in professional sports at least 4 times a week).

[b]Self-reported (diagnosed/taking medication for).

[c]Among those actively employed at cohort entry ($n = 18,725$).

whereas $PM_{2.5}$ was moderately correlated with NO_2 ($p = 0.65$) (Supplementary Table S3). Maps depicting the spatial distribution of each pollutant at baseline illustrate differences in air pollutant sources (Figure 1). $PM_{2.5}$ levels in Denmark are influenced by secondary pollution from central Europe (across southeastern Denmark) (Ellermann et al. 2020), whereas NO_2 (primarily traffic-related) and L_{den} levels were notably higher in urban areas.

Associations between 3-y mean L_{den} or $PM_{2.5}$ and AF showed no significant deviations from linearity, with likelihood ratio test *p*-values comparing restricted cubic splines to linear models of 0.94 and 0.25, respectively (Figure S1). In addition, we found no violations of the proportional hazards assumption (data not shown).

The hazard ratio (HR) and 95% confidence interval (95% CI) from Model 2 for AF in association with 3-y mean L_{den} was 1.03 (0.97, 1.09) per 10 dB in all women, with stronger but less precise associations when restricted to women with L_{den} exposures >53 dB or >58 dB (Table 2). Corresponding estimates were similar after additional adjustment for 3-y mean $PM_{2.5}$ (overall HR = 1.02; 95% CI: 0.95, 1.09) but stronger after adjustment for NO_2 (overall HR = 1.07; 95% CI: 0.99, 1.16) (Table 2). HRs for 3-y mean L_{den} as a categorical variable were 1.18 (95% CI: 1.02, 1.36) and 1.09 (95% CI: 0.96, 1.25) for exposure to >58 dB and 48–58 dB, respectively, relative to <48 dB. Estimates were similar after adjustment for $PM_{2.5}$ (HR = 1.17; 95% CI: 1.00, 1.37 and HR = 1.09; 95% CI: 0.95, 1.25), and stronger after adjustment for NO_2 (HR = 1.30; 95% CI: 1.09, 1.54 and HR = 1.13; 95% CI: 0.98, 1.30). Estimated associations were similar for 1-y L_{den}, but 23-y mean L_{den} was not associated with AF incidence before or after adjustment for NO_2.

In addition, 3-y mean $PM_{2.5}$ was associated with incident AF, with a Model 2 HR of 1.09 (95% CI: 1.00, 1.20) per 3.9 $\mu g/m^3$ that increased to 1.21 (95% CI: 1.06, 1.39) after adjustment for

