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ABSTRACT

Background: The potential health effects related to wind turbine noise (WTN) have received increased focus during the past decades, but evidence is sparse. We examined the association between long-term exposure to wind turbine noise and incidence of atrial fibrillation (AF).

Methods: First ever hospital admission of AF amongst 28,731 female nurses in the Danish Nurse Cohort were identified in the Danish National Patient register until ultimo 2013. WTN levels at residential addresses between 1982 and 2013 were estimated using the Nord2000 noise propagation model, as the annual means of L_{den}, L_{day}, $L_{evening}$ and L_{night} at the most exposed façade. Time-varying Cox proportional hazard regression models were used to examine the association between the 11-, 5- and 1-year rolling means of WTN levels and AF incidence.

Results: 1430 nurses developed AF by end of follow-up in 2013. Mean (standard deviation) baseline residential noise levels amongst exposed nurses were 26.3 (6.7) dB and slightly higher in those who developed AF (27.3 (7.31) dB), than those who didn't (26.2 (6.6)). We observed a 30% statistically significant increased risk (95% CI: 1.05–1.61) of AF amongst nurses exposed to long-term (11-year running mean) WTN levels ≥ 20 dB(A) at night compared to nurses exposed to levels < 20 dB(A). Similar effects were observed with day (HR 1.25; 95% CI: 1.01–1.54), and evening (HR 1.25; 95% CI: 1.01–1.54) noise levels.

Conclusions: We found suggestive evidence of an association between long-term exposure to WTN and AF amongst female nurses. However, interpretation should be cautious as exposure levels were low.

1. Introduction

There is presently a global focus on the development of renewable energy expansions and zero-carbon shares in energy systems and wind energy is a suitable solution to achieve this (Rockström et al., 2017). In 2016 wind power avoided over 637 million tons of CO_2 emissions globally (Global Wind Energy Council, 2017b), which has positive environmental and health implications, however, wind turbines contribute to environmental noise and the local-level potential risk to human health is the subject of much debate. Denmark, one of the world leaders in total wind capacity has set a goal to generate 50% of the country's electricity by wind energy by 2021. Thus implying continuing increase in numbers and size of wind turbines, as well as proportion of

the Danish population who live in close proximity to wind turbines (Global Wind Energy Council, 2017a).

Studies on health effects related to traffic noise (road, rail and air) exposures indicate complications other than annoyance, including risk of atrial fibrillation (AF) (Monrad et al., 2016). However, noise emissions from wind turbines are different and not associated with particulate or gaseous oxidative stressors (relevant for cardiovascular endpoints), highlighting the need for research of potential cardiovascular health effects of WTN (Pedersen et al., 2009; Pedersen and Waye, 2004). Wind turbines are typically located in rural areas in which background noise levels and sensitivity thresholds to noise may be lower. Epidemiological studies assessing the health impacts of wind turbines are sparse and no studies have previously investigated whether

exposure to WTN is associated with increased risk of AF.

AF is the most common type of arrhythmia in Denmark, affecting around 5% of the population and with higher incidence rates amongst men and persons over 50 years of age (Hjertetal (Heart disease statistics), Danish Heart Foundation [In Danish], 2018), and associated increased morbidity and mortality risks. Although prevalence is rising, the etiology behind this is largely unknown, but environmental or lifestyle factors are suspected. An association between WTN and AF may be biologically plausible. Exposure to WTN acts as a stressor with activation of the hypothalamic-pituitary-adrenal (HPA) axis and stress cascade (Chen et al., 2014), has been shown to induce systemic inflammation (Dewland et al., 2015) and lastly the cortisol released in the stress reaction cascade may increase blood glycogen within atrial myocytes (Embi et al., 2014; Embi and Scherlag, 2014), which are all are suggested risk factors for AF.

Rapidly increasing investments in wind turbines (WTs) worldwide, the intense debate regarding potential health effects of WTN and the lack of epidemiological studies, merit research. In this study, we examine the association between long-term exposure to WTN and risk of AF in a large, nationwide cohort of Danish female nurses.

2. Methods

2.1. Study population - The Danish Nurse Cohort

The Danish Nurse Cohort (Hundrup et al., 2012) was inspired by the American Nurses' Health Study to investigate the health effects of hormone replacement therapy (HRT) in a European population. In 1993, the cohort was initiated by sending a questionnaire to 23,170 female members of the Danish Nurse Organization who were at least 44 years old at the time. The Danish Nurse Organization includes 95% of all nurses in Denmark. In total, 19,898 (86%) nurses replied, and the cohort was reinvestigated in 1999 when first 10,534 new nurses (who had reached the age of 44 years in the period 1993–99) were invited of which 8344 responded) and second 2231 non-responders from 1993 were re-invited of which 489 responded. The questionnaire included questions on socio-economic and working conditions, parents' occupation, weight and height, lifestyle (diet, smoking, alcohol consumption and leisure time physical activity), self-reported health, family history of cardiovascular disease, use of oral contraceptives and HRT. In the present study, we used the earliest baseline information from 1993 (19,898) or 1999 (8833) for 28,731 of the included nurses.

Since establishment of the Central Population Register in 1968 (Schmidt et al., 2014), all citizens of Denmark have been given a unique personal identification number, which allows accurate linkage between registers. The cohort members were linked to the Central Population Register (Schmidt et al., 2014) to obtain the nurses vital status information at 31st December 2013 (active, date of death/emigration). Using the unique personal identification number of the cohort members, all residential histories were traced in the Central Population Register between 1982 and 2013. Each residential address contained a unique identification code composed of a municipality-, road- and house number code. The dates the persons had moved to and from each address were noted. The addresses were then linked to a database of all official addresses and their geographical coordinates in Denmark.

2.2. Identification of outcome - National Patient Register and Danish Registry of Causes of Death

The endpoint was incidence of AF (International Classification of Disease (ICD) 10: I48 and ICD 8:427.93 and 427.94), defined as first-ever hospital contact (emergency, in- or outpatient) for AF, identified in the Danish National Patient Registry, which has collected nationwide data on all non-psychiatric hospital admissions since 1977, and since 1995, patients discharged from emergency departments and outpatient clinics have also been registered. The Danish National Board of Health

maintains the registers and assures the quality of the data. Participants with a discharge diagnosis or self-report of AF before enrolment into the Nurses Cohort were excluded.

