











ORIGINAL RESEARCH

# Long-Term Exposure to Air Pollution, Road Traffic Noise, and Heart Failure Incidence: The Danish Nurse Cohort

Youn-Hee Lim , PhD; Jeanette T. Jørgensen, PhD; Rina So, MA; Tom Cole-Hunter , PhD; Amar J. Mehta, ScD; Heresh Amini , PhD; Elvira V. Bräuner , PhD; Rudi G. J. Westendorp, MD, PhD; Shuo Liu, MPH; Laust H. Mortensen, PhD; Barbara Hoffmann, MD, MPH; Steffen Loft, DMSc; Matthias Ketzel , PhD; Ole Hertel , DSc; Jørgen Brandt, PhD; Steen Solvang Jensen , PhD; Claus Backalarz , MSc; Mette K. Simonsen , PhD; Nebojsa Tasic, MD; Matija Maric, MD; Zorana J. Andersen , PhD

**BACKGROUND:** We examined the association of long-term exposure to air pollution and road traffic noise with incident heart failure (HF).

**METHODS AND RESULTS:** Using data on female nurses from the Danish Nurse Cohort (aged >44 years), we investigated associations between 3-year mean exposures to air pollution and road traffic noise and incident HF using Cox regression models, adjusting for relevant confounders. Incidence of HF was defined as the first hospital contact (inpatient, outpatient, or emergency) between cohort baseline (1993 or 1999) and December 31, 2014, based on the Danish National Patient Register. Annual mean levels of particulate matter with a diameter <2.5  $\mu\text{m}$  since 1990 and  $\text{NO}_2$  and road traffic noise since 1970 were estimated at participants' residences. Of the 22 189 nurses, 484 developed HF. We detected associations with all 3 pollutants, with hazard ratios (HRs) of 1.17 (95% CI, 1.01–1.36), 1.10 (95% CI, 0.99–1.22), and 1.12 (95% CI, 0.99–1.26) per increase of 5.1  $\mu\text{g}/\text{m}^3$  in particulate matter with a diameter <2.5  $\mu\text{m}$ , 8.6  $\mu\text{g}/\text{m}^3$  in  $\text{NO}_2$ , and 9.3 dB in road traffic noise, respectively. We observed an enhanced risk of HF incidence for those exposed to high levels of the 3 pollutants; however, the effect modification of coexposure was not statistically significant. Former smokers and nurses with hypertension showed the strongest associations with particulate matter with a diameter <2.5  $\mu\text{m}$  ( $P_{\text{effect modification}} < 0.05$ ).

**CONCLUSIONS:** We found that long-term exposures to air pollution and road traffic noise were independently associated with HF.

**Key Words:** air pollution ■ cohort study ■ heart failure ■ morbidity ■ road traffic noise

**H**earth failure (HF) is characterized by the reduced ability of the heart to pump or fill with blood, which affects 26 million people worldwide.<sup>1</sup> HF is associated with high mortality, frequent hospitalization, poor quality of life, or multiple comorbidities,<sup>2</sup> and risk factors of HF include smoking, alcohol consumption, and obesity as well as preexisting hypertension, coronary artery disease, diabetes, and myocardial infarction. Air pollution has been recognized as a risk factor

for ischemic and coronary cardiovascular disease,<sup>3,4</sup> whereas evidence on HF is more limited and novel. Air pollution may induce oxidative stress, inflammation, imbalance of the autonomic nervous system, and endothelial dysfunction, all associated with the cardiovascular disease progression related to HF.<sup>5,6</sup> A number of studies have shown that short-term exposure to high levels of particulate matter with a diameter <2.5  $\mu\text{m}$  ( $\text{PM}_{2.5}$ ) and  $\text{NO}_2$ , over several hours or days, can lead

Correspondence to: Youn-Hee Lim, Section of Environmental Health, Department of Public Health, Faculty of Health and Medical Sciences, University of Copenhagen, Øster Farimagsgade 5, Opgang B, Post Box 2099, 1014, Copenhagen, Denmark. E-mail: younhee.lim@sund.ku.dk

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## CLINICAL PERSPECTIVE

### What Is New?

- A large prospective cohort study including 22 189 Danish nurses with detailed information on historical exposures investigated environmental risk factors of heart failure.
- Associations with incident heart failure were strongest and most robust with particulate matter with a diameter  $<2.5 \mu\text{m}$  and suggestive with road traffic noise.
- Former smokers and patients who were hypertensive were most susceptible to the adverse effects of particulate matter with a diameter  $<2.5 \mu\text{m}$  on heart failure.

### What Are the Clinical Implications?

- The study suggests that air pollution and road traffic noise can increase the risk of heart failure, and that former smokers or those with hypertension may be most susceptible to the adverse effects of air pollution.
- Clinicians should inform their patients regarding air pollution and road traffic noise related adverse effects on the heart.

## Nonstandard Abbreviations and Acronyms

<b>DNC</b>	Danish Nurse Cohort
<b>IPW</b>	inverse probability weight
<b><math>L_{\text{den}}</math></b>	overall weighted 24-hour noise level
<b><math>\text{PM}_{2.5}</math></b>	particulate matter with a diameter $<2.5 \mu\text{m}$

to HF onset, leading to HF hospitalization or deaths.<sup>7</sup> Evidence on whether long-term exposure to air pollution over many years can lead to the development of HF is more limited, with 10 studies on HF incidence<sup>8–17</sup> and 1 on mortality,<sup>18</sup> with somewhat mixed results.

Road traffic noise is an increasingly recognized environmental stressor that can lead to inflammatory responses and oxidative stress as well as cause annoyance and sleep disturbance.<sup>19</sup> Road traffic noise has been linked to ischemic heart disease,<sup>19</sup> whereas only 4 studies considered HF,<sup>10,14,20,21</sup> 2 suggesting associations.<sup>14,20</sup> As air pollutants and road traffic noise share a major source—traffic—it is important to consider the independent or interactive effects of the 2 exposures on health. Only 3 studies on air pollution and HF had data on road traffic noise and suggested that  $\text{NO}_2$  and road traffic noise independently influence HF incidence or mortality.<sup>10,14,20</sup> Moreover, no studies

considered possible effect modification of coexposure on the association of  $\text{PM}_{2.5}$  and noise with HF, as high exposure to 1 pollutant may make the body more susceptible to the hazardous effects of another pollutant.<sup>14</sup>

Here we examined the associations of long-term exposure to air pollution ( $\text{PM}_{2.5}$  and  $\text{NO}_2$ ) and road traffic noise, independently and jointly, with incident HF, and considered possible effect modification by lifestyle and comorbidity.

## METHODS

Scripts for statistical analyses are available from the University of Copenhagen upon request. Data requests should be directed to the University of Copenhagen and are subject to their data access policies.

