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*Published in:*  
Journal of the American Heart Association

*DOI:*  
[10.1161/JAHA.119.013157](https://doi.org/10.1161/JAHA.119.013157)

*Publication date:*  
2019

*Document version*  
Publisher's PDF, also known as Version of record

*Document license:*  
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*Citation for published version (APA):*  
Bräuner, E. V., Jørgensen, J. T., Duun-Henriksen, A. K., Backalarz, C., Laursen, J. E., Pedersen, T. H., ... Andersen, Z. J. (2019). Association Between Long-Term Exposure to Wind Turbine Noise and the Risk of Stroke: Data From the Danish Nurse Cohort. *Journal of the American Heart Association*, 8(14), [e013157]. <https://doi.org/10.1161/JAHA.119.013157>

# Association Between Long-Term Exposure to Wind Turbine Noise and the Risk of Stroke: Data From the Danish Nurse Cohort

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**Background**—Epidemiological studies suggest that road traffic noise increases the risk of stroke. Similar effects may be expected from wind turbine noise (WTN) exposure, but epidemiological evidence is lacking. The present study investigated the association between long-term exposure to WTN and the risk for stroke.

**Methods and Results**—First-ever stroke in 28 731 female nurses in the Danish Nurse Cohort was identified in the Danish National Patient register until the end of 2013. WTN, traffic noise, and air pollution exposures were estimated for all historic and present residential addresses between 1982 and 2013. Time-varying Cox proportional hazard regression was used to examine the associations between the 11-, 5-, and 1-year rolling means of WTN levels and stroke incidence. Of 23 912 nurses free of stroke at the cohort baseline, 1097 nurses developed stroke by the end of follow-up. At the cohort baseline, 10.3% of nurses were exposed to WTN ( $\geq 1$  turbine within a 6000-meter radius of the residence) and 13.3% in 2013. Mean baseline residential noise levels among exposed nurses were 26.3 dB(A). No association between long-term WTN exposure and stroke incidence was found. The adjusted hazard ratios and 95% CIs for the 11-, 5-, and 1-year running mean residential WTN exposures preceding stroke diagnosis, comparing nurses with residential WTN levels above and below 20 dB(A) were 1.09 (0.90–1.31), 1.08 (0.89–1.31) and 1.08 (0.89–1.32), respectively.

**Conclusions**—This comprehensive cohort study lends no support to an association between long-term WTN exposure and stroke risk. (*J Am Heart Assoc.* 2019;8:e013157. DOI: 10.1161/JAHA.119.013157.)

**Key Words:** Danish Nurse Cohort • environmental long-term wind turbine exposure • epidemiology • prospective cohort study • stroke

Stroke is a major cause of disability and death in adults, and it is estimated that 5.8 million people die from stroke globally every year.<sup>1</sup> Exposure to persistent environmental noise is thought to increase the risk of cardiovascular disease and several epidemiological studies have implicated traffic noise (road, rail, and air) as a risk factor for increased

stroke incidence, particularly in the elderly.<sup>2,3</sup> The effects of wind turbine noise (WTN) on stroke may be similar, but this has only been investigated once.<sup>4</sup> Although the authors report a protective effect of WTN exposure in that study, they state that this should be interpreted with caution, as results were based on a small number of cases. WTN has consistently been associated with annoyance and reported to affect sleep in some studies.<sup>5–7</sup> Thus, WTN exposure is believed to act as a stressor with activation of the hypothalamus-pituitary-adrenal axis and stress response cascade,<sup>8</sup> and noise has been shown to induce systemic low-grade inflammation<sup>9</sup>; finally, the cortisol released in the stress reaction cascade may increase blood glycogen within atrial myocytes,<sup>10,11</sup> all of which are suggested risk factors for stroke.

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.<sup>12</sup> Denmark is one of the world leaders in total wind capacity, and in 2016 wind power represented 37.6% of Denmark's total electricity consumption,<sup>13</sup> and it is estimated that around 800 000 Danish homes ( $\approx 12\%$ ) are located within a 6000-meter radius of a wind turbine (WT). The Danish government has set a goal to generate 50% of the country's electricity by wind

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Accompanying Data S1, Tables S1 through S3, and Figure S1 are available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013157>

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Received May 2, 2019; accepted June 5, 2019.

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## Clinical Perspective

### What Is New?

- This large Danish study, including 24 000 Danish nurses followed for up to 20 years, is the first prospective cohort study examining the impact of long-term exposure to wind turbine noise and the risk of stroke.
- We found no evidence that long-term exposure to wind turbine noise increases the risk of stroke, in agreement with a single earlier study on the topic.

### What Are the Clinical Implications?

- While annoyance due to noise from wind turbines should be taken seriously, it is reassuring that this type of noise is unlikely to cause serious cerebrovascular disease such as stroke.

energy by 2021, implying a continued increase in the numbers and size of WTs, as well as in the proportion of the Danish population who live in close proximity to WTs.<sup>13</sup>

In 2016 the use of wind power avoided over 637 million tons of CO<sub>2</sub> emissions globally,<sup>14</sup> which has positive environmental and health implications. But despite this, WTs are also a source of environmental noise and the local-level potential risk to human health remains the subject of debate. Considering this debate and the continued increase in numbers of WTs, we aimed to elucidate the potential association between long-term exposure to WTN and risk of stroke, using a large, nationwide, prospective cohort of Danish nurses with long-term follow-up for stroke hospitalizations in high-quality and complete nationwide registries.

## Methods

### Study Population—The Danish Nurse Cohort

The study was based in the Danish Nurse Cohort, which was inspired by the American Nurses' Health Study to investigate the health effects of hormone replacement therapy (HRT) in a European population. The cohort has been described in detail previously,<sup>15</sup> and a detailed description is also provided in Data S1. In brief, the cohort was initiated in 1993 by sending a questionnaire to 23 170 nurses and reinvestigated in 1999. Information included socioeconomic 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, and use of oral contraceptives and HRT. In the present study, we used the earliest baseline information from 1993 (19 898 nurses) or 1999 (8833 nurses) for 28 731 nurses included in the cohort.

Since establishment of the Central Population Register in 1968,<sup>16,17</sup> 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<sup>16,17</sup> to obtain the nurses' vital status information at December 31, 2013 (active, date of death/emigration). Using the unique personal identification numbers 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 geographic coordinates in Denmark.

### Identification of Outcome—National Patient Register

The end point was incidence of stroke (*International Classification of Disease, Tenth Revision [ICD-10]*: D161, D163, and *ICD, Eighth Revision [ICD-8]*: 431.0, 431.9, 432.0, 432.9, 433.09, 433.99, 434.09, 436.0, and 436.9), defined as first-ever hospital contact (emergency, in- or outpatient) for stroke, identified in the Danish National Patient Registry.<sup>18,19</sup> The Danish National Patient Registry has collected nationwide data on all nonpsychiatric 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 ensures the quality of the data. Participants with a discharge diagnosis or self-report of stroke before enrollment into the Nurses Cohort were excluded.

### Exposure Assessment

#### Identification of Danish WTs

A total of 8768 onshore WTs in operation at any time in Denmark from 1982 to 2013 (offshore turbines were excluded; n=510) were identified, using the administrative Master Data Register of WTs maintained by the Danish Energy Agency.<sup>20</sup> It is mandatory for all WT owners to report to the register, which contains geographic coordinates, date of grid connection, cancellation date for decommissioned turbines, and output for each Danish power-producing WT. Further details on the identification are provided in Data S1.

#### WTN exposure data

The noise contribution from WTs at each nurse's home was calculated according to the Nord2000 method.<sup>21</sup> Sound power levels from WTs were calculated for each address for

the periods each cohort member had lived at the specific address. The model takes into consideration continuous meteorological data for each WT for the years 1982 through 2013. The applied noise exposure modeling has been described in detail elsewhere.<sup>21</sup> In brief, WTN exposure was estimated for all the different present and historic addresses at which the nurses had lived using the Nord2000 noise propagation model, which has been validated for WT and previously detailed.<sup>22,23</sup> Outdoor A-weighted sound pressure levels ( $LA_{eq}$ )—a metric commonly used in health studies, were calculated at the most exposed façade of all buildings within a 6000-meter radius. WTN exposure was aggregated as follows: day ( $L_d$ ; 07:00–19:00 hours), evening ( $L_e$ ; 19:00–22:00 hours), night ( $L_n$ ; 22:00–07:00 hours), expressed as  $L_{den}$  (the overall weighted 24-hour noise level during the day, evening [+5 dB], and night [+10 dB]), and  $L_{24h}$  (unweighted 24-hour average), as yearly averages. In this study we consider nurses who had at lived within a 6000-meter radius from at least 1 WT at some point of time in the period from January 1, 1982, to December 31, 2013, as exposed, and all others as unexposed to WTN.

### Air pollution and noise from road traffic

As previously described in detail,<sup>24,25</sup> we used the newly updated, high-resolution Danish air pollution dispersion modeling system (AirGIS) to estimate exposure to outdoor air pollution at the residence,<sup>26</sup> as annual mean levels of nitrogen oxide, road traffic–related pollutant, from 1982 to 2013. Road traffic noise at residential addresses of the nurses was estimated using the Nord2000 noise propagation 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 through 2013, as the equivalent continuous  $LA_{eq}$  at the most exposed façade of the dwelling for the  $L_d$ ,  $L_e$ ,  $L_n$ , and  $L_{den}$  as yearly averages.