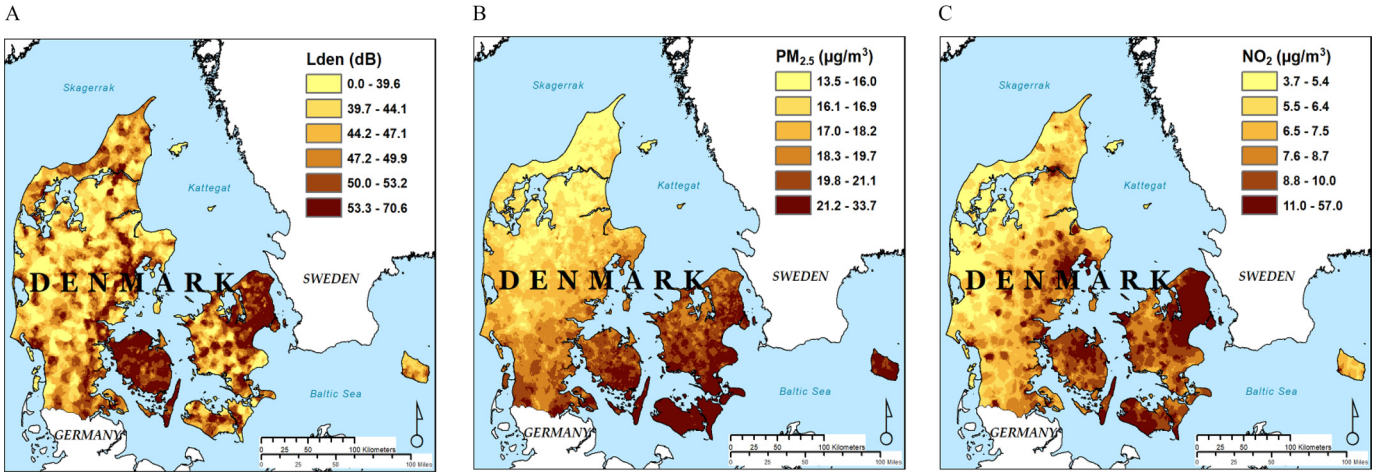

Figure 1. Smoothed maps of annual residential exposure levels for L_{den} (A), $PM_{2.5}$ (B), and NO_2 (C) (breaks represent quintiles of exposure) in the Danish Nurse Cohort at year of cohort entry (1993/1999).

NO_2 but was similar when adjusted for L_{den} (HR = 1.08; 95% CI: 0.97, 1.19) (Table 3). Associations between AF and 3-y mean $PM_{2.5}$ were similar when restricted to women with mean exposures <20 or <25 μg/m^3, whereas HRs were inverse but imprecise when restricted to women with 3-y mean exposures <10 μg/m^3, which included only 99 women with incident AF (Table 3). Associations between AF and 1-y mean $PM_{2.5}$ were positive but not significant (Model 2 HR = 1.05; 95% CI: 0.96, 1.13; HR = 1.10; 95% CI: 0.98, 1.22 after adjustment for NO_2.)

Additionally, 3-y mean NO_2 was not associated with incident AF before or after adjustment for L_{den} (Model 2 HRs of 1.00; 95%CI: 0.95, 1.06 and 0.97; 95% CI: 0.90, 1.04, respectively) but was inversely associated with AF after adjustment for $PM_{2.5}$ (HR = 0.86; 95% CI: 0.78, 0.95) (Table 3). Results followed a similar pattern for 1-y mean of NO_2, whereas HRs for 23-y mean NO_2 were null before and after adjustment for 23-y L_{den}.

We found no statistically significant interactions between 3-y mean L_{den} and baseline levels of any of the potential modifiers examined, though the association with AF was stronger in women with a history of myocardial infarction at baseline compared with other women [HR of 1.47 (95% CI: 0.81, 2.65) and HR of 1.05 (95% CI: 0.99, 1.12), respectively; p-interaction = 0.26] (Supplementary Table S4). The association between 3-y mean $PM_{2.5}$ and incident AF was also stronger among women with vs. without a history acute myocardial infarction [HR of 1.74 (95% CI: 1.15, 2.63) and HR of 1.06 (95% CI:

Table 2. Associations between road traffic noise and incident AF in the Danish Nurse Cohort.