### Participants

The Danish Nurse Cohort (DNC) was designed to examine the effects of hormone replacement therapy in the Danish population<sup>22</sup> and was initiated by sending questionnaires to members of the Danish Nurse Organization in 1993, and again, with the recruitment of new nurses, in 1999. Among 33 704 eligible female nurses aged  $>44$  years who either worked or were retired in 1993 or 1999, 28 731 (85.2%) were enrolled in the DNC. As 4 participants had missing information on vital status during the study period, the remaining 28 727 participants were considered in this study (Figure S1). Upon enrollment, participants answered a comprehensive questionnaire on body mass index (BMI), lifestyle factors (smoking, alcohol consumption, physical activity, and dietary habits), preexisting diseases, reproductive health, and working conditions. All participants were linked to the Danish Civil Registration System<sup>23</sup> to extract data on death or emigration date until December 31, 2014. Participants' residential addresses with complete moving history and moving dates since 1970 and until 2014 were obtained from the Danish Central Person Register.

The investigation conforms with the principles outlined in the Declaration of Helsinki. The DNC was approved by the Scientific and Ethical Committee of Copenhagen and Frederiksberg Municipalities (approval number [KF] 01-103/93) and the Danish Data Protection Agency (J. number 1993-1110-1151), and the nurses who were included in the original DNC provided informed written consent.

### Outcome Definitions

Information on HF was extracted by linking the cohort participants to the Danish National Patient Register, which includes records on all contacts in Danish hospitals since 1977.<sup>24</sup> We defined incidence of HF as a first hospital contact (inpatient, outpatient, or emergency

room) between cohort baseline in 1993 or 1999 and December 31, 2014, which resulted in a primary discharge diagnosis of HF (*International Classification of Diseases, Eighth Revision* [ICD-8] codes before 1994: 427.0 or 427.1; *International Classification of Diseases, Tenth Revision* [ICD-10] codes after 1994: I50, I11.0, I42.0, or I42.9). The HF discharge diagnoses from the Danish National Patient Register have been previously validated by comparison to the hospital records at a Danish University Hospital cardiac care unit in 2005 to 2007, showing high validity with positive predictive values of 84.0% for overall HF and 77.9% for incident HF.<sup>25</sup>

### Air Pollution and Road Traffic Noise

We estimated annual mean concentrations of PM<sub>2.5</sub> (since 1990) and NO<sub>2</sub> (since 1970) based on the participants' residential addresses using the Danish air pollution modeling system, DEHM/UBM/AirGIS ([www.au.dk/AirGIS](http://www.au.dk/AirGIS)).<sup>26</sup> Road traffic noise levels were estimated using the validated model system, Nord2000,<sup>27</sup> which included noise contributions from roads within a 3 km radius from participants' residential addresses. Road traffic noise was estimated as the overall weighted 24-h noise level adding a penalty of 5 dB to the evening hours and 10 dB to the night hours (overall weighted 24-hour noise level [ $L_{den}$ ]). For the year that participants changed the address, we calculated annual PM<sub>2.5</sub>, NO<sub>2</sub>, and  $L_{den}$  levels at the year of an address change as weighted means of the 2 addresses' exposure levels (the old address and the new one). We calculated 1-year, 3-year, and 23-year running means of PM<sub>2.5</sub>, NO<sub>2</sub>, and  $L_{den}$  and assigned the multiyear residential exposures in a yearly time interval between the baseline year and last year of follow-up. The 3-year mean exposure to all pollutants was considered as the main exposure as this was the longest available exposure window for all 3 pollutants (data for PM<sub>2.5</sub> available since 1990).

### Covariates

We used information on individual characteristics collected at the cohort baseline in 1993 or 1999, including smoking status (never, former, or current), alcohol consumption (never; moderate, 1–14 drinks per week; or heavy,  $\geq 15$  drinks per week), leisure time physical activity (low, medium, or high), marital status (married, separated, divorced, single, or widowed), parity (none or at least 1 child), employment status (working, homemaker, retired, unemployed/rehabilitation, or other), use of oral contraceptives (never or ever), and hormone replacement therapy (never, previous, or current). We categorized participants into 3 job strain categories (low, high, or unemployed) by combining the following 3 items: workload, busyness, and control of

work. Based on the municipality of the residential address, the level of urbanization was defined: urban (cities, ie, densely populated areas [at least 50% of the population lives in urban centers]), suburban (town and suburbs, ie, intermediate density areas [ $< 50\%$  of the population lives in rural grid cells and  $< 50\%$  of the population lives in urban centers]), and rural (thinly populated areas [ $\geq 50\%$  of the population lives in rural grid cells]). Average municipality income in Danish Kroner in 1993 was assigned to each participant.

### Statistical Analysis

We examined the association between air pollutants, noise, and HF using time-varying Cox regression models with age (years) as the underlying time scale. In model 1, we examined associations between 3-year running means of PM<sub>2.5</sub>, NO<sub>2</sub>, and  $L_{den}$  and incident HF, separately for each pollutant, after adjusting for age as a time scale and the year of cohort entry (1993 or 1999). In model 2, we additionally controlled for the individual-level (BMI, smoking status, alcohol consumption, leisure time physical activity, marital status, parity, employment status, use of oral contraceptives, hormone replacement therapy, and job strain) and area-level (the level of urbanization and average municipality income) confounders. We then fitted 2-pollutant and 3-pollutant models controlling for PM<sub>2.5</sub>, NO<sub>2</sub>, and  $L_{den}$  mutually to examine the independent effects of air pollutants and road traffic noise on incident HF. Akaike information criterion was used to evaluate the model fits.<sup>28</sup> The interquartile range (IQR) of the exposure was calculated as the difference between the 25th and 75th percentiles of the exposure levels. An association between exposure to a pollutant and incident HF was expressed as a hazard ratio (HR) with 95% CIs per IQR increase in the pollutant. We visualized the shape of an association between long-term exposure to PM<sub>2.5</sub>, NO<sub>2</sub>, and  $L_{den}$  and incident HF by using spline function with 3 degrees of freedom and tested for a deviation from linearity using a likelihood ratio test.

We investigated the effect modification of coexposures on the association between PM<sub>2.5</sub> and HF on a multiplicative scale.<sup>29</sup> We first categorized both NO<sub>2</sub> and  $L_{den}$  into 2 levels—low and high ( $\leq 75$ th and  $> 75$ th percentiles of exposure range)—and then estimated the association between PM<sub>2.5</sub> and HF in a single coexposure modifier (ie, NO<sub>2</sub>, low or high;  $L_{den}$ , low or high) or 2 coexposure modifiers (ie, a combination of NO<sub>2</sub> and  $L_{den}$ , low-low, low-high, high-low, or high-high). Effect modification on the multiplicative scale was presented as HRs of HF per IQR increase in PM<sub>2.5</sub>. In addition to the formal framework to investigate effect modification, we explored the risk of HF for those exposed to high levels of the 3 pollutants compared with low levels by stratifying the data into the following

3 groups: low levels of all 3 pollutants ( $PM_{2.5}$ ,  $NO_2$ , and  $L_{den}$ ), high levels of 1 or 2 pollutants, and high levels of all 3 pollutants. We then estimated HRs for each group compared with the reference group (low exposures to all 3 pollutants). In a sensitivity analysis, we estimated the risk of HF associated with the multiple exposures based on different cutoffs of the pollutants (eg, 25th and 50th percentiles).