### Statistical Analysis

We applied the Cox proportional hazards regression model to test the incidence of stroke 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 (April 1, 1993, or April 1, 1999), so nurses were considered at risk from recruitment, and end of follow-up was age at the date of first hospitalization discharge diagnosis of stroke, date of death,

emigration, or December 31, 2013, whichever came first. Nurses with a stroke 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 a priori selected potential confounding variables and risk factors for stroke: 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. The complete case analyses were considered valid, as we believe that the probability of being a complete case was independent of the outcome, given the covariates in Model 2.

We examined the following WTN exposures to assess chronic exposure using the 1-, 5-, and 11-year rolling mean during follow-up before diagnosis/censoring. In each rolling mean window, we considered  $L_d$ ,  $L_e$ ,  $L_n$ ,  $L_{den}$ , and  $L_{24h}$  separately. We used 2 categorical versions of WTN exposure: the first was our main exposure of interest with a cutoff at 20 dB, and the second was based on type-specific baseline quartiles, included for comparison with other studies. The cutoff at 20 dB was based on the rationale that in Denmark that low-frequency sound in the 10- to 160-Hz range is limited to an A-weighted level of 20 dB.<sup>27</sup> Furthermore, we modeled WTN as a continuous nonlinear (with a restricted cubic spline) and linear variable. The continuous variable reflects the relative increase in hazard for a 10-unit increase in exposure (10 dB) within the population of exposed nurses, and a 10-dB increase in noise level is equivalent to a subjective doubling in loudness.<sup>28</sup> WTN exposures were modeled as time-varying variables in all models. Further details of our statistical analysis are provided in Data S1. In brief, we carried out sensitivity analyses in separate models for possible mediators (body mass index, hypertension, diabetes mellitus, and socioeconomic status) and assessed potential effect modification (age, night-shift work, obesity, road traffic noise/nitrogen oxide traffic-related air pollution, and urbanicity index) and the competing effects of nonstroke death.

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

Research was conducted in accordance with the principles of the Declaration of Helsinki, and the Danish Nurse Cohort study was approved by the Scientific Ethics Committee for Copenhagen and Frederiksberg; written informed consent was

**Table 1.** Characteristics of the Danish Nurse Cohort (n=23 912) at Baseline (1993 and 1999) according to Incident Stroke (n=1097) Status at End of Follow-Up (December 31, 2013)

Baseline Characteristics Mean (SD) or n (%)	Total n=23 912	Stroke Event (Yes) n=1097	Stroke Event (No) n=22 815
Age, y, mean (SD)	53.3 (8.1)	60.3 (9.2)	52.9 (7.9)
Birth cohort			
<1930	5678 (23.7)	626 (57.1)	5052 (22.1)
1930–1940	7192 (30.1)	306 (27.8)	6886 (30.2)
1940–1950	5952 (24.9)	120 (10.9)	5832 (25.6)
≥1950	5090 (21.3)	45 (4.1)	5045 (22.1)
BMI, kg/m <sup>2</sup> , mean (SD)			
Underweight (BMI <18.5)	586 (2.4)	35 (3.2)	551 (2.4)
Normal (BMI 18.5–25)	16 323 (68.3)	713 (65.0)	15 610 (68.4)
Overweight (BMI 25–30)	5408 (22.6)	261 (23.8)	5147 (22.6)
Obese (BMI >30)	1350 (5.6)	64 (5.8)	1286 (5.6)
Missing	245 (1.0)	24 (2.2)	221 (1.0)
Smoking			
Never	8522 (35.6)	325 (29.6)	8197 (35.9)
Previous	7205 (30.1)	321 (29.3)	68 864 (30.2)
Current	8185 (34.2)	451 (41.1)	7734 (33.9)
Smoking pack-days, mean (SD)*	16.3 (14.8)	21.0 (19.3)	16.0 (14.5)
Alcohol consumption			
Never	3693 (15.4)	231 (21.1)	3462 (15.2)
Alcohol consumption <sup>†</sup> (g/wk), mean (SD)	114.4 (126.2)	105.2 (122.8)	114.8 (126.3)
Physical activity			
Low	1563 (6.5)	90 (8.2)	1473 (6.5)
Medium	15 958 (66.7)	769 (70.1)	15 189 (66.6)
High	6391 (26.7)	238 (21.7)	6153 (27.0)
Diet			
Regularly eat fruit	16 252 (68.0)	739 (67.4)	15 513 (68.0)
Avoid fatty meat	21 641 (90.5)	963 (87.8)	20 678 (90.6)
Hypertension	3072 (12.8)	251 (22.9)	2821 (12.4)
Missing	7 (0.03)	0 (0.00)	7 (0.03)
Diabetes mellitus	280 (1.2)	29 (2.6)	251 (1.1)
Missing	66 (0.3)	2 (0.2)	64 (0.3)
Use of hormone therapy			
Ever	6559 (27.4)	373 (34.0)	6186 (27.1)
Use of oral contraceptives			
Ever	14 036 (58.7)	395 (36.0)	13 641 (59.8)
Living in			
Urban area	3541 (14.8)	205 (18.7)	3336 (14.6)
Rural	9603 (40.1)	381 (34.7)	9222 (40.4)
Provincial	10 145 (42.4)	454 (41.1)	9691 (42.5)
Missing	623 (2.6)	57 (5.2)	566 (2.5)

Continued

Table 1. Continued

Baseline Characteristics Mean (SD) or n (%)	Total n=23 912	Stroke Event (Yes) n=1097	Stroke Event (No) n=22 815
<b>Marital status</b>			
Married	16 871 (70.6)	647 (59.0)	16 224 (71.1)
Separated	392 (1.6)	17 (1.5)	375 (1.6)
Divorced	2649 (11.1)	142 (12.9)	2507 (11.0)
Single	2395 (10.0)	156 (14.2)	2239 (9.8)
Widow	1609 (6.7)	135 (12.3)	1470 (6.4)
<b>Employment status</b>			
Employed	18 722 (78.3)	559 (51.0)	18 163 (79.6)
Homemaker and others	643 (2.7)	22 (2.0)	621 (2.5)
Retired	4386 (18.3)	509 (46.4)	3877 (17.0)
Unemployed	161 (0.7)	7 (0.6)	154 (0.7)
<b>Night-shift work</b>			
Day	11 747 (49.1)	338 (30.8)	11 409 (50.0)
Evening	1897 (7.9)	70 (6.4)	1828 (8.0)
Night	1046 (4.4)	56 (5.1)	990 (4.3)
Rotating	4115 (17.2)	96 (8.7)	4019 (17.6)
Missing	5107 (21.4)	537 (49.0)	4570 (20.0)
<b>Municipality annual income (DKK)<sup>‡</sup>, mean (SD)</b>			
Missing	623 (2.6)	2 (1.8)	621 (2.7)
<b>Annual air pollution, NO<sub>x</sub> (μg/m<sup>3</sup>), mean (SD)</b>			
Annual traffic noise, dB, mean (SD)	19.2 (24.5)	23.8 (31.1)	19.0 (24.1)
<b>WTN, dB, mean (SD)<sup>§</sup></b>			
Unexposed	26.3 (6.78)	26.2 (5.8)	26.3 (6.7)
<21.5 dB	21 427 (89.6)	1005 (91.6)	20 410 (89.5)
21.5–25.4 dB	622 (2.6)	24 (2.2)	598 (2.6)
25.4–29.9 dB	616 (2.6)	18 (1.6)	598 (2.6)
>29.9 dB	619 (2.6)	27 (2.5)	592 (2.6)
>29.9 dB	628 (2.6)	23 (2.1)	605 (2.7)

BMI indicates body mass index; DKK, Danish crown; NO<sub>x</sub>, nitrogen oxide; SD, standard deviation; WTN, wind turbine noise.

\*Among ever smokers.

†Among alcohol consumers.

‡Average annual gross income at the municipality level.

§Among nurses exposed to WTN.

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).

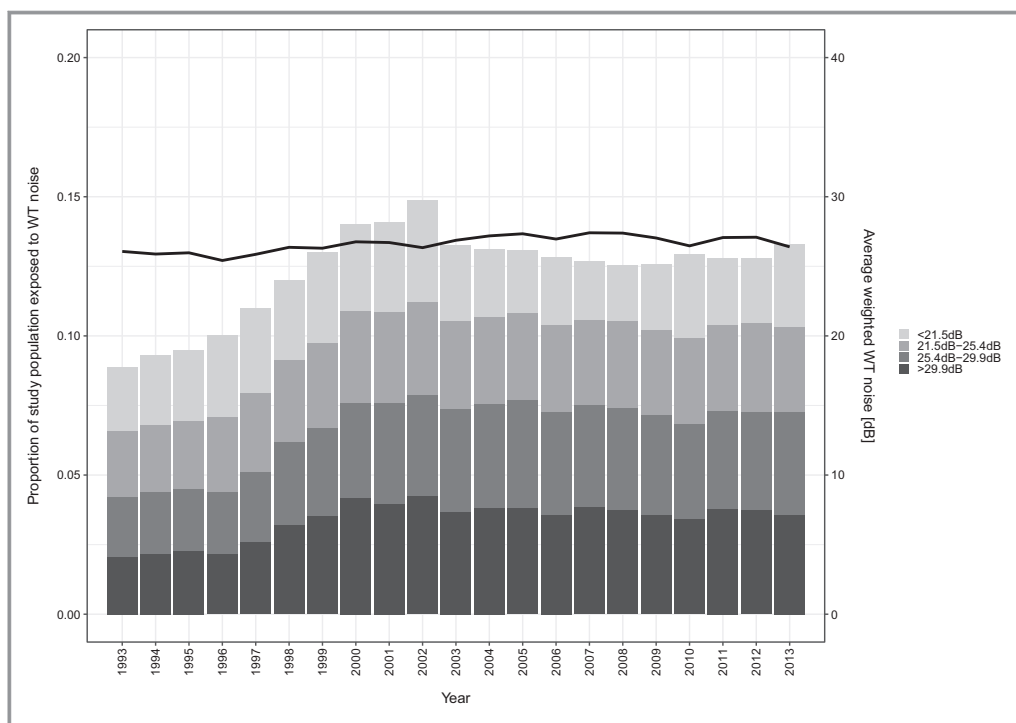
## Results

Of the total 28 731 recruited nurses in the Danish Nurse Cohort, we excluded 4819 because of death, missing geocodes, stroke prior to inclusion, or missing information on covariates, leaving 23 912 nurses for the final analyses.