	n (cases)	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)	Model 2[b]+$PM_{2.5}$ HR (95% CI)	Model 2[b]+NO_2 HR (95% CI)
1-y mean					
L_{den}, dB (categorical)					
Low (<48)	Ref	Ref	Ref	Ref	Ref
Medium (48–58)	16,082 (774)	1.08 (0.95, 1.23)	1.08 (0.95, 1.24)	1.09 (0.95, 1.25)	1.12 (0.97, 1.29)
High (>58)	9,259 (494)	1.22 (1.06, 1.39)	1.19 (1.03, 1.37)	1.20 (1.03, 1.41)	1.31 (1.11, 1.56)
L_{den}, dB (continuous)					
L_{den} per 10 dB	23,528 (1,522)	1.05 (0.99, 1.11)	1.04 (0.97, 1.10)	1.04 (0.97, 1.11)	1.07 (0.99, 1.16)
L_{den} > 53 per 10 dB	23,528 (1,522)	1.13 (1.02, 1.24)	1.08 (0.97, 1.20)	1.09 (0.98, 1.21)	1.09 (0.98, 1.22)
L_{den} > 58 per 10 dB	23,528 (1,522)	1.18 (1.01, 1.38)	1.11 (0.94, 1.31)	1.11 (0.93, 1.32)	1.12 (0.94, 1.33)
3-y mean					
L_{den}, dB (categorical)					
Low (<48)	Ref	Ref	Ref	Ref	Ref
Medium (48–58)	16,366 (783)	1.09 (0.96, 1.24)	1.09 (0.96, 1.25)	1.09 (0.95, 1.25)	1.13 (0.98, 1.30)
High (>58)	9,038 (487)	1.21 (1.06, 1.39)	1.18 (1.02, 1.36)	1.17 (1.00, 1.37)	1.30 (1.09, 1.54)
L_{den}, dB (continuous)					
L_{den} per 10 dB	23,528 (1,522)	1.04 (0.99, 1.10)	1.03 (0.97, 1.09)	1.02 (0.95, 1.09)	1.07 (0.99, 1.16)
L_{den} > 53 per 10 dB	23,528 (1,522)	1.11 (1.01, 1.23)	1.06 (0.95, 1.18)	1.07 (0.96, 1.19)	1.07 (0.96, 1.20)
L_{den} > 58 per 10 dB	23,528 (1,522)	1.17 (1.00, 1.38)	1.10 (0.92, 1.30)	1.09 (0.92, 1.30)	1.10 (0.93, 1.32)
23-y mean					
L_{den}, dB (categorical)					
Low (<48)	Ref	Ref	Ref	—[c]	Ref
Medium (48–58)	17,051 (841)	0.98 (0.87, 1.11)	0.96 (0.85, 1.09)	—[c]	0.99 (0.87, 1.13)
High (>58)	6,939 (384)	1.04 (0.91, 1.19)	0.99 (0.86, 1.15)	—[c]	1.07 (0.90, 1.28)
L_{den}, dB (continuous)					
L_{den} per 10 dB	23,528 (1,522)	1.02 (0.96, 1.08)	1.00 (0.93, 1.06)	—[c]	1.04 (0.95, 1.13)
L_{den} > 53 per 10 dB	23,528 (1,522)	1.07 (0.95, 1.19)	1.00 (0.88, 1.13)	—[c]	1.02 (0.89, 1.15)
L_{den} > 58 per 10 dB	23,528 (1,522)	1.10 (0.90, 1.35)	1.01 (0.81, 1.26)	—[c]	1.01 (0.80, 1.27)

Note: AF, atrial fibrillation; CI, confidence interval; dB, decibel; HR, hazard ratio; L_{den} nnual mean 24-h road traffic noise levels; NO_2, itrogen dioxide; $PM_{2.5}$, particulate matter with an aerodynamic diameter of <2.5 μg/m^3.
[a]Model 1, adjusted for age (underlying time) and year of cohort entry (1993/1999).
[b]Model 2, Model 1+smoking status, consumption of fruit, alcohol consumption, physical activity, marital status, degree of urbanization, and calendar year.
[c]—, 23 mean of $PM_{2.5}$ not available.

Table 3. Associations between incident AF and $PM_{2.5}$ (overall, and restricted to women with mean exposures <10, <20, and <25 $\mu g/m^3$) and NO_2 among women enrolled in the Danish Nurse Cohort in 1993 or 1999 and followed through 2014.