2.3. Exposure assessment

2.3.1. Identification of Danish WTs

8768 on-shore WTs in operation at any time in Denmark from 1982 to 2013 (off-shore turbines were excluded, n = 510) were identified, using the administrative Master Data Register of WTs maintained by the Danish Energy Agency (Danish Energy Authority, 2017). It is mandatory for all WT owners to report to the register, which contains geographical coordinates, date of grid connection, cancelation date for decommissioned turbines, and output for each Danish power producing WT. Each of the turbines was classified into one of 99 noise spectra classes detailing the noise spectrum from 10 Hz to 10,000 Hz in thirds of octaves for wind speeds from 4 to 25 m/s, based on individual WT data including height, model, type and operational settings (when relevant). These noise classes were formed from existing measurements of sound power for Danish WTs (Backalarz et al., 2016). At each WT location, the hourly wind speed and direction at hub height was estimated, using mesoscale model simulations (Hahmann et al., 2015; Pena and Hahmann, 2017). Temperature and relative humidity at 2 m height as well as the atmospheric stability were also estimated from these simulations.

2.3.2. WTN exposure data

Each of the nurses' homes was identified and geocoded. The noise contribution at each nurses' homes from WTs was calculated according Nord2000 method (Backalarz et al., 2016). Sound power levels from WTs were calculated for each address in the periods each cohort member had lived at the specific address. Each home address and each WT were geocoded, and the model takes into consideration, meteorological data for each WT every hour throughout the years 1982–2013. There are today > 5200 WTs in Denmark, and since 1980s, they have gradually decreased in number and increased in size. WTs range in size from 40 to 63 m in height with 42 m wingspan (older types which produce 660 KW) to 90-143 m in height and 107 m wingspan (newest types which produce 3,6 MW). The applied noise exposure modelling has been described in details elsewhere (Backalarz et al., 2016). In brief, WTN exposure was estimated for the all the addresses the nurses had lived in using the Nord2000 noise propagation model which has been validated for WTs and previously detailed, showing a fine agreement between measured and calculated noise levels (Kragh et al., 2001; Søndergaard et al., 2009). NORD2000 method performs well in calculating noise levels below 30 dB, but in practice such low noise levels can rarely be measured due to background noise from vegetation. For each home, the noise contribution from all WTs within a 6000 meter radius was calculated hour by hour. Outdoor A-weighted sound pressure level (L_{Aeq}) at the most exposed façade of all buildings were calculated and exposure was aggregated as follows: day (L_d; 07:00–19:00 h), evening (L_e; 19:00–22:00 h), night (L_n; 22:00–07:00 h), expressed as L_{den} (the overall weighted 24-hr noise level during the day, evening (+5 dB) and night (+10 dB)), and L_{24} (unweighted 24-hr average), as yearly averages. Geographical coordinates were obtained for 99.9% of all the addresses. In this study, we consider nurses who had at lived within a 6000 m radius from at least one WT at some point of time in the period from 1.1.1982 to 31.12.2013 as exposed, and all others as unexposed to WTN.

2.3.3. Air pollution and noise from road traffic

As previously described in detail (Hansen et al., 2016; Jørgensen et al., 2016), we used the newly updated, high-resolution Danish air pollution dispersion modelling system (AirGIS) to estimate exposure to outdoor air pollution at the residence (Jensen et al., 2001). The necessary input data for carrying out the exposure modelling has been

established for the first time in Denmark (Kakosimos et al., 2010). Road traffic noise at residential addresses of the nurses was estimated using the Nord2000 model. The input variables for the traffic noise model include the geocodes of the location, the height of apartments above street level, road lines with information on yearly average daily traffic, traffic composition and speed, road type (motorway, rural highway, road wider than 6 m, and other road), building polygons for all surrounding buildings (height of buildings, etc.), and meteorology. Noise from road traffic was calculated at individual residential addresses for the period 1982–2013, as the equivalent continuous L_{24h} at the most exposed façade of the dwelling for the L_d, L_e, L_n and L_{den} as yearly averages.

2.4. Statistical analysis

We applied the Cox proportional hazards regression model to test the incidence of AF as a function of WTN exposure *with age as the underlying time scale in all models*, ensuring comparison of individuals of the same age. Start of follow-up was at the age on the date of recruitment (1st April 1993 or 1st April 1999), so nurses were considered at risk from recruitment, and end of follow-up was age at the date of first AF event, date of death, emigration or 31st December 2013, whichever came first. Nurses with an AF event before enrollment were excluded from the analyses. The effect of WTN was evaluated in several steps: Model 1) A crude model, adjusted only for calendar year at recruitment into the cohort; Model 2) A main, fully adjusted model, additionally adjusted for smoking status (never, current, previous), smoking pack-years, alcohol consumption (g/week), physical activity (low, medium, high), the consumption of fruit (yes, no), avoidance of fatty meat consumption (yes, no), use of oral contraceptives, use of HRT, employment status (employed, unemployed, retired, other) and marital status (married, separated, divorced, unmarried, widow). The main analysis was performed on the cohort with complete information on all the covariates included in Model 2.

We examined several WTN exposure time windows using the 1-, 5- and 11-year rolling mean during follow-up prior to AF diagnosis. In each rolling mean window, we considered L_d, L_e, L_n, L_{den}, and L_{24} average time exposure separately. We estimated HRs for the categorical versions of WTN exposures using firstly a cut-off at 20 dB, based on the rationale that in Denmark, low-frequency sound in the 10–160 Hz range is limited to an A-weighted level of 20 dB (Jakobsen, 2012). Second, we used cut-offs based on quartiles of noise exposure range for each noise proxy. Third, we evaluated WTN modelled as a continuous nonlinear (with a restricted cubic spline) and linear variable. To avoid enforcement of linearity between being exposed to WTN and not being exposed, two variables were used in these models; a binary variable distinguishing unexposed from exposed (0/1) and a continuous variable with the actual exposure level for those exposed and the median exposure level for unexposed subjects. WTN exposures were modelled as time-varying variables in all models.

We carried out a number of sensitivity analyses to assess the effect of several covariates (some defined as effect mediators) on the association between WTN and AF in four additional separate models. Model 3) as for model 2, was further adjusted for Body Mass Index (BMI); Model 4) as for model 2, further adjusted for self-reported hypertension at baseline; the effect of diabetes and socio-economic status was assessed in Model 5) as for model 2, further adjusted for self-reported diabetes at baseline and Model 6) as for model 2, further adjusted for average gross income at the municipality at baseline, which we used as a proxy for socio-economic status. Continuous variables, year, smoking pack-years, alcohol consumption, BMI, and average gross income at the municipality were modelled with restricted cubic splines.