Potential effect modifiers of the association between  $PM_{2.5}$  and incident HF were identified from the literature<sup>8,9,11,14,16</sup> and included age (<65 years or  $\geq 65$  years), obesity (BMI <30 kg/m<sup>2</sup> or  $\geq 30$  kg/m<sup>2</sup>), smoking (never, former, or current), alcohol consumption (never, moderate, or heavy), physical activity (low, medium, or high), shift work (day, evening, night, or rotating), history of hypertension and diabetes (no or yes), and urbanization (urban, suburban, or rural). The effect modification was evaluated in model 2 by testing the analysis of variance for the 2 models with and without the product term of a pollutant and an effect modifier. All tests for effect modification for which  $P < 0.05$  were considered statistically significant.

We conducted several sensitivity analyses. First, we explored potential calendar effects caused by a linear association between the time-varying primary exposure and calendar time<sup>30</sup> by comparing the associations with and without adjustment for calendar year using a spline function with 3 degrees of freedom. Second, as 23% of the original DNC participants were excluded because of missing information on covariates and exposure, we estimated inverse probability weight (IPW)-adjusted HRs to reduce selection bias as a result of missing data<sup>31</sup> (N=22 189 for included and N=6509 for excluded). We regressed a binary variable (1=included and 0=excluded participants) on the following covariates: age, baseline year, marital status, parity, and use of oral contraceptives (N=28 277). We selected the covariates when they were most available and significantly associated with the binary variable (inclusion versus exclusion). From the logistic regression, we estimated the probability of inclusion, took the inverse of probability (ie, IPW), and assigned the IPW to each participant. All analyses were conducted using R (version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

Of 28 727 participants, 29 participants with HF hospital contacts before baseline, 3422 with missing information on exposure during the follow-up, and 3087 with missing information on covariates at baseline were excluded (Figure S1). The excluded participants were different at cohort baseline from those included in the

analyses; they were older and less likely to be married; had normal weight; were never and former smokers, physically active, moderate and heavy drinkers, and actively working; were more likely to have ever used hormone therapy and never used oral contraceptives; were more likely to have hypertension and diabetes; and developed HF during the follow-up (Table S1).

Of the remaining 22 189 participants, a total of 484 developed HF (mean age, 60.4 years) during 401 930 person-years (mean, 18.1 person-years) of follow-up. Those who developed HF were more likely to be older and have a history of hypertension or diabetes and less likely to use oral contraceptives at baseline compared with those who never had HF during the follow-up (Table 1).

The 3-year running means of  $PM_{2.5}$ ,  $NO_2$ , and  $L_{den}$  at baseline were 21.0  $\mu\text{g}/\text{m}^3$  (IQR, 5.1  $\mu\text{g}/\text{m}^3$ ), 13.5  $\mu\text{g}/\text{m}^3$  (IQR, 8.6  $\mu\text{g}/\text{m}^3$ ), and 52.6 dB (IQR, 9.3 dB), respectively. The 3-year running mean of  $NO_2$  was moderately correlated with  $PM_{2.5}$  (Spearman's rank correlation coefficient [ $\rho$ ]=0.58) and  $L_{den}$  ( $\rho$ =0.62), whereas a correlation between  $PM_{2.5}$  and  $L_{den}$  was low ( $\rho$ =0.38; Table 2). Similar patterns were observed with 1-year and 23-year mean exposures (Table S2). Those who developed HF lived in areas with higher levels of  $PM_{2.5}$ ,  $NO_2$ , and  $L_{den}$  at cohort baseline compared with those who remained free of HF at the end of follow-up (Table S3).

We observed linear relationships between exposures to air pollution ( $PM_{2.5}$  and  $NO_2$ ) and  $L_{den}$  and incident HF (Figure 1). The likelihood ratio tests suggested no deviations from linearity in the association between 3-year running means of exposures and HF ( $P$  value ranged between 0.3 and 0.5).

In the crude model, we observed a significant association between  $PM_{2.5}$  and incident HF with an HR of 1.36 (95% CI, 1.20–1.55) per 5.1  $\mu\text{g}/\text{m}^3$  increase in  $PM_{2.5}$ . With additional adjustment for the individual-level and area-level covariates in model 2, we observed an attenuated association (HR, 1.17 [95% CI, 1.01–1.36] per IQR increase in  $PM_{2.5}$ ; Table 3). Figure S2 shows a lower Akaike information criterion value in model 2 than in model 1 and models with mutual adjustment. Associations between  $PM_{2.5}$  and HF were suggestive in the 2-pollutant and 3-pollutant models, although statistical significance was attenuated (Table 3). Additional adjustment for the calendar year in the model increased the estimates of HRs (Table S4). IPW-adjusted HRs were similar to the main results (Table S5).

Associations between  $NO_2$  and incident HF were significant in the crude model with an HR of 1.18 (95% CI, 1.08–1.29) per 8.6  $\mu\text{g}/\text{m}^3$  increase in  $NO_2$ , and attenuated after adjustment for the individual-level and area-level covariates to 1.10 (95% CI, 0.99–1.22). Additional adjustment for  $PM_{2.5}$  and  $L_{den}$  resulted in a reduced HR for  $NO_2$  to unity (1.00; 95% CI, 0.85–1.17; Table 3).

**Table 1. Descriptive Statistics for Participants From the Danish Nurse Cohort at the Year of Cohort Entry in 1993 or 1999 by the Incident Heart Failure Status at the End of Follow-Up**