The mean follow-up was 19.4 years, giving a total of 408 183 person-years of observations, during which 1097

nurses were registered with a hospital discharge for stroke, with an incidence rate of 2.7 new cases per 1000 person-years.

The nurses who were registered with stroke were over 7 years older on average; smoked more; consumed less alcohol; were less physically active; ate slightly more fatty meat; had higher rates of hypertension, diabetes mellitus, 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 nitrogen oxide traffic-related air pollution but around the same levels of annual weighted road traffic noise; and body mass index and fruit consumption at baseline than nurses who were not



**Figure.** Average weighted  $L_{den}$  for WTN exposure per year (right axis) and proportion of women living at WTN-exposed addresses (left axis). WTN indicates wind turbine noise.

registered with a hospital discharge diagnosis for stroke within the follow-up period. At baseline, the nurses registered with stroke were exposed to similar levels of WTN as those without stroke (Table 1).

Nurses from the Danish Nurse Cohort resided all around Denmark with wide geographic variation, with 14.8% residing in urban areas (population density  $\geq 5220$  people/km<sup>2</sup>), 42.4% in provincial towns (180–5220 people/km<sup>2</sup>), and 40.3% in rural areas (<180 people/km<sup>2</sup>) 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% ( $n=1734$ ) exposed in 1993, almost 15% ( $n=3943$ ) in 2002, and 13% ( $n=3009$ ) in 2013 (Figure). Mean (standard deviation) WTN levels among exposed nurses were 26.1 (6.4) dB in 1993, 26.3 (7.1) dB in 2002, and 26.4 (6.6) dB in 2013 (Figure).

Compared with 21 427 unexposed nurses at the cohort baseline, the 2485 exposed nurses were slightly younger, had higher body mass index, smoked less, were less physically active, had slightly higher rates of oral contraceptive use but lower HRT use, tended to still be working, lived in rural rather than urban areas, had slightly lower incomes, and were exposed to half the levels of nitrogen oxide traffic-related air pollution 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 mellitus rates (Table S1).

We detected no nonlinear relationships between weighted WTN and stroke incidence (Figure S1). Table 2 shows the associations between weighted WTN and stroke ( $n=1097$ ) (hospitalization) incidence among 23 912 Danish Nurse Cohort participants. We found no association between WTN and stroke incidence: the adjusted hazard ratios and 95% CIs for the 11-, 5-, and 1-year running mean residential  $L_{den}$  exposures preceding hospitalization, comparing nurses with  $\geq 20$  dB(A) to nurses exposed to levels <20 dB(A) were 1.09 (0.90–1.31), 1.08 (0.89–1.31), and 1.08 (0.89–1.32), respectively. Results with  $L_{den}$  were comparable with WTN exposure at  $L_n$ ,  $L_d$ ,  $L_e$ , and  $L_{24h}$  (unweighted daily average) (Table 2). Likewise, when considering the same association according to exposure quartiles (Table S2), we found no significant associations.

### Identification of Confounders and Effect Modifiers

Only minor attenuation by the included a priori selected confounders in the fully adjusted model was observed (Table 2).

There was no evidence of effect by any of the assessed variables in the sensitivity analyses, with no marked deviation

from the main Model 2 (not shown in tables). We detected significant effect modification of the association between WTN with stroke by urbanicity, showing the strongest positive associations for nurses living in provincial areas, and negative association in rural and urban areas. No effect modification by age, obesity, road traffic noise, or air pollution was observed (Table S3).

### Competing Risk by Nonstroke Death

The number of competing risk events within the cohort during follow-up was high (nonstroke death,  $n=3568$ ), compared with the outcome of interest (stroke,  $n=1097$ ); however, there was no indication of competing risk in Model 2 (main model), and nonstroke death did not potentially mask the association of interest in this study.

### Discussion

In this nationwide, prospective cohort study of Danish female nurses, we found no evidence to support a causal relationship between long-term exposure to WTN and stroke incidence, within the exposure windows considered (11-, 5- and 1-year).

Our results are in line with another recent Danish nationwide study that explored the relationship between WTN exposure and stroke incidence reporting no consistent associations with outdoor WTN or indoor low-frequency WTN and all incidence rate ratios were null or inverse and nonsignificant. The results of the present comprehensive study along with that recent study with a representative distribution of present and historical addresses around Denmark provide novel insight into this relationship. The present results also support another recently published paper reporting no associations between WTN exposure and incidence of myocardial infarction.<sup>4,29</sup> In public health perspective this may help reassure concerned citizens and ease the ongoing concern regarding the potential cardiovascular-related health effects of WTN exposure.

Long-term exposure to transportation noise has been associated with higher risk for cardiovascular disease including myocardial infarction and stroke.<sup>2,3,30,31</sup> These same associations are not observed with WTN, which can be attributed to many factors: first, WTN is generally much lower than traffic noise, for example, in Denmark there is no legislation limiting noise emitted for road traffic, and it is estimated that almost one third of all domestic dwellings are exposed to levels of road traffic that exceed 58 dB(A), while legislation prohibits WTN at levels exceeding 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.<sup>32</sup> Second, WTN is characterized by a more rhythmic modulation of sound than traffic sources,

and seems to cause more annoyance and sleep disturbance than road traffic noise (and other environmental noise sources) at similar noise levels.<sup>33,34</sup> Third, WTs are typically located in rural areas in which background noise levels and sensitivity thresholds to noise may be lower. Finally, road traffic noise is ubiquitous, affecting everyone, and a source of particulate or gaseous oxidative stressors (relevant for cardiovascular end points), while WTN is nonubiquitous, predominantly a rural exposure, with around 800 000 homes ( $\approx 12\%$ ) located within a 6000-meter radius of at least 1 wind turbine in Denmark in 2016.

We benefited from objective assessment of stroke incidence based on high-quality Danish registries with near 100% coverage,<sup>18,35</sup> as well as detailed information on stroke risk factors. This assessment implies minimal possibility of recall and information bias and no selection bias. We furthermore benefited from the state-of-the-art high-resolution validated exposure models for WT and road traffic noise<sup>21–23</sup> as well as air pollution,<sup>36</sup> which were based on geocodes and also accounted for all address changes and meteorological conditions, as well as the size and the type of WT. Overall associations support no association with most CIs spanning 1, and the few HRs above 1 are thought to be chance findings or attributable to residual confounding and not true effects. This is also supported by the lack of linear dose-response relationships.

In the present study, the WTN levels were relatively low. Only 25% of nurses exposed to WTN, those living within a 6000-meter radius of  $\geq 1$  WT, were exposed to levels over 29.9 dB(A) throughout follow-up, which corresponds to around 3% of all included nurses. The majority of the included nurses ( $>80\%$ ) had never lived in proximity to a WT. Thus, only a small fraction of the Danish population is exposed to WTN levels that are considered dangerous for health. According to the World Health Organization, it is not plausible that noise levels  $\leq 30$  dB(A) would cause sleep disturbances, and that only modest health effects would be expected  $\leq 40$  dB(A).<sup>37</sup> In the most recent environmental guidelines for the European Union, the World Health Organization conditionally recommends that WT  $L_{den}$  levels should be reduced to below 45 dB(A),<sup>38</sup> 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.<sup>32</sup> This may imply that the noise levels in our study may not have induced intermediates (hypertension, sleep disturbance, etc) previously reported to be on the causal pathway from noise exposure to stroke,<sup>39–42</sup> and direct auditory effects leading to stroke at these levels are not expected.<sup>41</sup> These levels of WTN are also substantially lower than road traffic noise levels within the same cohort, which were  $>50$  dB(A) on average, noting that a 20-dB(A) difference between these 2 sources of noise levels is perceived as around 4 times the loudness, due to the logarithmic scale of sound.<sup>28</sup>



**Table 2.** Association Between Weighted WTN ( $L_{den}$ ,  $L_d$ ,  $L_e$ ,  $L_n$ , and  $L_{24h}$ ) and Stroke Incidence (n=1097) Among 23 912 Danish Nurse Cohort Participants for Exposure Above and Below 20 dB(A), Considering the 1-, 5- and 11-Year Rolling Means Before Diagnosis/Censoring