	n (cases)	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)	Model 2[b]+$PM_{2.5}$ HR (95% CI)	Model 2[b]+NO_2 HR (95% CI)	Model 2[b]+L_{den} HR (95% CI)
1-y mean						
NO_2 per 8 $\mu g/m^3$	23,528 (1,522)	1.03 (0.97, 1.08)	1.00 (0.94, 1.06)	0.90 (0.82, 0.98)	—[c]	0.96 (0.89, 1.04)
$PM_{2.5}$ per 3.9 $\mu g/m^3$	23,528 (1,522)	1.06 (0.98, 1.14)	1.05 (0.96, 1.13)	—[c]	1.10 (0.98, 1.22)	1.03 (0.94, 1.12)
<10 $\mu g/m^3$	17,974 (262)	1.01 (0.56, 1.83)	0.99 (0.55, 1.79)	—[c]	—[c]	0.98 (0.53, 1.82)
<20 $\mu g/m^3$	23,202 (1,432)	1.04 (0.94, 1.14)	1.03 (0.93, 1.13)	—[c]	—[c]	1.01 (0.91, 1.12)
<25 $\mu g/m^3$	23,503 (1,515)	1.05 (0.97, 1.15)	1.04 (0.96, 1.14)	—[c]	—[c]	1.03 (0.93, 1.13)
3-y mean						
NO_2 per 8 $\mu g/m^3$	23,528 (1,522)	1.03 (0.98, 1.08)	1.00 (0.95, 1.06)	0.86 (0.78, 0.95)	—[c]	0.97 (0.90, 1.04)
$PM_{2.5}$ per 3.9 $\mu g/m^3$	23,528 (1,522)	1.11 (1.01, 1.20)	1.09 (1.00, 1.20)	—[c]	1.21 (1.06, 1.39)	1.08 (0.97, 1.19)
<10 $\mu g/m^3$	15,147 (99)	0.91 (0.32, 2.62)	0.89 (0.31, 2.58)	—[c]	—[c]	0.84 (0.28, 2.52)
<20 $\mu g/m^3$	23,043 (1,416)	1.13 (1.01, 1.27)	1.11 (0.99, 1.25)	—[c]	—[c]	1.10 (0.97, 1.24)
<25 $\mu g/m^3$	23,489 (1,516)	1.12 (1.01, 1.24)	1.10 (1.00, 1.22)	—[c]	—[c]	1.09 (0.97, 1.22)
23-y mean						
NO_2 per 8 $\mu g/m^3$	23,528 (1,522)	1.01 (0.96, 1.06)	0.98 (0.93, 1.04)	—[c]	—[c]	0.96 (0.90, 1.04)

Note: Estimates are based on IQR increments: $PM_{2.5}$ (3.9 $\mu g/m^3$), NO_2, (8.0 $\mu g/m^3$), and L_{den} (10 dB). AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio; IQR, interquartile range; L_{den}, nnual mean 24-h road traffic noise levels; NO_2, itrogen dioxide; $PM_{2.5}$, articulate matter with an aerodynamic diameter of <2.5 $\mu g/m^3$.
[a]Model 1, adjusted for age (underlying time) and year of cohort entry (1993/1999).
[b]Model 2, Model 1+smoking status, consumption of fruit, alcohol consumption, physical activity, marital status, degree of urbanization, and calendar year.
[c]—, 23 mean of $PM_{2.5}$ not available.

0.97, 1.17), respectively; *p*-interaction = 0.02] (Supplementary Table S5). Furthermore, the association between 3-y mean $PM_{2.5}$ was stronger among women who were current users of hormone-replacement therapy at baseline than among never users and previous users [HR of 1.20 (95% CI: 1.04, 1.39), HR of 1.05 (95% CI: 0.95, 1.17), and HR of 0.96 (95% CI: 0.81, 1.14); *p*-interaction = 0.07)] and among women who were never smokers at baseline compared with former and current smokers [HR of 1.17 (95% CI: 1.03, 1.33), HR of 1.05 (95% CI: 0.92, 1.19), and HR of 1.03 (95% CI: 0.91, 1.16); *p*-interaction = 0.17].

Model 2 estimates of associations between AF and 3-y mean L_{den} and $PM_{2.5}$ (Tables 2 and 3) were largely unchanged after additional adjustment for area-level SES (mean individual income for each municipality after accounting for clustering by municipality) (Supplemental Table S6).

Discussion

In this nationwide, prospective cohort study of more than 23,000 female Danish nurses with up to 14 years of follow-up, we estimated positive associations between road traffic noise and incident AF that increased monotonically for medium and high vs. low 1- and 3-y moving average exposures, both before and after adjustment for concurrent $PM_{2.5}$ or NO_2 exposures. Three-year mean exposure to $PM_{2.5}$ was also associated with incident AF, with similar associations after adjustment for road traffic noise, and stronger associations after adjustment for NO_2.