	Total, N=22 189	No heart failure, N=21 705	Heart failure, N=484
Age at baseline, y, mean±SD	52.6±7.7	52.4±7.6	60.4±9.4
Marital status, n (%)			
Married	15 656 (70.6)	15 379 (70.9)	277 (57.2)
Separated	384 (1.7)	378 (1.7)	6 (1.2)
Divorced	2593 (11.7)	2530 (11.7)	63 (13.0)
Single	2224 (10.0)	2155 (9.9)	69 (14.3)
Widowed	1332 (6.0)	1263 (5.8)	69 (14.3)
Body mass index, kg/m <sup>2</sup> , mean±SD	23.7±3.5	23.7±3.5	24.6±4.2
Body mass index, n (%)			
Underweight, <18.5 kg/m <sup>2</sup>	542 (2.4)	522 (2.4)	20 (4.1)
Normal weight, 18.5–25 kg/m <sup>2</sup>	15 366 (69.3)	15 094 (69.5)	272 (56.2)
Overweight, 25–30 kg/m <sup>2</sup>	5032 (22.7)	4891 (22.5)	141 (29.1)
Obese, ≥30 kg/m <sup>2</sup>	1249 (5.6)	1198 (5.5)	51 (10.5)
Smoking status, n (%)			
Never	7724 (34.8)	7583 (34.9)	141 (29.1)
Former	6735 (30.4)	6600 (30.4)	135 (27.9)
Current	7730 (34.8)	7522 (34.7)	208 (43.0)
Alcohol consumption, n (%)			
None, 0 drinks/wk	3345 (15.1)	3236 (14.9)	109 (22.5)
Moderate, 1–14 drinks/wk	13 726 (61.9)	13 454 (62.0)	272 (56.2)
Heavy, ≥15 drinks/wk	5118 (23.1)	5015 (23.1)	103 (21.3)
Physical activity, n (%)			
Low	1445 (6.5)	1392 (6.4)	53 (11.0)
Medium	14 802 (66.7)	14 452 (66.6)	350 (72.3)
High	5942 (26.8)	5861 (27.0)	81 (16.7)
Diagnosis—hypertension, n (%)			
No	19 412 (87.5)	19 073 (87.9)	339 (70.0)
Yes	2750 (12.4)	2605 (12.0)	145 (30.0)
Diagnosis—diabetes, n (%)			
No	21 767 (98.1)	21 309 (98.2)	458 (94.6)
Yes	257 (1.2)	233 (1.1)	24 (5.0)
Hormone therapy use, n (%)			
Never	16 270 (73.3)	15 960 (73.5)	310 (64.0)
Past	2136 (9.6)	2048 (9.4)	88 (18.2)
Current	3783 (17.0)	3697 (17.0)	86 (17.8)
Oral contraceptive use, n (%)			
Never	8669 (39.1)	8373 (38.6)	296 (61.2)
Ever	13 520 (60.9)	13 332 (61.4)	188 (38.8)
Parity			
None	3172 (14.3)	3069 (14.1)	103 (21.3)
≥1 child	19 017 (85.7)	18 636 (85.9)	381 (78.7)

(Continued)

**Table 1. Continued**

	Total, N=22 189	No heart failure, N=21 705	Heart failure, N=484
Employment status, n (%)			
Actively working	17 901 (80.7)	17 667 (81.4)	234 (48.3)
Homemaker	379 (1.7)	367 (1.7)	12 (2.5)
Retired	3582 (16.1)	3349 (15.4)	233 (48.1)
Unemployed/rehabilitation	142 (0.6)	140 (0.6)	2 (0.4)
Other	185 (0.8)	182 (0.8)	3 (0.6)
Job strain, n (%)			
Low	17 147 (77.3)	16 927 (78.0)	220 (45.5)
High	803 (3.6)	788 (3.6)	15 (3.1)
Not working	4239 (19.1)	3990 (18.4)	249 (51.4)
Urbanization level, n (%)			
Urban	6827 (30.8)	6649 (30.6)	178 (36.8)
Suburban	5094 (23.0)	4994 (23.0)	100 (20.7)
Rural	10 268 (46.3)	10 062 (46.4)	206 (42.6)
Average municipality income, 1000 Danish Kroner, mean±SD	158.8±22.0	158.8±22.0	160.6±24.0

Similar to air pollutants, associations between  $L_{den}$  and incident HF were significant in the crude model with HRs of 1.18 (95% CI, 1.06–1.32) per 9.3 dB in  $L_{den}$ , and attenuated after adjustment for the individual-level and area-level covariates to 1.12 (95% CI, 0.99–1.26). The 3-year mean of  $L_{den}$  showed a suggestive association with incident HF after mutual adjustment for coexposures (PM<sub>2.5</sub> and NO<sub>2</sub>; HR, 1.09; 95% CI, 0.94–1.26; Table 3). Similar suggestive associations were also observed with 1-year and 23-year means of  $L_{den}$  (Table S6).

We observed no significant effect modification of coexposures (NO<sub>2</sub> and  $L_{den}$ ) on the association with PM<sub>2.5</sub> (Table S7). However, the exploratory analysis showed a higher risk of HF for those exposed to high levels (≤75th percentile) of the 3 pollutants (PM<sub>2.5</sub>, NO<sub>2</sub>, and  $L_{den}$ ): HRs of 1.15 (95% CI, 0.94–1.41) for high exposures to 1 or 2 pollutants and 1.43 (95% CI, 1.02–1.99) for high exposures to all 3 pollutants compared with those with low exposures to all 3 pollutants. Among the 25%, 50%, and 75% cutoff levels, those exposed to multiple pollutants ≥75% were most at risk (Table S8).

We observed significant effect modification by smoking status and hypertension at baseline on the association between a 3-year running mean of PM<sub>2.5</sub> and incident HF (Figure 2 and Table S9), showing the strongest associations in former smokers with an HR of 1.72 (95% CI, 1.25–2.36) and those with hypertension with an HR of 1.41 (95% CI, 1.02–1.93). Those with obesity and diabetes also showed greater

**Table 2. Distribution of 3-Year Running Means of Air Pollutants and Road Traffic Noise at the Cohort Baseline in 1993 or 1999 and Spearman’s Rank Correlation Coefficients Between the Exposure Levels**

Exposure	Mean±SD	Interquartile range	Percentile					Spearman’s rank correlation coefficient	
			5th	25th	50th	75th	95th	PM <sub>2.5</sub>	NO <sub>2</sub>
PM <sub>2.5</sub> , µg/m <sup>3</sup>	21.0±3.5	5.1	15.3	18.5	20.8	23.6	26.4		
NO <sub>2</sub> , µg/m <sup>3</sup>	13.5±8.1	8.6	5.6	8.2	11.1	16.8	28.4	0.58	
L <sub>den</sub> , dB	52.6±8.0	9.3	37.3	48.6	53.0	57.8	64.7	0.38	0.62

L<sub>den</sub> indicates overall weighted 24-hour noise level; and PM<sub>2.5</sub>, particulate matter with a diameter <2.5 µm.