The potential effect modification of the association between WTN amongst exposed Nurses and AF incidence by age, night shift work, obesity, road traffic noise/NO_x traffic related air pollution and urbanicity index was examined by introducing interaction terms to the main

linear model (model 2) with the continuous version of exposure. Traffic related air pollution was considered relevant as this is strongly correlated with road traffic noise, which has been associated with the increased risk of AF incidence and is traffic related air pollution causes oxidative stress, which is independently associated with risk of AF.

Noise estimates and traffic air pollution were available for every year of follow-up and all other potential confounding and effect mediating variables were available at baseline.

The cohort consists of elderly nurses (> 58 years old at the end of follow-up in 2013), thus the effect of non-AF death as a competing risk was also investigated as a function of WTN to assess whether time to AF in our main models was precluded by death.

All effects are reported as cause-specific hazard ratios (HRs) and 95% confidence intervals (CIs). All analysis and graphical presentations were performed using the R statistical software 3.2.0 (with packages: survival, rms, Epi, maptools, OpenStreetMaps, ggplot2).

Spearman correlation between metrics of WTN and traffic noise and air pollution were estimated, and these were not correlated (r = −0.14).

Research was conducted in accordance with principles of the Declaration of Helsinki and the Danish Nurses Cohort study was approved by the Scientific Ethics Committee for Copenhagen and Frederiksberg and written informed consent was obtained from all participants prior to enrollment. The present register based study was approved by the Danish Data Protection Agency (J.nr: 2016-41-4792). By Danish Law, ethical approval and informed consent are not required for entirely register-based studies.

3. Results

Of the total 28,731 recruited nurses in the Danish Nurses Cohort, we excluded 4 who died or emigrated before start of follow-up, 105 who were registered with a discharge diagnosis of an AF event in the Danish National Patient Registry before baseline. We additionally excluded 4471 nurses with missing information on covariates and 14 nurses due to missing address information or inability to geocode address, leaving 24,137 nurses for the final analyses.

Mean follow-up was 17 years giving a total of 409,309 person-years of observations, during which 1430 nurses developed AF, with an incidence rate of 3.5 new cases per 1000 person-years.

The nurses who developed AF were an average of 5 years older, had higher BMI, smoked slightly more, consumed less alcohol, were less physically active, ate more fatty meat and fruit, had higher rates of hypertension and HRT usage, but lower rates of ever using oral contraceptives, tended to be retired, lived in areas with slightly lower incomes, were exposed to higher levels of NO_x traffic related air pollution, and slightly higher levels of annual weighted road traffic noise at baseline than nurses who did not develop AF within the follow-up period (Table 1).

Nurses from Danish Nurse Cohort resided all around Denmark with wide geographical variation, with 14.8% residing in urban areas (population density ≥ 5220 persons/km^2), 42.3% in provincial towns (180–5220 persons/km^2) and 40.2% in rural areas (< 180 persons/km^2) at the cohort baseline, which corresponds closely to the distribution of the Danish population.

The estimated residential noise levels from WTs at baseline and distance to WT varied greatly, as did the proportion of women exposed throughout follow-up, with around 9% (n = 1766) exposed in 1993, almost 15% (n = 3980) in 2002 and 13% (n = 2970) in 2013 (Fig. 1). Mean (standard deviation, max) WTN levels amongst exposed nurses were 26.1 (6.4, 59.4) dB in 1993, 26.3 (7.1, 60.7) dB in 2002, and 26.4 (6.6, 53.6) dB in 2013 (Fig. 1). At the cohort baseline in 1993 or 1999, mean (standard deviation, max) baseline residential noise levels amongst exposed nurses were slightly higher in those who developed AF (27.3 dB (7.3, 45.9)) than in those who didn't develop AF (26.2 dB (6.6, 59.4)) (Table 1).

Table 1

Characteristics of the Danish Nurse Cohort (n = 24,137) at baseline (1993 and 1999) by incident AF status at end of follow-up (31 December 2013).