We identified an association between long-term (3-y moving average) exposure to road traffic noise and incident AF that persisted with adjustment for air pollution (NO_2 and $PM_{2.5}$), in contrast with two earlier studies. A London-wide study of 208,049 men and women without a history of AF at baseline reported no association between mean road traffic noise at night during the year prior to cohort baseline and a first diagnosis or hospitalization for AF during 2005–2011 [HRs of 0.95 (95% CI: 0.88, 1.04) and 0.93 (0.85, 1.01) comparing >60 dB and 55–60 dB to <55 dB, respectively], and no associations with traffic-related $PM_{2.5}$ or NO_x (Carey et al. 2016). In the Danish Diet Cancer and Health (DDCH) cohort, 5-y moving average road traffic noise was positively associated with incident AF in over 50,000 adults with up to 15 years of follow-up (adjusted incidence rate ratio: 1.06; 95% CI: 1.00, 1.12 per 10 dB). However, because the association was null following adjustment for NO_2 (1.01; 95% CI: 0.94, 1.09), the authors suggested the apparent association with road traffic noise may have been driven by coexposure to traffic-related air pollution (Monrad et al. 2016). Monrad et al. also found no association between railway noise and AF. Although our model predicted noise exposures at the individual residential address level with very high (1 m^2) spatial resolution, Carey et al. (2016) assigned road traffic noise at the postcode level (20 m^2) and may not have captured local within-urban variations in noise that may be relevant to health. In addition, exposures were estimated only for the year before baseline, and associations were adjusted only for age, gender, smoking, and an area-level measure of material deprivation. Monrad et al. estimated L_{den} road traffic noise levels at the same spatial resolution as our study and ascertained incident AF through the Danish National Patient Register. However, the DDCH is an urban cohort (limited to residents of Copenhagen and Aarhus); it is possible that effects from NO_2 and road traffic noise exposure could not be distinguished due to major shared sources and homogeneity in exposure in the urban populations, although, notably, correlation between L_{den} and NO_2 was similar in two studies, 0.61 in ours and 0.63 in Monrad et al. In addition, in our nationwide cohort, we may have benefited from larger contrasts in road traffic noise levels among urban, suburban, and rural populations, which were necessary to detect associations with AF: range of L_{den}in our study was (minimum–maximum) 5–82.7 dB, whereas in Monrad et. al it was from 40 to around 70 dB. In our recent study in DNC, we presented novel results of the association of long-term, 11-y mean exposure to wind turbine noise (L_{den}, as well as L_{night}) with incident AF, in analyses adjusted for smoking and other lifestyle, road traffic noise, and air pollution (Bräuner et al. 2019). These findings suggest that environmental noise may be a risk factor for AF and demonstrates a need for further investigation.

Mechanisms through which environmental noise might affect health are not entirely understood; however, currently, two hypotheses prevail. One suggests that health effects of noise may be mediated through a stress response caused by direct effects of noise on the central nervous system, or indirect effects related to annoyance (Babisch et al. 2013). The other hypothesis posits that noise results in disturbed sleep, which in turn causes health effects, especially of a cardiometabolic nature (Basner and McGuire 2018; Münzel et al. 2017). In this study, we did not examine associations of noise at night with AF, because it is highly correlated (0.99) with L_{den}. A recent cross-sectional study of >14,000 participants in the Gutenberg Health Study found that annoyance by noise was

strongly associated with AF prevalence (Hahad et al. 2018). Though we were unable to measure annoyance in our study, it is possible that the observed effects of noise on AF incidence are explained by the stress–response hypothesis. The mechanisms underlying AF pathogenesis are not fully elucidated; however, there is clear evidence of a metabolic component (Reddy et al. 2017), suggesting the biologic plausibility of this line of inquiry.