WTN [dB(A)]	Person-Years	N Cases	Incidence Rate per 1000 Person-Years	Model 1* HR (95% CI)	Model 2† HR (95% CI)
$L_{den}$					
$L_{den}$ 11-year					
<20	362 451	976	2.7	1	1
≥20	45 731	121	2.6	1.06 (0.87–1.28)	1.09 (0.90–1.31)
Linear‡		1097		0.98 (0.81–1.18)	0.99 (0.81–1.20)
$L_{den}$ 5-year					
<20	362 547	980	2.7	1	1
≥20	45 636	117	2.6	1.05 (0.87–1.27)	1.08 (0.89–1.31)
Linear‡		1097		1.07 (0.86–1.35)	1.09 (0.86–1.37)
$L_{den}$ 1-year					
<20	364 939	984	2.7	1	1
≥20	44 244	113	2.6	1.06 (0.87–1.28)	1.08 (0.89–1.32)
Linear‡		1097		1.21 (0.92–1.60)	1.23 (0.93–1.62)
$L_d$					
$L_d$ 11-year					
<20	385 834	1043	2.7	1	1
≥20	22 349	54	2.4	0.97 (0.74–1.28)	1.00 (0.76–1.32)
Linear‡		1097		0.99 (0.81–1.20)	1.00 (0.82–1.21)
$L_d$ 5-year					
<20	384 533	1031	2.7	1	1
≥20	23 649	66	2.8	1.17 (0.91–1.50)	1.20 (0.94–1.54)
Linear‡		1097		1.09 (0.87–1.36)	1.10 (0.88–1.38)
$L_d$ 1-year					
<20	384 346	1031	2.7	1	1
≥20	23 837	66	2.8	1.18 (0.92–1.51)	1.21 (0.94–1.55)
Linear‡		1097		1.22 (0.93–1.61)	1.24 (0.94–1.63)
$L_e$					
$L_e$ 11-year					
<20	386 146	1043	2.7	1	1
≥20	22 037	54	2.5	0.98 (0.75–1.29)	1.01 (0.77–1.33)
Linear‡		1097		0.99 (0.81–1.20)	1.00 (0.82–1.21)
$L_e$ 5-year					
<20	384 647	1032	2.7	1	1
≥20	23 535	65	2.8	1.15 (0.89–1.47)	1.18 (0.92–1.52)
Linear‡		1097		1.08 (0.86–1.36)	1.09 (0.87–1.38)
$L_e$ 1-year					
<20	384 327	1031	2.7	1	1
≥20	23 856	66	2.8	1.17 (0.91–1.50)	1.20 (0.93–1.54)
Linear‡		1097		1.22 (0.92–1.61)	1.23 (0.93–1.63)

Continued

Table 2. Continued

WTN [dB(A)]	Person-Years	N Cases	Incidence Rate per 1000 Person-Years	Model 1* HR (95% CI)	Model 2† HR (95% CI)
<b>L<sub>n</sub></b>					
<b>L<sub>n</sub> 11-year</b>					
<20	387 151	1045	2.7	1	1
≥20	21 031	52	2.5	0.99 (0.75–1.31)	1.02 (0.77–1.35)
Linear‡		1097		0.97 (0.80–1.18)	0.98 (0.81–1.19)
<b>L<sub>n</sub> 5-year</b>					
<20	385 721	1034	2.7	1	1
≥20	22 462	63	2.8	1.17 (0.90–1.50)	1.20 (0.93–1.55)
Linear‡		1097		1.07 (0.85–1.34)	1.08 (0.86–1.36)
<b>L<sub>n</sub> 1-year</b>					
<20	385 284	1032	2.7	1	1
≥20	22 899	65	2.8	1.20 (0.94–1.55)	1.24 (0.96–1.59)
Linear‡		1097		1.21 (0.92–1.60)	1.22 (0.93–1.62)
<b>L<sub>24 h</sub></b>					
<b>L<sub>24 h</sub> 11-year</b>					
<20	386 364	1044	2.7	1	1
≥20	21 819	53	2.4	0.98 (0.74–1.29)	1.01 (0.76–1.33)
Linear‡		1097		0.98 (0.81–1.19)	1.00 (0.82–1.21)
<b>L<sub>24 h</sub> 5-year</b>					
<20	385 003	1033	2.7	1	1
≥20	23 179	64	2.8	1.15 (0.89–1.48)	1.18 (0.92–1.53)
Linear‡		1097		1.08 (0.86–1.36)	1.09 (0.87–1.37)
<b>L<sub>24 h</sub> 1-year</b>					
<20	384 679	1033	2.7	1	1
≥20	23 504	64	2.7	1.15 (0.89–1.48)	1.19 (0.92–1.53)
Linear‡		1097		1.22 (0.92–1.61)	1.23 (0.93–1.63)

HR indicates hazard ratio.

\*Adjusted for age (underlying timeline) and calendar year at entrance into the cohort.

†Main model, as for Model 1+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.

‡Linear trend per 10 dB(A).

The main limitation in the present study is the exposure misclassification in the modeled WTN concentrations, as these are only proxies of personal exposure and we did not have a measure of indoor levels of WTN. Also, 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 while overseas in areas with either higher or lower noise exposures. Finally, the A-weighted nature of our estimates is not informative about any peaking characteristics of the WTN throughout follow-up, and there may have been peaks we did not address.

Another major weakness of our study is the small number of stroke cases exposed to high levels of WTN, limiting the power to detect effects in this range of noise exposure. 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 causal pathway between noise exposure and health effects.<sup>5,6,43–45</sup> However, these self-reports may have introduced bias, as they include highly motivated persons with possible negative attitudes to WTs, which have repeatedly been reported to play an important role as the underlying cause of reported health and sleep problems.<sup>7,34,46,47</sup> In our study, it was not feasible

to consider all noise sources including noise from neighbors, bedroom snoring, aircraft, railways, and ventilation. Another weakness is that we lacked data on personal and household income, important determinants of socioeconomic status. Information on confounding and effect-modifying variables were collected at cohort baseline, and we acknowledge that these may have changed throughout the 20-year average follow-up time. Finally, we consider only women and are thus unable to account for effects in men or eventual differences in effect according to sex.

The results of this study infer no association between long-term exposure to WTN and stroke in women above age 44.

## Acknowledgments

We thank the Board of the Danish Nurse Cohort for access to data.

## Sources of Funding

This work was supported by the Danish Heart Foundation and Danish Council for Independent Research (DFF-4 183-00353).

## Disclosures

None.