Baseline characteristics	Total n = 24,137	AF event (yes) n = 1430	AF event (no) n = 22,707
Age, years, mean (SD)	53.3 (8.1)	58.2 (9.0)	53.0 (8.0)
Birth cohort			
< 1930, n (%)	5741 (23.8)	670 (46.9)	5071 (22.3)
1930–1940, n (%)	7276 (30.1)	455 (31.8)	6821 (30.0)
1940–1950, n (%)	6002 (24.9)	193 (13.5)	5809 (25.6)
≥1950, n (%)	5118 (21.2)	112 (7.8)	5006 (22.0)
BMI, kg/m^2, mean (SD)	23.7 (3.5)	24.6 (4.1)	23.7 (3.5)
Underweight (BMI < 18.5 kg/m^2), n (%)	604 (2.5)	38 (2.7)	566 (2.5)
Normal (BMI 18.5–25 kg/m^2), n (%)	16,465 (68.2)	837 (58.5)	15,628 (68.8)
Overweight (BMI 25–30 kg/m^2), n (%)	5460 (22.6)	388 (27.2)	5072 (22.3)
Obese (BMI > 30 kg/m^2), n (%)	1357 (5.6)	141 (9.9)	1216 (5.4)
Missing, n (%)	251 (1.0)	26 (1.8)	225 (1.0)
Smoking[a]			
Never smoked, n (%)	8591 (35.6)	476 (33.3)	8115 (35.7)
Previously smoked, n (%)	7275 (30.1)	454 (31.7)	6821 (30.0)
Current smoker, n (%)	8271 (34.3)	500 (35)	7771 (34.2)
Smoking pack–days, mean (SD)	16.3 (14.8)	18.6 (17.2)	16.2 (14.6)
Alcohol consumption			
Never consumes alcohol, n (%)	3746 (15.5)	281 (19.6)	3465 (15.3)
Alcohol consumption[b] (g/week), mean (SD)	114.6 (127.1)	107.3 (126.8)	115.0 (127.2)
Physical activity			
Low physical activity, n (%)	1614 (6.6)	109 (7.6)	1505 (6.6)
Medium physical activity, n (%)	16,085 (66.6)	965 (67.4)	15,120 (66.6)
High physical activity, n (%)	6438 (26.7)	356 (24.9)	6082 (26.8)
Diet			
Regularly eat fruit, n (%)	16,400 (67.90)	1010 (70.6)	15,390 (67.8)
Avoid fatty meat, n (%)	21,842 (90.5)	1266 (88.5)	20,5876(90.6)
Hypertension, n (%)	3149 (13.0)	314 (22.0)	2835 (12.5)
Missing, n (%)	22 (0.1)	2 (0.1)	20 (0.1)
Diabetes, n (%)	290 (1.2)	19 (1.3)	271 (1.2)
Missing, n (%)	162 (0.7)	8 (0.6)	154 (0.7)
Use of hormone therapy			
Ever, n (%)	6620 (27.4)	511 (35.7)	6109 (26.9)
Use of oral contraceptives			
Ever, n (%)	14,159 (58.7)	619 (43.3)	13,540 (59.6)
Living in			
Urban Area, n (%)	3565 (14.8)	214 (15.0)	3351 (14.8)
Rural, n (%)	9716 (40.3)	594 (41.5)	9122 (40.2)
Provincial, n (%)	10,218 (42.3)	561 (39.2)	9657 (42.5)
Missing, n (%)	638 (2.6)	61 (4.3)	577 (2.5)
Marital status			
Married, n (%)	17,030 (70.6)	915 (63.9)	16,115 (71.0)
Separated, n (%)	397 (1.6)	19 (1.3)	378 (1.7)
Divorced, n (%)	2678 (11.1)	156 (10.9)	2522 (11.1)
Single, n (%)	2405 (10.0)	178 (12.4)	2227 (9.8)
Widow, n (%)	1627 (6.7)	162 (11.3)	1462 (6.5)
Employment status			
Employed, n (%)	18,845 (78.1)	872 (60.9)	17,973 (79.1)
Homemaker and others, n (%)	435 (1.8)	29 (2.0)	406 (1.8)
Retired, n (%)	4478 (18.6)	520 (36.4)	3958 (17.4)
Unemployed, n (%)	161 (0.7)	6 (0.4)	155 (0.7)
Other, n (%)	218 (0.9)	3 (0.2)	215 (0.9)
Night shift work			
Day	11,825 (49.0)	525 (36.7)	11,300 (49.8)
Evening	1911 (7.9)	100 (7.0)	1811 (8.0)
Night	1055 (4.4)	71 (5.0)	984 (4.3)
Rotating	4139 (17.1)	175 (12.2)	3964 (17.5)
Missing, n (%)	5207 (21.6)	559 (39.1)	4648 (20.5)
Municipality annual income (DKK)[c], mean (SD)	164,432 (24,807)	162,892 (23,745)	164,474 (24,834)
Missing, n, (%)	638 (2.6)	61 (4.3)	577 (2.5)
Annual air pollution, NOx (µg/m^3), mean(SD)	19.2 (24.5)	20.1 (23.3)	19.1 (24.5)
Annual traffic noise, dB, (mean, SD)	52.8 (8.2)	53.1 (7.8)	52.8 (8.2)
Wind-turbine noise, dB, (mean, SD)[d]	26.3 (6.7)	27.3 (7.3)	26.2 (6.6)
Unexposed, n (%)	21,618 (89.6)	1307 (91.4)	20,311 (89.4)
< 21.6 dB, n (%)	652 (2.7)	28 (2.0)	624 (2.7)
21.6–25.4 dB, n (%)	609 (2.5)	29 (2.0)	580 (2.6)
25.4–29.9 dB, n (%)	624 (2.6)	26 (1.8)	598 (2.6)
> 29.9 dB, n (%)	634 (2.6)	40 (2.8)	594 (2.6)

SD: standard deviation. BMI: body mass index. DKK: Danish crown.

  [a] Amongst ever smokers.

  [b] Amongst alcohol consumers.

  [c] Average annual gross income at the municipality level.

  [d] Amongst nurses exposed to wind turbine noise, based on the noise contribution from all WTs within a 6000 meter radius of the nurse's home. Unexposed nurses have not lived in proximity of a wind turbine within the rolling mean window.
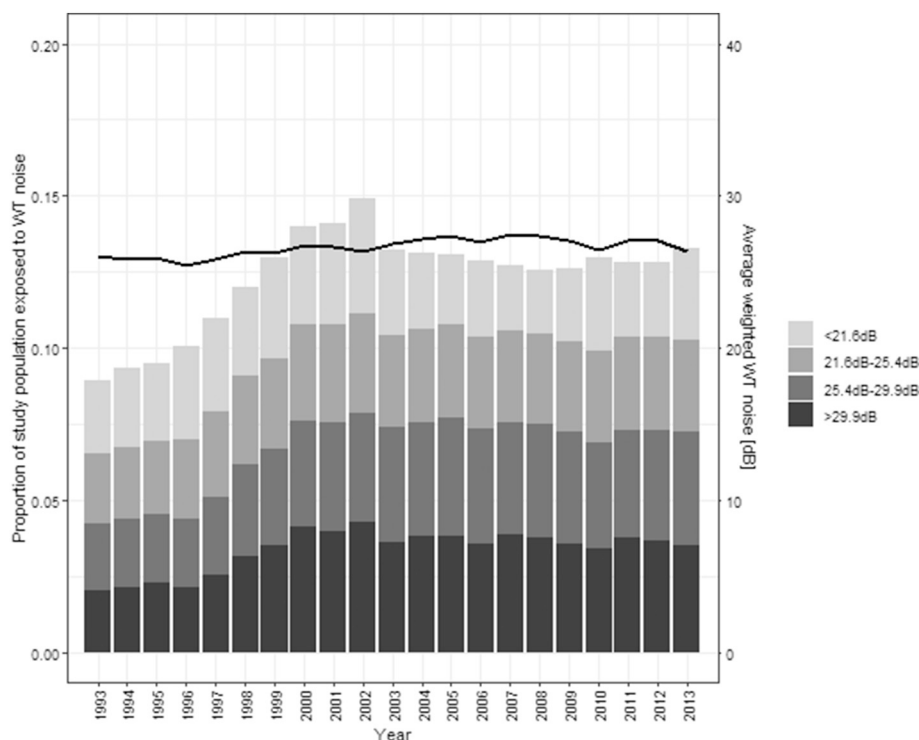
Fig. 1. Average weighted L_{den} for wind turbine noise exposure per year (right axis) and proportion of women living at wind turbine noise exposed addresses (left axis).

Compared to 21,618 nurses unexposed to WTN at the cohort base-line, the 2519 exposed nurses were slightly younger, had higher BMI, smoked less, were less physically active, had slightly higher rates of diabetes and oral contraceptive use, but lower HT use, tended to still be working, lived in rural rather than urban areas, had slightly lower in-comes, were exposed to half the levels of NO_x traffic related air pollu-tion and lower annual levels of weighted road traffic noise but were similar in regards to hypertension, avoiding consumption of fatty meats, fruit consumption, and diabetes rates (supplementary informa-tion, Table S1). Amongst the nurses unexposed at cohort baseline, 1307 developed AF during the 367,229 person-years, with an incidence rate of 3.6 per 1000 person-years while 123 of the nurses exposed at cohort baseline developed AF within 42,080 person-years, with an incidence rate of 2.9 per 1000 person-years (supplementary information, Table S1).