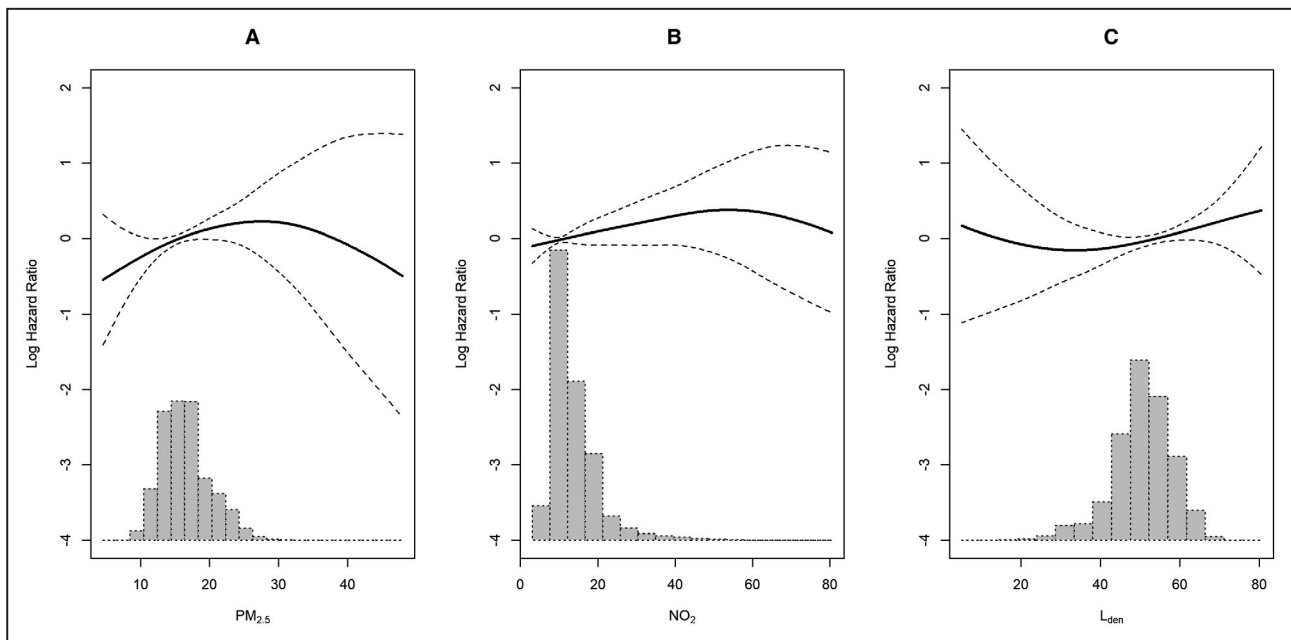
HRs, but the differences in HRs were not statistically significant.

## DISCUSSION

In a nationwide cohort of Danish female nurses, we found that long-term exposures to PM<sub>2.5</sub> and road traffic noise were associated with HF incidence. The associations remained suggestive even after mutual adjustment for copollutants. We observed an enhanced risk of HF incidence for those exposed to high levels of 3 pollutants; however, the effect modification of coexposure was weak. Former smokers and nurses with hypertension seemed to be most susceptible to air pollution exposure with respect to the risk of HF.

As this is the first study to consider the associations between PM<sub>2.5</sub>, NO<sub>2</sub>, and road traffic noise

simultaneously with incident HF, we cannot compare our results on effect modification of coexposure to these 3 pollutants directly to previous findings. However, the results from single pollutant models were generally in line with previous studies, suggesting an association between long-term exposure to PM<sub>2.5</sub> and incident HF.<sup>8,9,11,16,17</sup> Among the previous studies, Carey et al reported the greatest risk of incident HF associated with long-term exposure to PM<sub>2.5</sub> based in Greater London, United Kingdom, with 209 215 cohort participants with an HR of 2.04 (95% CI, 1.09–3.81) per 5.1 µg/m<sup>3</sup> increase in PM<sub>2.5</sub>,<sup>11</sup> followed by the Netherlands Cohort Study on Diet and Cancer (N=120 852) with an HR of 1.66 (95% CI, 1.18–2.33),<sup>18</sup> and the Primary Prevention Study (N=5850) from Sweden with an HR of 1.50 (95% CI, 1.06–2.13).<sup>15</sup> North American studies also demonstrated positive associations between PM<sub>2.5</sub> and HF, with HRs ranging



**Figure 1. Relationship between exposure to 3-year means of (A) PM<sub>2.5</sub>, (B) NO<sub>2</sub>, and (C) road traffic noise and incident heart failure in the Danish nurse cohort (N=22 189).**

Associations between 3-year exposures to (A) PM<sub>2.5</sub>, (B) NO<sub>2</sub>, and (C) road traffic noise and incident heart failure in the Danish nurse cohort were expressed in a solid spline line with 95% CIs (dashed spline lines). Histograms of distribution of 3-year exposures are drawn in light gray. Models adjusting for age (underlying time), a strata term of year of cohort entry (1993/1999), and individual-level and area-level covariates. L<sub>den</sub> indicates overall weighted 24-hour noise level; and PM<sub>2.5</sub>, particulate matter with a diameter <2.5 µm.

**Table 3. Hazard Ratios (95% CI) of Incident Heart Failure Associated With an Interquartile Range Increase in 3-Year Mean Exposures to PM<sub>2.5</sub>, NO<sub>2</sub>, and L<sub>den</sub> in the Danish Nurse Cohort (N=22 189)**

Exposure	Crude model	Fully adjusted model	Model of 2 pollutants			Model of 3 pollutants
	Model 1	Model 2	Model 2+PM <sub>2.5</sub>	Model 2+NO <sub>2</sub>	Model 2+L <sub>den</sub>	Model 2+PM <sub>2.5</sub> , NO <sub>2</sub> , and L <sub>den</sub>
PM <sub>2.5</sub>	1.36 (1.20–1.55)*	1.17 (1.01–1.36)*	—	1.13 (0.93–1.37)	1.14 (0.97–1.33)	1.14 (0.94–1.38)
NO <sub>2</sub>	1.18 (1.08–1.29)*	1.10 (0.99–1.22)†	1.04 (0.91–1.19)	—	1.06 (0.93–1.20)	1.00 (0.85–1.17)
L <sub>den</sub>	1.18 (1.06–1.32)*	1.12 (0.99–1.6)†	1.09 (0.96–1.23)	1.08 (0.93–1.24)	—	1.09 (0.94–1.26)

Model 1 adjusts for age (underlying time) and a strata term of year of cohort entry (1993/1999). Model 2 adjusts for individual-level and area-level covariates in addition to the covariates in model 1. HR indicates hazard ratio; L<sub>den</sub>, overall weighted 24-hour noise level (interquartile range, 9.3 dB); NO<sub>2</sub>, nitrogen dioxide (interquartile range, 8.6 µg/m<sup>3</sup>); and PM<sub>2.5</sub>, particulate matter with a diameter <2.5 µm (interquartile range, 5.1 µg/m<sup>3</sup>).

\*P<0.05.

†P<0.05.

between 1.07 and 1.30.<sup>9,16,17</sup> In contrast, a Dutch cohort study, the European Prospective Investigation Into Cancer and Nutrition (N=33 831), did not find an association between annual PM<sub>2.5</sub> concentrations and incident HF, with an HR of 0.43 (95% CI, 0.16–1.20<sup>12</sup>; Table S10).