## References

- Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Barker-Collo S, Bartels DH, Bell ML, Benjamin EJ, Bennett D, Bhalla K, Bikbov B, Bin AA, Birbeck G, Blyth F, Bolliger I, Boufous S, Bucello C, Burch M, Burney P, Carapetis J, Chen H, Chou D, Chugh SS, Coffeng LE, Colan SD, Colquhoun S, Colson KE, Condon J, Connor MD, Cooper LT, Corriere M, Cortinovis M, de Vaccaro KC, Couser W, Cowie BC, Criqui MH, Cross M, Dabhadkar KC, Dahodwala N, De Leo D, Degenhardt L, Delossantos A, Denenberg J, Des Jarlais DC, Dharmaratne SD, Dorsey ER, Driscoll T, Duber H, Ebel B, Erwin PJ, Espindola P, Ezzati M, Feigin V, Flaxman AD, Forouzanfar MH, Fowkes FG, Franklin R, Fransen M, Freeman MK, Gabriel SE, Gakidou E, Gaspari F, Gillum RF, Gonzalez-Medina D, Halasa YA, Haring D, Harrison JE, Havmoeller R, Hay RJ, Hoen B, Hotez PJ, Hoy D, Jacobsen KH, James SL, Jasrasaria R, Jayaraman S, Johns N, Karthikeyan G, Kassebaum N, Keren A, Khoo JP, Knowlton LM, Kobusingye O, Koranteng A, Krishnamurthi R, Lipnick M, Lipshultz SE, Ohno SL, Mabweijano J, MacIntyre MF, Mallinger L, March L, Marks GB, Marks R, Matsumori A, Matzopoulos R, Mayosi BM, McAnulty JH, McDermott MM, McGrath J, Mensah GA, Merriman TR, Michaud C, Miller M, Miller TR, Mock C, Mocumbi AO, Mokdad AA, Moran A, Mulholland K, Nair MN, Naldi L, Narayan KM, Nasseri K, Norman P, O'Donnell M, Omer SB, Ortblad K, Osborne R, Ozgediz D, Pahari B, Pandian JD, Rivero AP, Padilla RP, Perez-Ruiz F, Perico N, Phillips D, Pierce K, Pope CA III, Porrini E, Pourmalek F, Raju M, Ranganathan D, Rehm JT, Rein DB, Remuzzi G, Rivara FP, Roberts T, De Leon FR, Rosenfeld LC, Rushton L, Sacco RL, Salomon JA, Sampson U, Sanman E, Schwebel DC, Segui-Gomez M, Shepard DS, Singh D, Singleton J, Sliwa K, Smith E, Steer A, Taylor JA, Thomas B, Tleyjeh IM, Towbin JA, Truelsen T, Undurraga EA, Venketasubramanian N, Vijayakumar L, Vos T, Wagner GR, Wang M, Wang W, Watt K, Weinstock MA, Weintraub R, Wilkinson JD, Woolf AD, Wulf S, Yeh PH, Yip P, Zabetian A, Zheng ZJ, Lopez AD, Murray CJ, AlMazroa MA, Memish ZA. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380:2095–2128.
- Sorensen M, Hvidberg M, Andersen J, Nordsborg RB, Lillelund KG, Jakobsen J, Tjønneland A, Overvad K, Raaschou-Nielsen O. Road traffic noise and stroke: a prospective cohort study. *Eur Heart J*. 2011;32:737–744.
- Halonen JI, Hansell AL, Gulliver J, Morley D, Blangiardo M, Fecht D, Toledano MB, Beevers SD, Anderson HR, Kelly FJ, Tonne C. Road traffic noise is associated with increased cardiovascular morbidity and mortality and all-cause mortality in London. *Eur Heart J*. 2015;36:2653–2661.
- Poulsen AH, Raaschou-Nielsen O, Pena A, Hahmann AN, Nordsborg RB, Kettel M, Brandt J, Sorensen M. Long-term exposure to wind turbine noise and risk for myocardial infarction and stroke: a nationwide cohort study. *Environ Health Perspect*. 2019;127:37004.
- Hanning CD, Evans A. Wind turbine noise. *BMJ*. 2012;344:e1527.
- Bakker RH, Pedersen E, van den Berg GP, Stewart RE, Lok W, Bouma J. Impact of wind turbine sound on annoyance, self-reported sleep disturbance and psychological distress. *Sci Total Environ*. 2012;425:42–51.
- Pedersen E. Health aspects associated with wind turbine noise—results from three field studies. *Noise Control Eng J*. 2011;59:47–53.
- Chen PS, Chen LS, Fishbein MC, Lin SF, Nattel S. Role of the autonomic nervous system in atrial fibrillation: pathophysiology and therapy. *Circ Res*. 2014;114:1500–1515.
- Dewland TA, Vittinghoff E, Harris TB, Magnani JW, Liu Y, Hsu FC, Satterfield S, Wassel C, Marcus GM. Inflammation as a mediator of the association between race and atrial fibrillation: results from the Health, Aging, and Body Composition Study. *JACC Clin Electrophysiol*. 2015;1:248–255.
- Embi AA, Scherlag BJ. An endocrine hypothesis for the genesis of atrial fibrillation: the hypothalamic-pituitary-adrenal axis response to stress and glycogen accumulation in atrial tissues. *N Am J Med Sci*. 2014;6:586–590.
- Embi AA, Scherlag BJ, Ritchey JW. Glycogen and the propensity for atrial fibrillation: intrinsic anatomic differences in glycogen in the left and right atria in the goat heart. *N Am J Med Sci*. 2014;6:510–515.
- Rockström J, Gaffney O, Rogelj J, Meinshausen M, Nakicenovic N, Schellnhuber H. A roadmap for rapid decarbonization. *Science*. 2017;355:1269.
- Global Wind Energy Council. Global Wind Report. 2017.
- Global Wind Energy Council. Wind in Numbers. 2017.
- Hundrup YA, Simonsen MK, Jorgensen T, Obel EB. Cohort profile: the Danish Nurse Cohort. *Int J Epidemiol*. 2012;41:1241–1247.
- Pedersen CB. The Danish Civil Registration System. *Scand J Public Health*. 2011;39(7 suppl):22–25.
- Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol*. 2014;29:541–549.
- Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449–490.
- Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health*. 2011;39:30–33.
- Danish Energy Authority. The master data register for wind turbines [In Danish]. 2017.
- Backalarz C, Søndergaard LS, Laursen JE. Big noise data for wind turbines. In: Schulte-Fortkam B, ed. *Wolfgang Kropp, O.INTERNOISE 2016*. Hamburg: German Acoustical Society (Dega).
- Kragh J, Plovsing B, Storeheier SA, Jonasson HG. Nordic environmental noise prediction methods, Nord2000 summary report general Nordic sound propagation model and applications in source-related prediction methods. In: DELTA Danish Electronics, Light & Acoustics, Lyngby, Denmark Report 45. 2001.
- Søndergaard B, Plovsing B, Sørensen T. Noise and Energy Optimization of Wind Farms, validation of the Nord2000 Propagation Model for use on Wind Turbine Noise, Final Report AV 1238/09 DELTA, Hørsholm, Denmark. 2009.
- Jørgensen JT, Johansen MS, Ravnskjaer L, Andersen KK, Bräuner EV, Loft S, Kettel M, Becker T, Brandt J, Hertel O, Andersen ZJ. Long-term exposure to ambient air pollution and incidence of brain tumours: the Danish Nurse Cohort. *Neurotoxicology*. 2016;35:122–130.
- Hansen AB, Ravnskjaer L, Loft S, Andersen KK, Bräuner EV, Bastrup R, Yao C, Kettel M, Becker T, Brandt J, Hertel O, Andersen ZJ. Long-term exposure to fine particulate matter and incidence of diabetes in the Danish Nurse Cohort. *Environ Int*. 2016;91:243–250.
- Jensen SS, Berkowicz R, Hansen HS, Hertel O. A Danish decision-support GIS tool for management of urban air quality and human exposures. *Transp Res D*. 2001;6:229–241.
- Jakobsen J. *Danish Regulation of Low Frequency Noise from Wind Turbines*. 31st ed. 2012.
- Stevens SS. The measurement of loudness. *J Acoust Soc Am*. 1955;27:815–829.
- Brauner EV, Jørgensen JT, Duun-Henriksen AK, Backalarz C, Laursen JE, Pedersen TH, Simonsen MK, Andersen ZJ. Long-term wind turbine noise exposure and incidence of myocardial infarction in the Danish Nurse Cohort. *Environ Int*. 2018;121:794–802.
- Heritier H, Vienneau D, Foraster M, Eze IC, Schaffner E, Thiesse L, Rudzik F, Habermacher M, Kopfli M, Pieren R, Brink M, Cajochen C, Wunderli JM, Probst-Hensch N, Roosli M. Transportation noise exposure and cardiovascular

- mortality: a nationwide cohort study from Switzerland. *Eur J Epidemiol*. 2017;32:307–315.
31. Vienneau D, Schindler C, Perez L, Probst-Hensch N, Roosli M. The relationship between transportation noise exposure and ischemic heart disease: a meta-analysis. *Environ Res*. 2015;138:372–380.
  32. Statutory Order on Noise from Wind Turbines, Statutory Order no. 1284 of 15. 2011.
  33. Pedersen E, Wayne KP. Perception and annoyance due to wind turbine noise—a dose-response relationship. *J Acoust Soc Am*. 2004;116:3460–3470.
  34. Pedersen E, van den Berg F, Bakker R, Bouma J. Response to noise from modern wind farms in The Netherlands. *J Acoust Soc Am*. 2009;126:634–643.
  35. Helweg-Larsen K. The Danish register of causes of death. *Scand J Public Health*. 2011;39:26–29.
  36. Ketzler M, Berkowicz R, Hvidberg M, Jensen SS, Raaschou-Nielsen O. Evaluation of AIRGIS: a GIS-based air pollution and human exposure modelling system. *Int J Environ Pollut*. 2011;46:226–248.
  37. WHO, Regional Office for Europe. Burden of disease from environmental noise: quantification of healthy life years lost in Europe. 2011.
  38. WHO Regional Office for Europe CD. Environmental noise guidelines for the European region. 2018.
  39. Munzel T, Herzog J, Schmidt FP, Sorensen M. Environmental stressors and cardiovascular disease: the evidence is growing. *Eur Heart J*. 2017;38:2297–2299.
  40. Munzel T, Sorensen M, Gori T, Schmidt FP, Rao X, Brook J, Chen LC, Brook RD, Rajagopalan S. Environmental stressors and cardio-metabolic disease: part I—epidemiologic evidence supporting a role for noise and air pollution and effects of mitigation strategies. *Eur Heart J*. 2017;38:550–556.
  41. Munzel T, Sorensen M, Gori T, Schmidt FP, Rao X, Brook FR, Chen LC, Brook RD, Rajagopalan S. Environmental stressors and cardio-metabolic disease: part II—mechanistic insights. *Eur Heart J*. 2017;38:557–564.
  42. Babisch W, Beule B, Ising H, Kersten N, Schust M, Wende H. Noise burden and the risk of myocardial infarction: false interpretation of results due to inadequate treatment of data. *Eur Heart J*. 2006;27:623–624.
  43. Kuwano S, Yano T, Kageyama T, Sueoka S, Tachibana H. Social survey on wind turbine noise in Japan. *Noise Control Eng J*. 2014;62:503–520.
  44. Shepherd D, McBride D, Welch D, Dirks KN, Hill EM. Evaluating the impact of wind turbine noise on health-related quality of life. *Noise Health*. 2011;13:333–339.
  45. McCallum LC, Whitfield Aslund ML, Knopper LD, Ferguson GM, Ollson CA. Measuring electromagnetic fields (EMF) around wind turbines in Canada: is there a human health concern? *Environ Health*. 2014;13:9.
  46. Knopper LD, Ollson CA, McCallum LC, Whitfield Aslund ML, Berger RG, Souweine K, McDaniel M. Wind turbines and human health. *Front Public Health*. 2014;2:63.
  47. Blanes-Vidal V, Schwartz J. Wind turbines and idiopathic symptoms: the confounding effect of concurrent environmental exposures. *Neurotoxicol Teratol*. 2016;55:50–57.

# Supplemental Material

## Data S1.

### Supplemental Methods

#### Study population - The Danish Nurse Cohort

The study was based in the Danish Nurse Cohort <sup>1</sup> which 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 firstly 10,534 new nurses (who had reached the age of 44 years in the period 1993-99) were invited of which 8,344 responded) and secondly 2,231 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 (8,833) for 28,731 of nurses.

Since establishment of the Central Population Register in 1968 <sup>2, 3</sup>, 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 <sup>2, 3</sup> 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.

#### Identification of outcome - National Patient Register

The endpoint was incidence for stroke (International Classification of Disease (ICD) 10: D161, D163 and ICD 8:431.0, 431.9, 432.0, 432.9, 433.09, 433.99, 434.09, 436.0 and 436.9), defined as first-ever hospital contact (emergency, in- or outpatient) for stroke, identified in the Danish National Patient Registry<sup>4, 5</sup>. The Danish National Patient Registry 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 stroke before enrolment into the Nurses Cohort were excluded.