The relationship between WTN exposure and AF was characterized by a non-linear non-monotonic pattern means without strong evidence of an exposure-response relationship (cf. Fig. 2 for 11-year, 5-year, and 1-year rolling means).

When assessing the effects of the 11-year rolling mean night ex-posure to WTN (L_n), we found a 30% statistically significant increased risk of AF (95% CI: 1.05–1.61) comparing $\geq$ to < 20 dB(A) exposure, and similar effects for evening (L_e) (HR: 1.25; 95% CI: 1.01–1.54) and day (L_d) (HR: 1.24; 95% CI: 1.00–1.53) exposure, as well as for overall 24-h un-weighted mean (L_{24}) (HR: 1.27; 95% CI: 1.03–1.57). The overall associations between the overall weighted 24-hr exposure, L_{den} WTN and AF was not significant when comparing women exposed to levels of noise $\geq$ 20 dB(A) to those exposed to levels < 20 dB(A), with adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of 1.01 (0.85–1.19), 1.05 (0.89–1.23) and 1.10 (0.93–1.30), for the 11-year, 5-year and 1-year rolling mean preceding diagnosis, respectively (Table 2).

3.1. Identification of confounders, mediators and effect modifiers

The effect of the included a-priori selected confounders (smoking,

alcohol, physical activity, diet, oral contraceptives, hormone therapy, employment status, marital status) in Model 2 compared to the crude model was very minor and HRs were slightly amplified in the fully adjusted model (Table 2).

There was no evidence of attenuation by BMI, self-reported hy-pertension, diabetes or socio-economic status (municipal level gross average annual income as a proxy) in the sensitivity analyses with no marked deviation from the main model 2 (Table 2, models 3–6).

There was evidence of effect modification by age with a higher risk of AF amongst nurses above 60 years of age, but none by obesity, road traffic noise, road traffic pollution or urbanicity index (Table 3).

3.2. Competing risk by non-AF death

The number of competing events (non-AF death) within the cohort during follow-up was high (n = 3661), compared to the outcome of interest (AF, n = 1430), but when assessing competing risk in model 2 (the main model), we observed no association between WTN exposure and non-AF death in our data. Thus, there is no evidence that death is a competing event potentially masking the association of interest in this study.

4. Discussion

The results from this first nationwide, prospective cohort study of Danish female nurses assessing the relationship between WTN exposure and AF offer suggestive evidence of an association.

We used a large nationwide prospective cohort with a re-presentative distribution of present and historical addresses around entire Denmark and benefited from objective assessment of AF in-cidence based on high quality Danish registries with near 100% cov-erage (Helweg-Larsen, 2011; Lynge et al., 2011; Schmidt et al., 2015), as well as detailed information on AF risk factors. This assessment implies minimal possibility of recall and information bias and no se-lection bias. We furthermore benefited from the state-of-the-art high-resolution validated exposure models for WT and road traffic noise
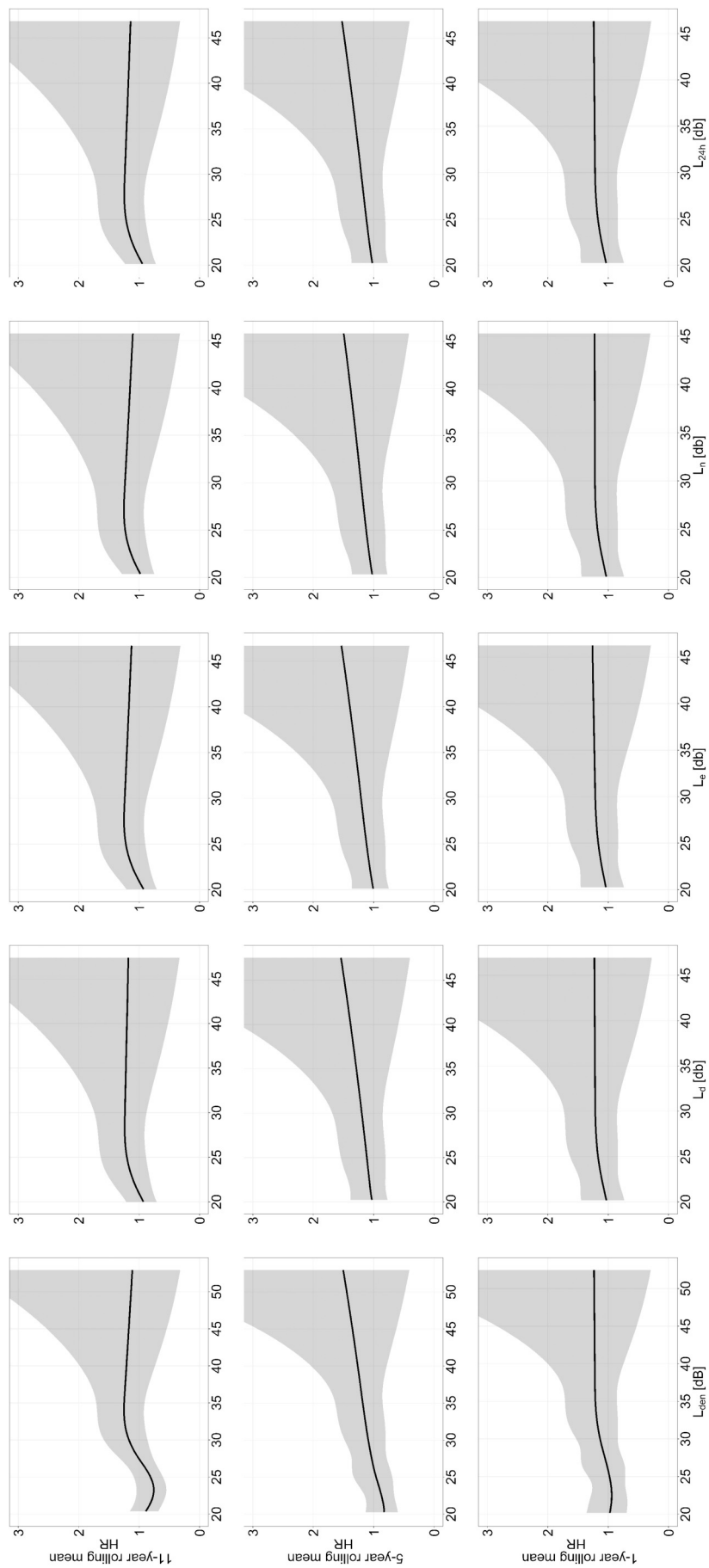
Fig. 2. Exposure-response curves (filled lines; 95% CIs indicated by dashed lines) between AF and 11, 5, and 1-y wind turbine (L_{den}, L_d, L_e and L_n) noise exposure at residences from 1982 onwards, based on fully adjusted model. The reported HR is based on unexposed nurses as reference.