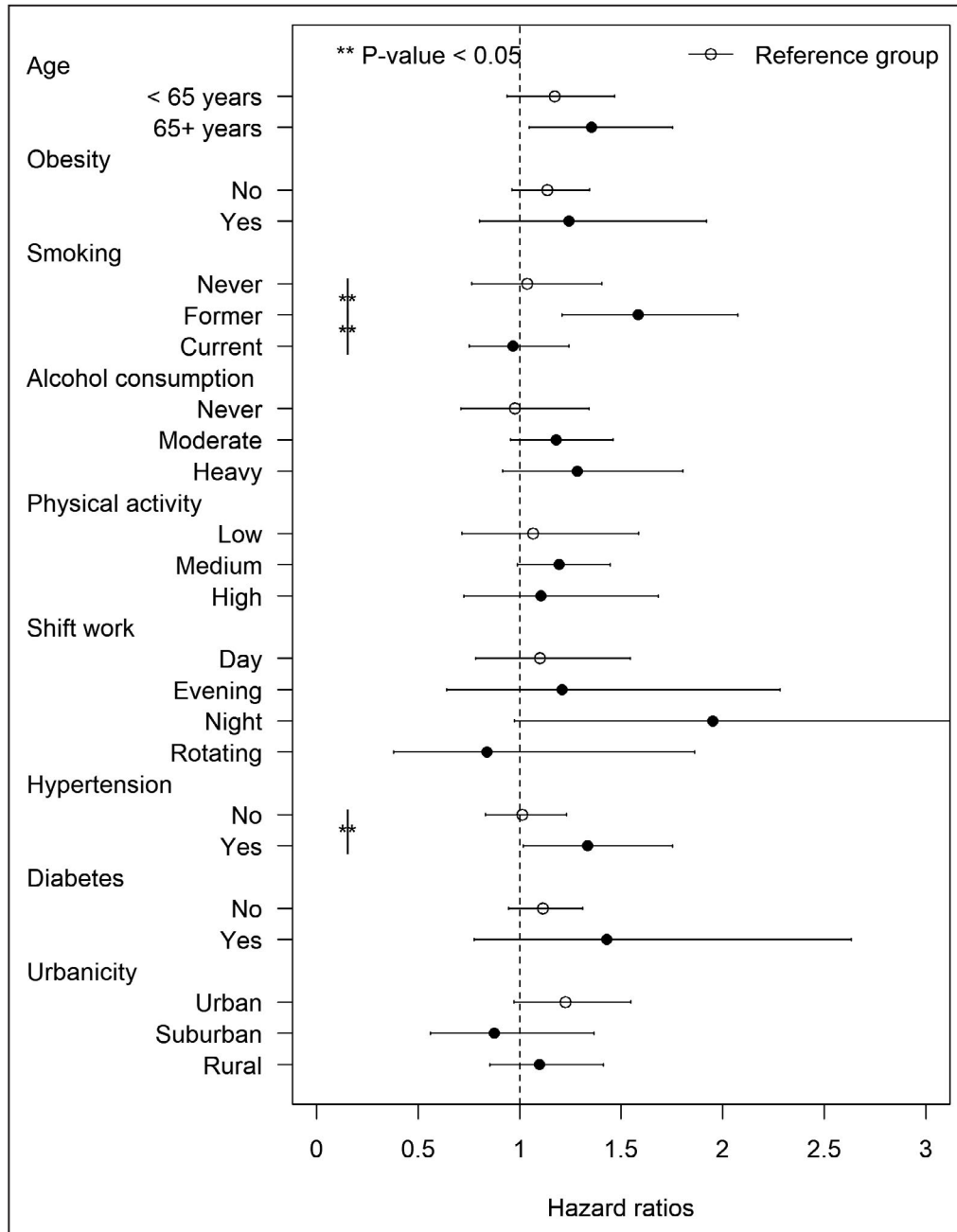
We found that the association of NO<sub>2</sub> with incident HF was sensitive to adjustment for PM<sub>2.5</sub> or L<sub>den</sub>, after which it attenuated to null. Evidence to date on NO<sub>2</sub> and HF suggested positive associations. However, few studies provided 2-pollutant models for NO<sub>2</sub>. In contrast to our results, Bai et al reported that the association with NO<sub>2</sub> remained robust even after adjustment for PM<sub>2.5</sub>.<sup>10</sup> On the other hand, 4 other studies detecting associations between NO<sub>2</sub> and HF did not additionally adjust for PM<sub>2.5</sub> or noise.<sup>8,9,12,13</sup> In another Danish cohort based on the 2 largest cities (Copenhagen and Aarhus), Sørensen et al reported a robust association of NO<sub>2</sub> with incident HF even after adjustment for L<sub>den</sub>,<sup>14</sup> but lacked data on PM<sub>2.5</sub>. The discrepancy between Sørensen et al's study and the present study could be explained by different follow-up periods (mean follow-up: 13.4 years in Sørensen et al study versus 18.1 years in the present study), age distribution at baseline (mean age at baseline 56.2 versus 52.6 years), sex (52.9% women versus 100% women), urbanicity (2 largest metropolitan areas versus all Denmark), NO<sub>2</sub> levels at baseline (15.7 µg/m<sup>3</sup> versus 13.5 µg/m<sup>3</sup>), and incidence rate of HF in 2 studies (5.0% versus 2.2%).

Of the 4 studies on road traffic noise and HF, 2 studies found no associations,<sup>10,21</sup> whereas 2 others detected associations, robust to adjustment for NO<sub>2</sub>.<sup>14,20</sup> These mixed results may be explained by different noise-modeling approaches. In the city of Toronto, Canada (1996–2012), poor resolution of noise estimated at the postal code level may explain the null association with HF in the study,<sup>10</sup> whereas the finer resolution of road traffic noise exposure (10 m×10 m) in the same population resulted in a positive association with HF (HR, 1.07; 95% CI, 1.06–1.09).<sup>20</sup> A total

of 2 European studies with road traffic noise at the address level also found significant positive associations between residential road traffic noise and HF.<sup>14,21</sup> We observed strong associations between residential road traffic noise and incident HF in the crude model, but the estimates attenuated after adjustment for NO<sub>2</sub> or PM<sub>2.5</sub>. Although previous studies on road traffic noise and HF have considered a confounding effect of NO<sub>2</sub>,<sup>10,14,20</sup> this is the first study to examine whether PM<sub>2.5</sub> confounded the association between road traffic noise and HF. However, as correlations among the 3 pollutants were high or moderate, caution is warranted when interpreting the results.

We explored calendar effects as Griffin et al reported that estimated effect size was deviated from the true estimation in the model with adjustment for calendar time that was correlated with time-varying exposure.<sup>30</sup> In the present study, we observed that PM<sub>2.5</sub> levels decreased over time; however, NO<sub>2</sub> and L<sub>den</sub> levels were not linearly related to calendar time. Accordingly, we observed that the estimated HR associated with PM<sub>2.5</sub> was sensitive (ie, increased) to adjustment for calendar year, but estimated HRs with NO<sub>2</sub> and L<sub>den</sub> were robust to the adjustment. This is in line with the authors' previous studies<sup>32,33</sup> showing that the estimated effect size was higher in the model with adjustment for calendar year compared with the model without adjustment for calendar year. Although this study ascertained that the higher estimated effect size of PM<sub>2.5</sub> may come from the negative linear relationship between PM<sub>2.5</sub> and calendar year, the impact of calendar year should be explored in other cohort studies.