Our findings suggest an association between chronic $PM_{2.5}$ exposures and the development of AF, which are consistent with the findings from three other studies. In a nationwide study of 432,587 participants from South Korea, an 18% (HR 1.179; 95% CI 1.176, 1.183) increase in AF incidence for each $10\,\mu g/m^3$ increase in $PM_{2.5}$ was reported (Kim et al. 2019). This finding is consistent with an estimated 23% increase in AF incidence per $10\,\mu g/m^3$ in $PM_{2.5}$ reported among 124,010 residents of Seoul, South Korea (HR 1.23; 95% CI 0.75, 2.03) (Kwon et al. 2019). A large population-based cohort study in Ontario also reported an association between long-term exposure to $PM_{2.5}$ and incident AF, with an HR of 1.03 (95% CI 1.01, 1.04) per IQR ($4.8\,\mu g/m^3$) increase (Shin et al. 2019). In contrast, Stockfelt et al. found no association with incident AF in two cohorts from Gothenburg, Sweden, with HRs (per $5\,\mu g/m^3$ increase in 1-y mean $PM_{2.5}$) of 0.92 (95% CI: 0.77, 1.10) for the Primary Prevention Study cohort and 0.78 (95% CI: 0.54, 1.14) for the GOT-MONICA cohort (Stockfelt et al. 2017). Furthermore, though they did not explore $PM_{2.5}$, Atkinson et al. found no association between long-term exposure to PM_{10} with the incidence of arrhythmias, including cardiac arrest, in a large study of 836,557 English men and women (Atkinson et al. 2013). Similarly, in a subset of Atkinson et al. cohort, Carey et al. found no association between traffic-related $PM_{2.5}$ and incident AF in London-wide cohort (Carey et al. 2016). In our study, 3-y mean $PM_{2.5}$ exposure was positively associated with AF incidence when restricted to women with exposures below the current European Union limit of $25\,\mu g/m^3$ (Gemmer and Bo 2013) (Model 2 HR = 1.10; 95% CI: 1.00, 1.22 for a 3.9-$\mu g/m^3$ increase), and when restricted to 3-y mean exposures $<20\,\mu g/m^3$ (HR = 1.11; 95% CI: 0.9, 1.25). We found no association between incident AF and 3-y mean $PM_{2.5}$ exposures $<10\,\mu g/m^3$, though this analysis was limited by a small number of observations (15,147 women and 99 AF cases).

We did not find evidence of an association between chronic (1-, 3-, or 23-y mean) NO_2 exposures with AF, in line with four other studies (Atkinson et al. 2013; Carey et al. 2016; Kwon et al. 2019; Stockfelt et al. 2017), and in contrast with two studies (Monrad et al. 2017; Shin et al. 2019). In a Danish study by Monrad et al., a statistically significant 8% increase in AF incidence for each $10\,\mu g/m^3$ increase in 10-y mean NO_2 was observed among 57,053 men and women from the DDCH cohort, after adjustment for road traffic noise (Monrad et al. 2017). Despite marked similarities in exposure estimation and study design, the study was based on an urban cohort (Denmark's two largest cities) that included both men and women. Notably, the authors found no differences in associations by gender.

Our results suggest that road traffic noise may contribute to AF development. The association between L_{den} and AF persisted after adjustment for NO_2, a proxy for exposure to local traffic, and $PM_{2.5}$, which in Denmark mainly reflects secondary transported particles and biomass burning, with only a minor contribution from traffic. Moderate and low correlations for 1-y mean values of L_{den} with NO_2 and $PM_{2.5}$ at baseline (0.61 and 0.36, respectively), and the lack of associations between traffic-related NO_2 and AF, suggest that associations between road traffic noise and AF in our study population were unlikely to have been driven only by effects of traffic-related air pollution on AF. Furthermore, AF was positively associated with $PM_{2.5}$ but not NO_2 in single pollutant models, and associations between $PM_{2.5}$ and AF were stronger when adjusted for NO_2, whereas associations between NO_2 and AF went from null to inverse after adjustment for $PM_{2.5}$. Moderate correlation between $PM_{2.5}$ and NO_2 (0.65) suggests that we may have been able to separate effects of these two pollutants on AF. Overall, our results point to the relevance of traffic related noise and secondary and biomass burning particles for the development of AF, and less to local traffic gasses or particles that NO_2 may be proxy for (black carbon or ultrafine particles). Still, additional research is needed to clarify the potential contributions of traffic-related noise and traffic-related air pollution to the incidence of AF.