Table 2

Association between weighted wind-turbine noise L$_{den}$ and atrial fibrillation incidence (n = 1430) amongst 24,137 Danish Nurse Cohort participants, considering the 1-, 5- and 11-year rolling means prior to diagnosis/censoring.

	Person-years (PY)	N cases	Incidence rate per 1000 PY	Model 1[a] HR (95% CI)	Main model Model 2[b] HR (95% CI)	Model 3[c] HR (95% CI)	Model 4[d] HR (95% CI)	Model 5[e] HR (95% CI)	Model 6[f] HR (95% CI)
1. Lden									
L$_{den}$ 11-year rolling mean									
< 20 dB(A)	363,371	1269	3.49	1	1	1	1	1	1
≥ 20 dB(A)	45,937	161	3.50	1.00 (0.85–1.18)	1.01 (0.85–1.19)	0.99 (0.84–1.17)	1.00 (0.85–1.19)	1.00 (0.85–1.19)	1.01 (0.85–1.20)
L$_{den}$ 5-year rolling mean									
< 20 dB(A)	363,478	1271	3.50	1	1	1	1	1	1
≥ 20 dB(A)	45,831	159	3.47	1.04 (0.88–1.23)	1.05 (0.89–1.23)	1.03 (0.87–1.22)	1.04 (0.88–1.23)	1.05 (0.88–1.24)	1.04 (0.88–1.23)
L$_{den}$ 1-year rolling mean									
< 20 dB(A)	364,877	1271	3.48	1	1	1	1	1	1
≥ 20 dB(A)	44,432	159	3.58	1.09 (0.93–1.29)	1.10 (0.93–1.30)	1.09 (0.92–1.28)	1.10 (0.93–1.30)	1.10 (0.93–1.30)	1.10 (0.93–1.30)
2. Lnight									
L$_{night}$ 11-year rolling mean									
< 20 dB(A)	388,231	1337	3.44	1	1	1	1	1	1
≥ 20 dB(A)	21,078	93	4.41	1.28 (1.04–1.58)	1.30 (1.05–1.61)	1.27 (1.02–1.57)	1.29 (1.05–1.60)	1.29 (1.05–1.60)	1.31 (1.06–1.62)
L$_{night}$ 5-year rolling mean									
< 20 dB(A)	386,742	1342	3.47	1	1	1	1	1	1
≥ 20 dB(A)	22,566	88	3.90	1.18 (0.95–1.47)	1.19 (0.96–1.48)	1.16 (0.93–1.45)	1.19 (0.95–1.48)	1.19 (0.96–1.48)	1.19 (0.96–1.49)
L$_{night}$ 1-year rolling mean									
< 20 dB(A)	386,291	1342	3.47	1	1	1	1	1	1
≥ 20 dB(A)	23,017	88	3.82	1.19 (0.96–1.47)	1.20 (0.97–1.49)	1.17 (0.94–1.45)	1.20 (0.96–1.49)	1.20 (0.96–1.49)	1.20 (0.96–1.50)
3. Levening									
L$_{evening}$ 11-year rolling mean									
< 20 dB(A)	387,217	1336	3.45	1	1	1	1	1	1
≥ 20 dB(A)	22,092	94	4.25	1.23 (1.00–1.52)	1.25 (1.01–1.54)	1.21 (0.98–1.50)	1.24 (1.00–1.53)	1.24 (1.00–1.53)	1.24 (1.00–1.54)
L$_{evening}$ 5-year rolling mean									
< 20 dB(A)	385,645	1341	3.48	1	1	1	1	1	1
≥ 20 dB(A)	23,662	89	3.76	1.13 (0.91–1.40)	1.15 (0.92–1.42)	1.11 (0.89–1.38)	1.14 (0.92–1.42)	1.14 (0.92–1.42)	1.14 (0.92–1.42)
L$_{evening}$ 1-year rolling mean									
< 20 dB(A)	385,319	1340	3.48	1	1	1	1	1	1
≥ 20 dB(A)	23,989	90	3.75	1.16 (0.94–1.44)	1.17 (0.95–1.45)	1.14 (0.91–1.41)	1.17 (0.94–1.45)	1.17 (0.94–1.45)	1.17 (0.94–1.46)
4. Lday									
L$_{day}$ 11-year rolling mean									
< 20 dB(A)	386,908	1336	3.45	1	1	1	1	1	1
≥ 20 dB(A)	22,401	94	4.20	1.22 (0.99–1.51)	1.24 (1.00–1.53)	1.21 (0.98–1.49)	1.23 (1.00–1.52)	1.23 (1.00–1.53)	1.23 (1.00–1.53)
L$_{day}$ 5-year rolling mean									
< 20 dB(A)	385,549	1340	3.48	1	1	1	1	1	1
≥ 20 dB(A)	23,760	90	3.79	1.15 (0.93–1.43)	1.17 (0.94–1.44)	1.14 (0.91–1.41)	1.16 (0.93–1.44)	1.16 (0.94–1.44)	1.16 (0.94–1.45)
L$_{day}$ 1-year rolling mean									
< 20 dB(A)	385,355	1339	3.47	1	1	1	1	1	1
≥ 20 dB(A)	23,953	91	3.80	1.19 (0.96–1.47)	1.20 (0.97–1.48)	1.17 (0.94–1.45)	1.19 (0.96–1.48)	1.20 (0.96–1.48)	1.20 (0.97–1.49)
5. L$_{24}$ (unweighted)									
L$_{24}$ 11-year rolling mean									
< 20 dB(A)	387,564	1337	3.45	1	1	1	1	1	1
≥ 20 dB(A)	21,877	94	4.30	1.25 (1.01–1.54)	1.27 (1.03–1.57)	1.24 (1.00–1.53)	1.26 (1.02–1.56)	1.26 (1.02–1.56)	1.26 (1.02–1.56)

Table 2 (continued)