We identified populations that are vulnerable to exposure to PM<sub>2.5</sub>. Former smokers and those with pre-existing hypertension at baseline showed enhanced associations between long-term exposure to PM<sub>2.5</sub> and incident HF, as compared with never smokers and those without hypertension, respectively. However, previous studies have reported mixed results: a Canadian study found greater estimates among smokers compared with nonsmokers,<sup>16</sup> whereas other



**Figure 2. Hazard ratios of incident heart failure associated with 3-year exposure to PM<sub>2.5</sub> by subgroups in the Danish Nurse Cohort study (N=22 189).**

Solid circles indicate hazard ratios of incident heart failure per interquartile range (5.1 µg/m<sup>3</sup>) increase in PM<sub>2.5</sub> among the subgroups compared with the reference groups (empty circles). Horizontal lines indicate 95% CIs. Models adjusting for age (underlying time), a strata term of year of cohort entry (1993/1999), and individual-level and area-level covariates. PM<sub>2.5</sub> indicates particulate matter with a diameter <2.5 µm.

studies found either no significant differences of estimates by smoking status or stronger associations among never smokers.<sup>8,11,18</sup> Smoking is a well-known risk factor for HF, with markedly increased risk among current smokers and more moderately increased risk among former smokers.<sup>34</sup> One potential explanation of our finding of the increased risk associated with PM<sub>2.5</sub>

exposure among former smokers might be that they are already at an increased risk as a result of earlier smoking priming for the effect of ambient air pollution. In contrast, the effect of current smoking is so strong that the effects of air pollution are difficult to detect. Another explanation is that those who stopped smoking might have done so, as they have already



noticed some bad influence on their health, whereas those who continued were potentially a more resistant subpopulation.

We did not observe multiplicative effect modification of coexposure on the association between  $PM_{2.5}$  and HF. However, the exploratory analysis showed that those exposed to high levels of the 3 pollutants had a higher risk of HF compared with those exposed to low levels. The result suggested a susceptible population who live in high levels of air pollutants and road traffic noise, and they may be targeted for the greatest potential to prevent HF. However, given these findings, the effect modification of coexposure should be explored in other cohorts.

Our finding of greater associations between  $PM_{2.5}$  and HF in individuals with hypertension and diabetes is in line with Sørensen et al, who detected a stronger association between  $NO_2$  exposure incident HF among participants who were hypertensive and diabetic compared with participants who were neither hypertensive nor diabetic, respectively.<sup>14</sup> Shin et al suggested a strong link between road traffic noise and hypertension and diabetes.<sup>35</sup> However, another study observed no difference by comorbidities (eg, hypertension, diabetes) on the association between exposure to  $PM_{2.5}$  and HF incidence.<sup>9</sup> Nevertheless, it is still important to identify susceptible populations and treat them with effective preventive strategies because diabetes and hypertension may induce hemodynamic and myocardial changes and narrow and block blood vessels, which lead to cardiac dysfunction or an increased predisposition to other HF risk factors.<sup>36,37</sup>

The major strength of this study is access to a large prospective cohort study with detailed information on historical exposures to several air pollutants ( $PM_{2.5}$  and  $NO_2$ ) and road traffic noise, for the first time, allowing for a detailed study of their independent effects on HF and effect modification of coexposures on the association. We also benefited from detailed information on potential confounders and HF risk factors that improved model fits as well as an objective and valid definition of HF incidence from the nationwide hospital register. The study covered all of Denmark, in contrast to the majority of previous studies based in urban areas, providing large contrasts in exposures to environmental factors. We benefited from a unique air pollution modeling system providing historical estimates of exposure to air pollution and road traffic noise with fine spatial resolution and taking residential mobility into account. Finally, we quantified the possible extent of selection bias and adjusted for it using IPW. The IPW generates weights that affect selection based on collected data of included and excluded participants.<sup>31</sup>

The present study also has several limitations. We lacked information on individual-level socioeconomic status, indoor air pollution sources at work and home,

individuals' time activity patterns (eg, time spent outdoors), the residence's window thickness or direction toward major roads or sound barriers, hearing impairment, annoyance by noise, and occupational noise exposure. Second, because of missing information on covariates and exposures, we excluded 23% of participants from the original DNC data and cannot rule out selection bias. Indeed, the excluded and included participants had different characteristics at baseline (Table S1). We estimated IPW from the logistic regression and estimated IPW-adjusted HRs to reduce the selection bias. However, we found that the IPW-adjusted and unweighted HRs showed similar results. Therefore, selection bias caused by missing information on covariates and exposures likely does not play a significant role in our analyses. It is noteworthy to address that the IPW cannot account for differences in selection caused by unmeasured factors, as the IPW generates weights based on collected data. Finally, when we compared the relative associations across pollutants, we did not account for relative measurement errors of exposures that could occur when we reflected participants' true exposures. These errors may differ by pollutant, which might modify observed associations with health in either direction.

In conclusion, our study suggests that long-term exposures to air pollution and road traffic noise were independently associated with HF incidence. Associations with HF were strongest and most robust with  $PM_{2.5}$ , whereas associations with  $NO_2$  attenuated to unity after adjustment for copollutants. We found a positive association between road traffic noise and HF, which attenuated slightly after adjustment for air pollutants. Former smokers and patients who are hypertensive seemed most susceptible to the adverse effects of  $PM_{2.5}$  on HF.

## ARTICLE INFORMATION

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### Affiliations

Section of Environmental Health, Department of Public Health, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark (Y.L., J.T.J., R.S., T.C., H.A., S.L., S.L., Z.J.A.); Seoul National University Medical Research Center, Seoul, Republic of Korea (Y.L.); Centre for Air Pollution, Energy and Health Research, University of Sydney, Australia (T.C.); Statistics Denmark, Copenhagen, Denmark (A.J.M., L.H.M.); Section of Epidemiology, Department of Public Health, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark (A.J.M., R.G.W., L.H.M.); Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA (H.A.); Department of Growth and Reproduction, Copenhagen University Hospital-Rigshospitalet, University of Copenhagen, Denmark (E.V.B.); Center for Healthy Aging, University of Copenhagen, Denmark (R.G.W.); Institute for Occupational, Social and Environmental Medicine, Centre for Health and Society, Medical Faculty, Heinrich-Heine-University of Düsseldorf, Germany (B.H.); Department of Environmental Science, Aarhus University, Roskilde, Denmark (M.K., O.H., J.B., S.S.J.); Global Centre for Clean Air Research, University of Surrey, United Kingdom (M.K.); iClimate-Aarhus University Interdisciplinary Center for Climate Change, Aarhus University, Roskilde, Denmark (J.B.); FORCE Technology,

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### Disclosures

None.