Our study differs from previous studies in the literature because we provide results based on an occupational cohort of female nurses. AF incidence is higher in men than in women, but little is known whether etiology of AF differs by gender (Humphries et al. 2001; Magnussen et al. 2017). Similarly, there is no evidence to date to suggest that associations between road traffic noise or air pollution with AF differ by gender. Of two studies on road traffic noise and incident AF, Carey et al. reported that there was no appreciable difference in results when stratified by gender (Carey et al. 2016), whereas Monrad et al. reported associations between NO_2 and incident AF that were nearly identical between men and women (Monrad et al. 2016). Studies on air pollution and incident AF that have examined effect modification by gender and reported mixed results. Monrad et al. reported associations between 10-y mean NO_2 and incident AF that were indistinguishable between men and women (Monrad et al. 2017) in line with Shin et al. who found identical associations between 5-y $PM_{2.5}$ and incident AF in men and women, and slightly stronger associations with NO_2 in women [HR 1.03 (95% CI: 1.01, 1.05), for a 10.5 ppb increase] than men [HR 1.01 (95% CI: 1.00, 1.03); p-interaction 0.12] (Shin et al. 2019). Kim et al. reported a significantly stronger association between average $PM_{2.5}$ during follow-up (mean duration 46 months) and incident AF in men compared with women, but HRs were similar in magnitude (1.187; 95% CI: 1.183, 1.192 and 1.178; 95% CI: 1.174, 1.182, respectively, for a 10-$\mu g/m^3$ increase), whereas the small interaction p-value (<0.001) reflected the large number of observations [>430,000 subjects (Kim et al. 2019)]. Three additional studies of air pollution and incident AF did not examine effect modification by gender (Atkinson et al. 2013; Kwon et al. 2019; Stockfelt et al. 2017).

A major limitation of the present study is the lack of individual-level information on SES. Furthermore, we lacked information on noise annoyance, sensitivities, and measures of sleep disturbance and thus could not examine the potential roles of these factors on AF development in our study. Additionally, exposure misclassification cannot be ruled out; we did not have information on workplace exposures or information on window thickness or other sound barriers that may have influenced noise exposure levels inside each residence. Covariates were classified at the time of enrollment, and we could not account for changes in confounding over time. Due to the missing exposure and covariate data, we excluded a large portion of DNC participants, which may have resulted in selection bias. Another limitation of our approach is that we have conducted complete case analyses, although the missing data were not missing at random, and nurses who were excluded were older, had higher incidence of AF, and had poorer lifestyles than those who were included in the analyses. Another limitation is a lack of historical validation of the air pollution and noise models prior to the 1990s, and model performance may be lower for estimating exposures further back in time compared with more recent exposures. However, the main findings for this study are based on 3-y moving average exposures between 1990 and 2015, when validation studies suggest good performance for both noise and air pollution models (DELTA 2006; Hvidtfeldt et al. 2018; Ketzel et al. 2012).

We estimated a positive association between higher 3-y mean exposures to road traffic noise and the incidence of AF, before and after adjustment for concurrent air pollution exposures, in a prospective cohort of more than 23,000 Danish women with an average follow-up time of 18 y. Our findings also suggest that long-term exposure to $PM_{2.5}$ may increase the risk of AF, independent of road traffic noise, even when restricted to women with $PM_{2.5}$ exposures below the current European Union limit value of 25 $\mu g/m^3$. These results suggest that stricter control of air pollution and road traffic noise may reduce the incidence of AF.

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