#### Exposure assessment

*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 Wind Turbines maintained by the Danish Energy Agency<sup>6</sup>. It is mandatory for all WT owners to report to the register, which contains geographical coordinates, date of grid connection, cancellation 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<sup>7</sup>. At each WT location, wind speed and direction at hub height was estimated, using mesoscale model simulations<sup>8, 9</sup>. Temperature and relative humidity at 2m height as well as the atmospheric stability were also estimated from these simulations.

*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<sup>7</sup>. Sound power levels from WTs were calculated for each address in the periods each cohort member had lived at the specific address. The model takes into consideration, continuous meteorological data for each WT throughout the years 1982-2013. The applied noise exposure modelling has been described in detail elsewhere<sup>7</sup>. In brief, WTN exposure was estimated for the all the different present and historic addresses the nurses had lived in using the Nord2000 noise propagation model which has been validated for WT and previously detailed<sup>10, 11</sup>. Outdoor A-weighted sound pressure level ( $LA_{eq}$ ) – a metric commonly used in health studies was calculated at the most exposed façade of all buildings within a 6000 m radius. WTN exposure was aggregated as follows: day ( $L_d$ ; 07:00–19:00h), evening ( $L_e$ ; 19:00–22:00h), night ( $L_n$ ; 22:00–07:00h), expressed as  $L_{den}$  (the overall weighted 24-hr noise level during the day, evening (+5dB) 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 6000m 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.

*Air pollution and noise from road traffic:* As previously described in detail<sup>12, 13</sup>, we used the newly updated, high-resolution Danish air pollution dispersion modeling system (AirGIS) to estimate exposure to outdoor air pollution at the residence<sup>14</sup>, as annual mean levels of nitrogen oxide ( $NO_x$ ), road traffic related pollutant, from 1982-2013. Road traffic noise at residential addresses of the nurses was estimated using the Nord2000 noise propagation 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 6m, 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  $LA_{eq}$  at the most exposed façade of the dwelling for the  $L_d$ ,  $L_e$ ,  $L_n$ , and  $L_{den}$  as yearly averages.

### Statistical analysis

We applied the Cox proportional hazards regression model to test the incidence of stroke 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 (1<sup>st</sup> April 1993 or 1<sup>st</sup> April 1999), so nurses were considered at risk from recruitment, and end of follow-up was age at the date of first hospitalization discharge diagnosis of stroke, date of death, emigration or 31<sup>st</sup> December 2013, whichever came first. Nurses with a stroke 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 *a-priori* selected potential confounding variables: 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 the following WTN exposures to assess chronic exposure using the 1-, 5- and 11-year rolling mean during follow-up prior to diagnosis/censoring. In each rolling mean window, we considered  $L_d$ ,  $L_e$ ,  $L_n$ ,  $L_{den}$  and  $L_{24h}$  separately. We used two categorical versions of WTN exposure: the first with a cut off at 20dB and the second was based on type-specific baseline quartiles.

Furthermore, we modelled WTN 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 for those exposed and the median exposure level for unexposed subjects. The continuous variable reflects the relative increase in hazard for ten units increase in exposure (10 dB) within the population of exposed nurses, and a 10 dB increase in noise level is equivalent to a subjective doubling in loudness<sup>15</sup>. Furthermore, we estimated HRs for the categorical versions of WTN exposures with 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<sup>16</sup>. WTN exposures were modelled as time-varying variables in all models.

We carried out sensitivity models to assess possible mediators of an association between WTN and stroke in four additional separate models. Model 3) as for model 2, further adjusted for Body Mass Index (BMI); Model 4) as for model 2, further adjusted for self-reported hypertension at baseline; 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. Noise estimates and traffic air NO<sub>x</sub> pollution were available for every year of follow-up and all potential confounding and effect mediating variables were available at baseline.

The potential effect modification of the association between WTN amongst exposed nurses and stroke incidence by age, night shift work, obesity, road traffic noise/NO<sub>x</sub> traffic related air pollution and urbanicity index were examined by introducing interaction terms to the main model (model 2) with WTN as a linear variable and tested by the likelihood ratio test.

The cohort consists of elderly nurses (> 44 at the recruitment, and > 58 years old at the end of follow-up in 2013), thus the effect of non-stroke death as a competing risk was also investigated as a function of WTN to assess whether time to stroke 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.

**Table S1. Characteristics of the Danish Nurse Cohort (n = 23,912) at baseline (1993 and 1999) by baseline exposure.**

Baseline Characteristics	Unexposed n = 21,427	Exposed (yes) n = 2,485
Stroke, n (%)	1005	92
Person-years of follow-up, n	366,471	41,711
Incidence rate per 1,000 person-years	2.7	2.2
Age, years, mean (SD)	53.4 (8.2)	51.8 (7.2)
Birth cohort		
< 1930, n (%)	5,214 (24.3)	464 (18.7)
1930-1940, n (%)	6,557 (30.6)	635 (25.6)
1940-1950, n (%)	5,260 (24.5)	692 (27.8)
>1950, n (%)	4,396 (20.5)	694 (27.9)
BMI, kg/m <sup>2</sup> , mean (SD)	23.7 (3.5)	24.0 (3.6)
Underweight (BMI <18.5 kg/m <sup>2</sup> ), n (%)	533 (2.5)	53 (2.1)
Normal (BMI 18.5-25 kg/m <sup>2</sup> ), n (%)	14,688 (68.5)	1,635 (65.8)
Overweight (BMI 25-30 kg/m <sup>2</sup> ), n (%)	4,800 (22.4)	608 (24.5)
Obese (BMI >30 kg/m <sup>2</sup> ), n (%)	1,186 (5.5)	164 (6.6)
Missing, n (%)	220 (1.0)	25 (1.0)
Smoking		
Never smoked, n (%)	7,533 (35.2)	989 (39.8)
Previously smoked, n (%)	6,486 (30.3)	719 (28.9)
Current smoker, n (%)	7,408 (34.6)	777 (31.3)
Smoking pack--days, mean (SD)*	16.4 (14.9)	15.3 (13.5)
Alcohol consumption		
Never consumes alcohol, n (%)	3,315 (15.5)	378 (15.2)
Alcohol consumption <sup>†</sup> (g/week), mean (SD)	115.6 (126.4)	104.2 (123.5)
Physical activity		
Low physical activity, n (%)	1,417 (6.6)	146 (5.9)
Medium physical activity, n (%)	14,418 (67.3)	1,540 (62.0)
High physical activity, n (%)	5,592 (26.1)	799 (32.2)
Diet		
Regularly eat fruit, n (%)	14,593 (68.1)	1,659 (66.8)
Avoid fatty meat, n (%)	19,425 (90.7)	2,216 (89.2)
Hypertension, n (%)	2,775 (13.0)	297 (12.0)
Missing, n (%)	7 (0.03)	0 (0.00)
Diabetes, n (%)	243 (1.1)	37 (1.5)
Missing, n (%)	55 (0.3)	11 (0.4)
Use of hormone therapy		
Ever, n (%)	5,956 (27.8)	603 (24.3)
Use of oral contraceptives		
Ever, n (%)	12,464 (58.2)	1,572 (63.3)
Living in		
Urban Area, n (%)	3,492 (16.3)	49 (2.0)
Rural, n (%)	7,808 (36.4)	1,795 (72.2)
Provincial, n (%)	9,542 (44.5)	603 (24.3)
Missing, n (%)	585 (2.8)	38 (1.5)
Marital status		
Married, n (%)	14,856 (69.3)	2,015 (81.1)
Separated, n (%)	364 (1.7)	28 (1.1)
Divorced, n (%)	2,465 (11.5)	184 (7.4)
Single, n (%)	2,259 (10.5)	136 (5.5)
Widow, n (%)	1,483 (6.9)	122 (4.9)
Employment status		

Employed, n (%)	16,686 (77.9)	2,036 (81.9)
Homemaker and others, n (%)	554 (2.6)	89 (3.5)
Retired, n (%)	4,043 (18.9)	343 (13.8)
Unemployed, n (%)	144 (0.7)	17 (0.7)
Night shift work		
Day	10,474 (48.9)	1,273 (51.2)
Evening	1,686 (7.9)	211 (8.5)
Night	933 (4.4)	113 (4.5)
Rotating	3,659 (17.1)	456 (18.4)
Missing, n, (%)	4,675 (21.8)	456 (18.4)
Municipality annual income (DKK) <sup>‡</sup> , mean (SD)	165.05 (25.77)	157.567 (11.76)
Missing n, (%)	585 (2.4)	38 (1.6)
Annual Air Pollution: NO <sub>x</sub> (µg/m <sup>3</sup> ), mean(SD)	20.2 (25.5)	10.8 (9.8)
Annual traffic noise, dB, (mean, SD)	53.3 (7.9)	48.3 (9.2)
Wind-turbine noise, dB, (mean, SD) <sup>§</sup>	-	26.25 (6.61)
Unexposed, n (%)	21,427 (100)	0 (0.0)
< 21.5 dB, n (%)	0 (0.0)	622 (25.0)
21.5-25.4 dB, n (%)	0 (0.0)	616 (24.8)
25.4-29.9 dB, n (%)	0 (0.0)	619 (24.9)
> 29.9 dB, n (%)	0 (0.0)	628 (25.3)