	Person-years (PY)	N cases	Incidence rate per 1000 PY	Model 1[a] HR (95% CI)	Main model Model 2[b] HR (95% CI)	Model 3[c] HR (95% CI)	Model 4[d] HR (95% CI)	Model 5[e] HR (95% CI)	Model 6[f] HR (95% CI)
L_{24} 5-year rolling mean									
< 20 dB(A)	386,134	1342	3.48	1	1	1	1	1	1
≥ 20 dB(A)	23,306	89	3.83	1.16 (0.93–1.43)	1.17 (0.94–1.45)	1.14 (0.92–1.42)	1.16 (0.94–1.44)	1.17 (0.94–1.45)	1.17 (0.94–1.45)
L_{24} 1-year rolling mean									
< 20 dB(A)	385,810	1341	3.48	1	1	1	1	1	1
≥ 20 dB(A)	23,630	90	3.81	1.19 (0.96–1.47)	1.20 (0.97–1.48)	1.16 (0.94–1.45)	1.19 (0.96–1.48)	1.19 (0.96–1.48)	1.20 (0.96–1.49)

HR: hazard ratio; CI: confidence intervals.

[a] Adjusted for age (underlying timeline) and calendar year at entrance into the cohort.

[b] Main model, as for model 1[a] + smoking (status, pack-years), alcohol consumption, physical activity, avoid fatty meat consumption, fruit consumption, use of oral contraceptives, use of hormone therapy, marital status, employment status.

[c] As for model 2[b] + body mass index; Note that the number of nurses in this analysis is different from model 2 due to missing information on body mass index.

[d] As for model 2[b] + self-reported hypertension at baseline; Note that the number of nurses in this analysis is different from model 2 due to missing information on self-reported hypertension at baseline.

[e] As for model 2[b] + self-reported diabetes at baseline. Note that the number of nurses in this analysis is different from model 2 due to missing information on self-reported diabetes at baseline.

[f] As for model 2[b] + gross annual average income at the municipality level at baseline. Note that the number of nurses in this analysis is different from model 2 due to missing information on gross average income at the municipality level at baseline.

(Backalarz et al., 2016; Kragh et al., 2001; Søndergaard et al., 2009) as well as air pollution (Kakosimos et al., 2010; Ketzel et al., 2011), which were based on geocodes and also accounted for all address changes, meteorological conditions as well as the size and the type of WTs.

Another large Danish cohort study has previously investigated the association between long-term noise exposure from road traffic and AF (Monrad et al., 2016). That study was based on over 50,000 men and women, participants of the Danish Diet, Cancer and Health cohort, recruited from general population, from the two largest cities in Denmark (Copenhagen and Aarhus), and found a 6% increased risk (95% CI 1.00–1.12) associated with each 10 dB increase in road traffic noise and a dose-response effect. But after adjusting for air pollution the association was attenuated and without statistical significance. In other words, the association between traffic noise and AF seems to have been largely explained by the association with air pollution, which is a closely related exposure to road traffic noise, as the two share a major source, thus making it difficult to separate effects of noise from those of air pollution. Unlike traffic noise exposure, WTN is not correlated with particulate or gaseous oxidative stressors that are considered risk factors and relevant mediators for cardiovascular endpoints.

The mechanisms of the association between environmental noise and cardiovascular outcomes, including AF are not fully elucidated but according to early work by Babisch et al. (2013) the noise stress reaction is thought to have two pathways; the first being direct effects of noise on the central auditory and nervous system and the second being an indirect non-auditory pathway mediated by annoyance. In our present study, we did not have any measures of annoyance effects amongst the nurses. However, annoyance is the most plausible explanation for the associations we observe. This has recently been reported in a cross-sectional study assessing the association between day and night-time noise (industrial, traffic (air, road, train) and neighborhood) annoyance and AF within the German Gutenberg Health Study, on 14,639 participants (Hahad et al., 2018). Although they did not have data on annoyance by WTN, a review of three cross-sectional studies, found that annoyance was consistently directly associated with WTN, but that no other measure of health or wellbeing (e.g. headache, tiredness, sleep disturbance) was consistently related to sound pressure levels (Pedersen, 2011). In another previous study, annoyance was reported to be strongly correlated with a negative attitude toward the visual impact of WTs on the landscape, and the authors further demonstrate that people who benefit economically from WTs have a significantly decreased risk of annoyance, despite exposure to similar sound levels (Pedersen et al., 2009), as replicated in more recent studies (Jalali et al., 2016a, 2016b; Janssen et al., 2011). This supports the concept that annoyance due to visual rather than auditory aspects is the underlying cause (indirect effects) via stress and sleep disturbance mediated pathways (Pedersen et al., 2009).

We found a significant effect of exposure to WTN above 20 dB compared to < 20 dB at night. We acknowledge that noise levels below 20 dB and probably not able to cause sleep disturbance, but if real this implies that night exposure to WTN is important in the causal pathway. This is plausible as the second mechanism involved in the effects of noise exposure relate to indirect noise-induced sleep disturbances, which are proposed pathways implicated in the development of metabolic changes (Munzel et al., 2017a, 2017b, 2017c). Transportation noise has been consistently associated with both self-reported and measured sleep disturbances and we expect similar disturbance could occur according to WTN (Miedema and Vos, 2007; Pirrera et al., 2010). Sleep has a regulatory influence on the immune system (Ali and Orr, 2014; Gomez-Gonzalez et al., 2012) and disturbed sleep has been associated with systemic impairment of the immune system. Sleep disturbances are similarly associated with impairment of the immune system, including changes in circulating white blood cells and increases in pro-inflammatory molecules (Aho et al., 2013; Irwin et al., 2016) that are on the causal pathway to AF. Notably, our results suggesting a strong association between nighttime WTN and AF, are supported by a

Table 3
Modification of association[a] within population of exposed Nurses between incidence of atrial fibrillation and wind-turbine noise (11-year rolling mean per 10 dB(A)) by baseline characteristics and co-morbid conditions amongst 24,137 female participants in the Danish Nurse Cohort.