SD: Standard deviation

BMI: body mass index

DKK: Danish crown

\* among ever smokers

† among alcohol consumers

‡ average annual gross income at the municipality level

§ among Nurses exposed to WTN

**Table S2. Association between long-term wind-turbine noise exposure ( $L_{den}$ ,  $L_{day}$ ,  $L_{evening}$ ,  $L_{night}$ , and  $L_{24-h}$ ) and stroke incidence (n = 1,097) among 23,912 Danish Nurse Cohort participants, considering 1-, 5- and 11-yrs rolling means preceding diagnosis/censoring according to quartiles for our crude and main adjusted models.**

	Person-years (PY)	$N_{cases}$	Incidence Rate per 1,000 PY	Model 1 <sup>†</sup> HR (95% CI)	Model 2 <sup>‡</sup> HR (95% CI)
<b>1. <math>L_{den}</math></b>					
<b><math>L_{den}</math> 11-year rolling mean</b>					
Unexposed	341357	921	2.7	1 (ref)	1 (ref)
< 21.5 dB(A)	26874	67	2.4	1.03 (0.80-1.32)	1.05 (0.81-1.34)
21.5-25.4 dB(A)	14086	43	3.1	1.22 (0.90-1.65)	1.24 (0.92-1.69)
25.4-29.9 dB(A)	13006	34	2.6	1.01 (0.72-1.43)	1.04 (0.74-1.47)
> 29.9 dB(A)	12858	32	2.5	1.04 (0.73-1.48)	1.08 (0.76-1.54)
<b><math>L_{den}</math> 5-year rolling mean</b>					
Unexposed	350294	948	2.7	1 (ref)	1 (ref)
< 21.5 dB(A)	17504	42	2.4	0.99 (0.72-1.34)	1.01 (0.74-1.37)
21.5-25.4 dB(A)	13113	27	2.1	0.84 (0.57-1.23)	0.85 (0.58-1.25)
25.4-29.9 dB(A)	13483	45	3.3	1.32 (0.98-1.78)	1.36 (1.01-1.84)
> 29.9 dB(A)	13787	35	2.5	1.08 (0.77-1.52)	1.12 (0.80-1.57)
<b><math>L_{den}</math> 1-year rolling mean</b>					
Unexposed	358208	973	2.7	1 (ref)	1 (ref)
< 21.5 dB(A)	10447	20	1.9	0.78 (0.50-1.22)	0.80 (0.51-1.25)
21.5-25.4 dB(A)	12057	26	2.2	0.88 (0.59-1.30)	0.89 (0.60-1.31)
25.4-29.9 dB(A)	13266	42	3.2	1.26 (0.92-1.71)	1.29 (0.94-1.75)
> 29.9 dB(A)	14205	36	2.5	1.10 (0.79-1.53)	1.14 (0.81-1.59)
<b>2. <math>L_{day}</math></b>					
<b><math>L_{day}</math> 11-year rolling mean</b>					
Unexposed	341358	921	2.7	1 (ref)	1 (ref)
<15.1 dB (A)	27252	70	2.6	1.05 (0.83-1.34)	1.07 (0.84-1.37)
15.1-19.0 dB(A)	13800	40	2.9	1.15 (0.84-1.58)	1.17 (0.85-1.61)
19.0-23.6 dB(A)	13191	35	2.7	1.04 (0.74-1.46)	1.07 (0.76-1.50)
>23.6 dB(A)	12583	31	2.5	1.03 (0.72-1.48)	1.07 (0.75-1.53)
<b><math>L_{day}</math> 5-year rolling mean</b>					
Unexposed	350297	948	2.7	1 (ref)	1 (ref)
<15.1 dB (A)	17918	44	2.4	1.01 (0.75-1.37)	1.03 (0.76-1.39)
15.1-19.0 dB(A)	12940	28	2.1	0.87 (0.60-1.27)	0.89 (0.61-1.29)
19.0-23.6 dB(A)	13649	43	3.3	1.25 (0.92-1.70)	1.29 (0.95-1.76)
>23.6 dB(A)	13378	34	2.5	1.09 (0.77-1.54)	1.13 (0.80-1.59)
<b><math>L_{day}</math> 1-year rolling mean</b>					
Unexposed	358211	973	2.7	1 (ref)	1 (ref)
<15.1 dB (A)	10929	24	1.9	0.89 (0.59-1.34)	0.91 (0.61-1.37)
15.1-19.0 dB(A)	11992	25	2.2	0.84 (0.56-1.25)	0.85 (0.57-1.26)
19.0-23.6 dB(A)	13307	40	3.2	1.21 (0.88-1.66)	1.24 (0.90-1.70)

>23.6 dB(A)	13743	35	2.5	1.11 (0.79-1.55)	1.14 (0.82-1.61)
<b>3. Levening</b>					
<b>Levening 11-year rolling mean</b>					
Unexposed	341559	921	2.7	1 (ref)	1 (ref)
<15.0 dB(A)	26903	66	2.5	1.01 (0.79-1.30)	1.03 (0.80-1.33)
15.0-18.9 dB(A)	14130	43	3.0	1.21 (0.89-1.64)	1.23 (0.91-1.68)
18.9-23.5 dB(A)	13286	35	2.6	1.02 (0.73-1.43)	1.05 (0.75-1.47)
>23.5 dB(A)	12505	32	2.6	1.07 (0.75-1.53)	1.11 (0.78-1.58)
<b>Levening 5-year rolling mean</b>					
Unexposed	350298	948	2.7	1 (ref)	1 (ref)
<15.0 dB(A)	17475	40	2.9	0.94 (0.69-1.30)	0.96 (0.70-1.32)
15.0-18.9 dB(A)	13196	29	2.2	0.89 (0.62-1.29)	0.91 (0.63-1.31)
18.9-23.5 dB(A)	13749	47	3.4	1.35 (1.00-1.80)	1.39 (1.03-1.86)
>23.5 dB(A)	13465	33	2.5	1.05 (0.74-1.49)	1.09 (0.77-1.54)
<b>Levening 1-year rolling mean</b>					
Unexposed	358212	973	2.7	1 (ref)	1 (ref)
<15.0 dB(A)	10411	21	2.0	0.82 (0.53-1.27)	0.84 (0.55-1.30)
15.0-18.9 dB(A)	12120	23	1.9	0.78 (0.51-1.18)	0.79 (0.52-1.19)
18.9-23.5 dB(A)	13525	44	3.3	1.28 (0.94-1.73)	1.31 (0.97-1.78)
>23.5 dB(A)	13915	36	2.6	1.12 (0.81-1.57)	1.16 (0.83-1.62)
<b>4. Lnight</b>					
<b>Lnight 11-year rolling mean</b>					
Unexposed	341361	921	2.7	1 (ref)	1 (ref)
<14.7 dB(A)	26972	67	2.5	1.02 (0.80-1.31)	1.04 (0.81-1.34)
14.7-18.6 dB(A)	14063	43	3.1	1.22 (0.90-1.66)	1.25 (0.92-1.70)
18.6-23.1 dB(A)	12989	34	2.6	1.01 (0.72-1.43)	1.04 (0.74-1.47)
>23.1 dB(A)	12798	32	2.5	1.05 (0.73-1.49)	1.08 (0.76-1.54)
<b>Lnight 5-year rolling mean</b>					
Unexposed	350301	948	2.7	1 (ref)	1 (ref)
<14.7 dB(A)	17564	42	2.4	0.98 (0.72-1.34)	1.00 (0.73-1.37)
14.7-18.6 dB(A)	13132	26	2.0	0.81 (0.55-1.19)	0.82 (0.55-1.21)
18.6-23.1 dB(A)	13454	46	3.4	1.35 (1.01-1.82)	1.39 (1.03-1.87)
>23.1 dB(A)	13732	35	2.5	1.09 (0.78-1.53)	1.13 (0.80-1.58)
<b>Lnight 1-year rolling mean</b>					
Unexposed	358215	973	2.7	1 (ref)	1 (ref)
<14.7 dB(A)	10520	20	1.9	0.78 (0.50-1.21)	0.80 (0.51-1.24)
14.7-18.6 dB(A)	12062	26	2.2	0.88 (0.59-1.29)	0.89 (0.60-1.31)
18.6-23.1 dB(A)	13234	42	3.2	1.26 (0.92-1.71)	1.29 (0.95-1.76)
>23.1 dB(A)	14152	36	2.5	1.10 (0.79-1.54)	1.14 (0.82-1.59)
<b>5. L24-h</b>					
<b>L24h 11-year rolling mean</b>					
Unexposed	341357	921	2.7	1 (ref)	1 (ref)
<14.9 dB(A)	26974	67	2.5	1.02 (0.80-1.31)	1.04 (0.81-1.34)
14.9-18.9 dB(A)	14301	43	3.0	1.19 (0.88-1.62)	1.22 (0.90-1.66)
18.9-23.4 dB(A)	12882	36	2.8	1.08 (0.78-1.51)	1.11 (0.80-1.56)
>23.4 dB(A)	12669	30	2.4	0.99 (0.69-1.43)	1.03 (0.71-1.48)

<b>L<sub>24h</sub> 5-year rolling mean</b>					
Unexposed	350294	948	2.7	1 (ref)	1 (ref)
<14.9 dB(A)	17578	42	2.4	0.98 (0.72-1.34)	1.00 (0.73-1.36)
14.9-18.9 dB(A)	13394	30	2.2	0.91 (0.63-1.31)	0.92 (0.64-1.33)
18.9-23.4 dB(A)	13369	42	3.1	1.24 (0.91-1.70)	1.28 (0.94-1.75)
>23.4 dB(A)	13548	35	2.6	1.11 (0.79-1.55)	1.14 (0.82-1.61)
<b>L<sub>24h</sub> 1-year rolling mean</b>					
Unexposed	358208	973	2.7	1 (ref)	1 (ref)
<14.9 dB(A)	10570	21	2.0	0.81 (0.52-1.25)	0.83 (0.54-1.28)
14.9-18.9 dB(A)	12337	27	2.2	0.89 (0.61-1.30)	0.90 (0.61-1.32)
18.9-23.4 dB(A)	13136	40	3.0	1.21 (0.88-1.66)	1.24 (0.90-1.70)
>23.4 dB(A)	13931	36	2.6	1.12 (0.81-1.57)	1.16 (0.83-1.62)

HR: Hazard Ratio; CI: Confidence Intervals;

† Adjusted for age (underlying timeline) and calendar year at entrance into the cohort

‡ Main model, as for model 1† + 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.



**Table S3. Modification of association<sup>†</sup> within population of exposed Nurses between incidence of stroke (n = 1097) and WTN (11-year rolling mean per 10 dB(A)) by baseline characteristics and co-morbid conditions among 23,912 female participants in the Danish Nurse Cohort.**

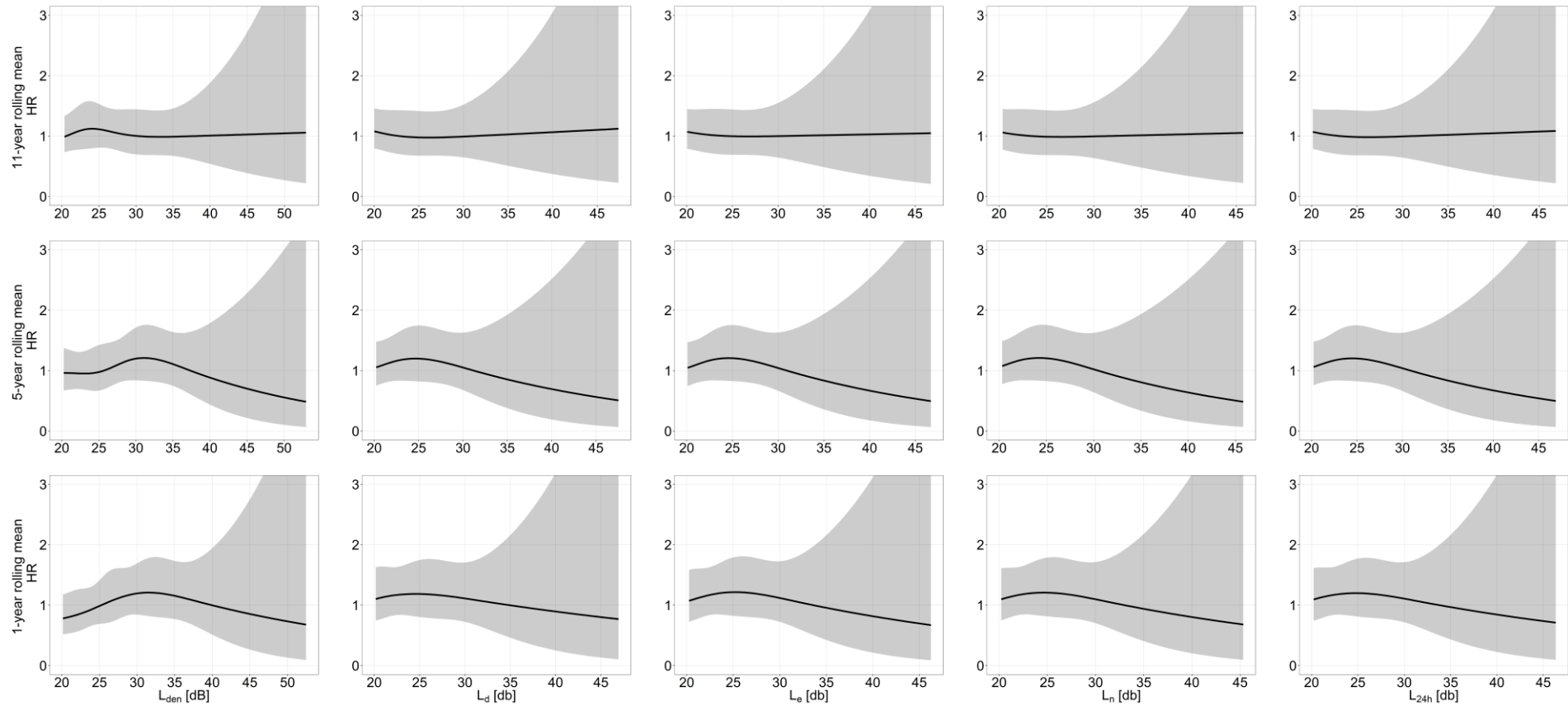
Covariate		N (cases)	HR (95% CI)	<i>p</i> <sup>‡</sup>
Age	<60 years	34	0.88 (0.58-1.33)	<i>0.54</i>
	≥60 years	142	1.02 (0.82-1.27)	
BMI	< 25 kg/m <sup>2</sup>	109	0.95 (0.74-1.21)	<i>0.41</i>
	≥ 25 kg/m <sup>2</sup>	65	1.05 (0.77-1.45)	
Traffic noise (dB)	< 53.7 dB	110	1.04 (0.82-1.33)	<i>0.82</i>
	≥ 53.7	63	0.92 (0.66-1.27)	
Traffic air pollution (NOx)	< 15.2 µg/m <sup>3</sup>	107	1.01 (0.79-1.30)	<i>0.71</i>
	≥ 15.2 µg/m <sup>3</sup>	62	1.01 (0.73-1.39)	
Night shift	Night only	15	1.40 (0.69-2.81)	<i>0.17</i>
	Day, evening, rotating	91	1.08 (0.83-1.41)	
Level of Urbanization	Urban	7	0.26 (0.12-0.56)	<i>0.004*</i>
	Rural	123	0.97 (0.77-1.22)	
	Provincial	44	1.32 (0.89-1.96)	

HR: Hazard Ratio; CI: Confidence Interval;

<sup>†</sup>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.

<sup>‡</sup>From likelihood ratio test for interaction, test of the null hypothesis that linear trends are identical.

**Figure S1. Exposure-response (HR (hazard ratio) filled lines; 95% CIs indicated by dashed lines) between stroke (n=1097) and 11, 5, and 1-y WT ( $L_{den}$ ,  $L_d$ ,  $L_e$ ,  $L_n$  and  $L_{24h}$ ) noise exposure at residences from 1982 onwards, based on fully adjusted main model 2. The reported HR (hazard risk) is based on unexposed nurses as reference.**



## Supplemental References:

- (1) Hundrup YA, Simonsen MK, Jorgensen T, Obel EB. Cohort profile: the Danish nurse cohort. *Int J Epidemiol* 2012;41:1241-7.
- (2) Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011;39:22-5.
- (3) Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol* 2014;29:541-9.
- (4) Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;7:449-90.
- (5) Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011;39:30-3.
- (6) Danish Energy Authority. The master data register for wind turbines [In Danish]. 2017.
- (7) Backalarz C, Søndergaard LS, Laursen JE. Big Noise data for wind turbines. In: Schulte-Fortkam, B (Ed.), Wolfgang Kropp, O. INTERNOISE 2016 Hanburg, German Acoustical Society (Dega). 2016.
- (8) Hahmann AN, Vincent CL, Pena A, ange J, Hasager CB. Wind climate estimation using WRF model output: method and model sensitivities over the sea. *Int J Climatol* 2015;35:3422-39.
- (9) Pena A, Hahmann AN. 30-year mesoscale model simulations for the "Noise from wind turbines and risk of cardiovascular disease" project. 2017.
- (10) Kragh J, Plovsing B, Storeheier SA, Jonasson HG. Nordic environmental noise prediction methods, Nord2000 summary report general Nordic sound propagation model and applications in source-related prediction methods. In: DELTA Danish Electronics, Light & Acoustics, Lyngby, Denmark Report 45. 2001.
- (11) Søndergaard B, Plovsing B, Sørensen T. Noise and Energy Optimization of Wind Farms, validation of the Nord2000 Propagation Model for use on Wind Turbine Noise, Final Reprot AV 1238/09 DELTA, Hørsholm, Denmark. 2009.
- (12) Jørgensen JT, Johansen MS, Ravnskjaer L, Andersen KK, Bräuner EV, Loft S, Ketznel M, Becker T, Brandt J, Hertel O, Andersen ZJ. Long-term exposure to ambient air pollution and incidence of brain tumours: The Danish Nurse Cohort. *Neurotoxicology* 2016;55:122-30.
- (13) Hansen AB, Ravnskjaer L, Loft S, Andersen KK, Bräuner EV, Baastrup R, Yao C, Ketznel M, Becker T, Brandt J, Hertel O, Andersen ZJ. Long-term exposure to fine particulate matter and incidence of diabetes in the Danish Nurse Cohort. *Environ Int* 2016;91:243-50.
- (14) Jensen SS, Berkowicz R, Hansen HS, Hertel O. A Danish decision-support GIS tool for management of urban air quality and human exposures. *Transportation Research Part D-Transport and Environment* 2001;6:229-41.
- (15) Stevens SS. The measurement of loudness. *The Journal of the Acoustical Society of America* 1955;27:815-29.
- (16) Jakobsen J. *Danish Regulation of Low Frequency Noise from Wind Turbines*. 31 ed. 2012.