Covariate		N (cases)[b]	HR (95%CI)	P[c]
Age	< 60 years	44	0.74 (0.51–1.06)	0.26
	≥ 60 years	203	1.01 (0.84–1.21)	
BMI	< 25 kg/m^2	143	0.87 (0.70–1.07)	0.62
	≥ 25 kg/m^2	102	1.01 (0.79–1.31)	
Traffic noise (dB)	< 53.7 dB	145	0.91 (0.73–1.12)	0.41
	≥ 53.7 dB	97	1.04 (0.80–1.36)	
Traffic air pollution (NOx)	< 15.2 µg/m^3	154	1.01 (0.82–1.25)	0.04*
	≥ 15.2 µg/m^3	84	0.89 (0.68–1.17)	
Night shift	Night only	12	0.83 (0.40–1.74)	0.94
	Day, evening, rotating	149	0.82 (0.67–1.00)	
Level of urbanization	Urban	6	1.23 (0.35–4.37)	0.55
	Rural	174	0.87 (0.72–1.06)	
	Provincial	63	1.12 (0.81–1.56)	

HR: hazard ratio; CI: confidence interval.
  [a] Adjusted for age, calendar year at entrance into the cohort, smoking (status, pack-years), alcohol consumption, physical activity, avoid fatty meat consumption, fruit consumption, use of oral contraceptives, use of hormone therapy, marital status, employment status. However, with no adjustment for the modification variable.
  [b] Note that the number of nurses and cases in these analyses are different from the main model 2 due to missing information on BMI, traffic noise, traffic air pollution, night shift and level of urbanization (cf. Table 1).
  [c] From likelihood ratio test for interaction, test of the null hypothesis that linear trends are identical.

recent study of noise annoyance and AF, where the authors report that annoyance due to noise at night was most strongly associated with AF prevalence (Hahad et al., 2018). However, although we find strongest effects with exposure to WTN at night, we note that estimated exposure to L_{24}, L_{day}, L_e and L_n are all highly correlated, limiting our ability to distinguish between which exposure window is most relevant. Because we also found associations with evening and day exposure, this implies that exposure to noise at any time is likely relevant for development of AF.

In the present study, we found that the WTN levels were relatively low. Only around 13% of nurses were exposed, defined as living within a 6000-m radius of one or more WTs as a large proportion of the included nurses had never lived in proximity of a WT and only 3% of all nurses were exposed to levels over 29.9 dB(A) throughout follow-up. According to the World Health Organization it is not plausible that noise levels at and below 30 dB(A) would cause sleep disturbances, and that only modest health effects would be expected at and below 40 dB(A) (WHO and Regional Office for Europe, 2011). In the most recent environmental guidelines for the European Union, the WHO conditionally recommends that WT L_{den} levels should be reduced to below 45 dB(A) (WHO Regional Office for Europe, 2018), much in line with the limits set by the Danish Environmental Protection Agency; of 44 dB(A) (wind speed of 8 m/s) and 42 dB(A) (wind speed of 6 m/s) for dwellings in open country (Statutory Order no.1284 of 15.December 2011, 2011). This may imply that our findings were chance and that the noise levels in our study may not have induced intermediates (high blood pressure, sleep disturbance, etc.) previously reported to be on the causal pathway from noise exposure to AF (Babisch et al., 2006; Munzel et al., 2017a, 2017b, 2017c), and direct auditory effects leading to AF at these levels are not expected (Munzel et al., 2017b). These levels of WTN are also substantially lower than road traffic noise levels within the same cohort, which were over 50 dB(A) in average, noting that a 20 dB(A) difference between these two sources of noise levels is perceived as around four times the loudness, due to the logarithmic scale of sound (Stevens, 1955).

We found no evidence of confounding of the relationship between WTN and AF in the present study, implying a robust estimate. Although valid, the information on confounding and effect mediating variables were collected at cohort baseline, and we acknowledge that these may have changed throughout the 20-year average follow-up time.

The main limitation in our present study is the exposure misclassification in modelled WTN concentrations since these are only proxies of personal exposure. Although our estimation of WTN exposure is based on complete residential histories, we cannot account for exposures via temporary migration to other destinations, at work in other regions in Denmark or whilst overseas in areas with either higher or lower noise exposures. Also, we had no access to individual information related to bedroom orientation to the closest WT or noise exposure moderators such as façade insulation measures, window types. Finally, the A-weighted nature of our estimates is not informative about any peaking characteristics of the WTN throughout follow up. So although, the average A-weighted WTN levels we report are in fact in accordance with the noise limits for WTs as specified by statutory order of the Danish Environmental Protection Agency (Statutory Order no.1284 of 15.December 2011, 2011), there may have been peaks we didn't address.

Another major weakness of our study is a small number of AF cases exposed to high levels of WTN, limiting the power to detect effects in this range of noise exposure. We did not have information on individual-level exposure or exposure modifiers, such as bedroom location within the residence, use of earplugs, or window or other insulating materials, and cannot rule out instances of exposure misclassification. Furthermore, we had no available information on personal sensitivity to noise, levels of annoyance or sleep quality, which have all been reported to be on the casual pathway between noise exposure and health effects (Bakker et al., 2012; Hanning and Evans, 2012; Kuwano et al., 2014; McCallum et al., 2014; Shepherd et al., 2011). Albeit, these self-reports may have introduced bias as they include highly motivated persons with possible negative attitudes to WTs which have been repeatedly reported to play an important role as the underlying cause of reported health and sleep problems (Blanes-Vidal and Schwartz, 2016; Knopper et al., 2014; Pedersen, 2011; Pedersen et al., 2009). In our study, it was not feasible to consider all noise sources including noise from neighbors, bedroom snoring, aircraft, railways, industrial noise, and ventilation nor did we have estimates of indoor WTN exposure. Selander et al. (2009) found increased effects estimates of noise in relation to AF when excluding all those exposed to other noise sources as well as hearing impaired persons. Hence, we may have underestimated the effects of WTN in our present study. Another weakness is that we lacked data on personal and household income, important determinants of socio-economic status. Finally, we only consider women, and are thus unable to account for eventual differences in effect according to gender, albeit the effects of gender do remain unclear with some studies showing stronger effects amongst men

(Babisch et al., 2005; Huss et al., 2010; Jarup et al., 2008) and others reporting no difference in gender (Beelen et al., 2009; Selander et al., 2009; Sorensen et al., 2011).

5. Conclusions

We found suggestive evidence of an association between long-term exposure to WTN and AF amongst in women above age 44. This should be interpreted with caution as levels of WTN exposure were low and direct auditory effects leading to AF are not expected.

Declaration of Competing Interest

None.

Author contribution statement

EVB drafted the manuscript. AKD performed statistical analyses and contributed to the manuscript preparation. ZJA contributed to the concept and design for the study, secured funding, prepared data for analyses, and supervised AKD in statistical analyses. JTJ contributed with data clean-up. MKS provided all nurse cohort data. CB, JEL and THP calculated all WTN estimations and provided expertise on noise and sound. All authors contributed to critical interpretation of data, and the final draft of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.104915.

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