### Supplementary Material

Table S1–S10

Figure S1–S2

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# **Supplemental Material**

**Table S1. Descriptive statistics for the excluded and included participants in the Danish Nurse Cohort**

Variables	Total	Excluded	Included	P-value
	N = 28,698	N = 6,509	N = 22,189	
Age, mean $\pm$ SD	53.9 $\pm$ 8.5	58.2 $\pm$ 9.7	52.6 $\pm$ 7.7	<0.001
HF cases, n (%)	768 (2.7)	284 (4.4)	484 (2.2)	<0.001
Marital status, n (%)				<0.001
Married	19,871 (69.2)	4,215 (64.8)	15,656 (70.6)	
Separated	459 (1.6)	75 (1.2)	384 (1.7)	
Divorced	3,127 (10.9)	534 (8.2)	2,593 (11.7)	
Single	2,910 (10.1)	686 (10.5)	2,224 (10.0)	
Widowed	2,085 (7.3)	753 (11.6)	1,332 (6.0)	
Body mass index (kg/m <sup>2</sup> ), mean $\pm$ SD	23.7 $\pm$ 3.5	23.7 $\pm$ 3.6	23.7 $\pm$ 3.5	0.354
Body mass index (kg/m <sup>2</sup> ), n (%)				<0.001
Underweight (< 18.5)	750 (2.6)	208 (3.2)	542 (2.4)	
Normal weight (18.5-25)	19,467 (67.8)	4,101 (63.0)	15,366 (69.3)	
Overweight (25-30)	6,532 (22.8)	1,500 (23.0)	5,032 (22.7)	
Obese ( $\geq$ 30)	1,591 (5.5)	342 (5.3)	1,249 (5.6)	
Smoking status, n (%)				<0.001
Never	9,428 (32.9)	1,704 (26.2)	7,724 (34.8)	
Former	8,485 (29.6)	1,750 (26.9)	6,735 (30.4)	
Current	9,825 (34.2)	2,095 (32.2)	7,730 (34.8)	
Alcohol consumption, n (%)				<0.001
None (0 drinks/week)	4,589 (16.0)	1,244 (19.1)	3,345 (15.1)	
Moderate (1-15 drinks/week)	16,965 (59.1)	3,239 (49.8)	13,726 (61.9)	
Heavy (> 15 drinks/week)	6,285 (21.9)	1,167 (17.9)	5,118 (23.1)	
Physical activity, n (%)				<0.001
Low	2,044 (7.1)	599 (9.2)	1,445 (6.5)	
Medium	18,801 (65.5)	3,999 (61.4)	14,802 (66.7)	
High	7,496 (26.1)	1,554 (23.9)	5,942 (26.8)	

Diagnosis or medication - Hypertension, n (%)				<0.001
No	24,756 (86.3)	5,344 (82.1)	19,412 (87.5)	
Yes	3,899 (13.6)	1,149 (17.7)	2,750 (12.4)	
Diagnosis or medication - Diabetes, n (%)				<0.001
No	28,065 (97.8)	6,298 (96.8)	21,767 (98.1)	
Yes	374 (1.3)	117 (1.8)	257 (1.2)	
Hormone therapy use, n (%)				<0.001
Never	20,334 (70.9)	4,064 (62.4)	16,270 (73.3)	
Past	2,947 (10.3)	811 (12.5)	2,136 (9.6)	
Current	4,914 (17.1)	1,131 (17.4)	3,783 (17.0)	
Oral contraceptive use, n (%)				<0.001
Never	12,332 (43.0)	3,663 (56.3)	8,669 (39.1)	
Ever	16,188 (56.4)	2,668 (41.0)	13,520 (60.9)	
Employment status, n (%)				<0.001
Actively working	21,231 (74.0)	3,330 (51.2)	17,901 (80.7)	
Home-maker	525 (1.8)	146 (2.2)	379 (1.7)	
Retired	5,841 (20.4)	2,259 (34.7)	3,582 (16.1)	
Unemployed/rehabilitation	192 (0.7)	50 (0.8)	142 (0.6)	
Other	241 (0.8)	56 (0.9)	185 (0.8)	
Urbanization level, n (%)				0.821
Urban	8,827 (30.8)	2,000 (30.7)	6,827 (30.8)	
Suburban	6,606 (23.0)	1,512 (23.2)	5,094 (23.0)	
Rural	13,248 (46.2)	2,980 (45.8)	10,268 (46.3)	
Average municipality income (1,000 Danish Kroner (DKK), mean $\pm$ SD)	158.8 $\pm$ 22.0	158.8 $\pm$ 22.0	160.6 $\pm$ 24.0	0.999

P-value for the difference between excluded versus included participants (chi-square test for categorical variables and t-test for continuous variables)

**Table S2. Distribution of 1- and 23- year running means of air pollutants and road traffic noise at the cohort baseline in 1993 or 1999 and Spearman's rank correlation coefficients ( $\rho$ ) between the exposure levels**

	Runnin g mean year(s)	Mean $\pm$ SD	Interquar tile Range	Percentile					Spearman's rank correlation coefficients ( $\rho$ )	
				5 <sup>th</sup>	25 <sup>th</sup>	50 <sup>th</sup>	75 <sup>th</sup>	95 <sup>th</sup>	PM <sub>2.5</sub>	NO <sub>2</sub>
PM <sub>2.5</sub> , $\mu\text{g}/\text{m}^3$	1	19.4 $\pm$ 3.9	6.0	13.0	16.6	19.2	22.5	25.2		
	23	21.7 $\pm$ 3.1	4.5	16.8	19.3	21.8	23.8	26.5		
NO <sub>2</sub> , $\mu\text{g}/\text{m}^3$	1	12.9 $\pm$ 8.0	8.2	5.4	7.8	10.5	16.0	27.4	0.50	
	23	12.4 $\pm$ 6.5	7.5	5.5	8.0	10.7	15.5	23.7	-	
L <sub>den</sub> , dB	1	52.7 $\pm$ 8.1	9.4	37.0	48.6	53.1	58.0	64.9	0.32	0.61
	23	52.2 $\pm$ 6.8	7.7	39.9	48.9	52.7	56.6	62.0	-	0.61

PM<sub>2.5</sub>: particulate matter with a diameter < 2.5  $\mu\text{m}$  (23-year running means are not available); NO<sub>2</sub>: nitrogen dioxide; L<sub>den</sub>: 24-hour weighted average road traffic noise level

**Table S3. Mean exposure levels at cohort entry (1993 or 1999) by heart failure (HF) status, mean  $\pm$  standard deviation**

Exposure	Running mean year(s)	Total N = 22,189	No incident HF N = 21,705	Incident HF N = 484	P-value <sup>§</sup>
PM <sub>2.5</sub> , $\mu\text{g}/\text{m}^3$	1	19.4 $\pm$ 3.9	19.3 $\pm$ 3.9	21.5 $\pm$ 3.7	<0.001
	3	21.0 $\pm$ 3.5	21.0 $\pm$ 3.5	22.7 $\pm$ 3.5	<0.001
	23	21.7 $\pm$ 3.1	21.7 $\pm$ 3.1	23.0 $\pm$ 3.3	<0.001
NO <sub>2</sub> , $\mu\text{g}/\text{m}^3$	1	12.9 $\pm$ 8.0	12.9 $\pm$ 7.9	14.4 $\pm$ 9.8	<0.001
	3	13.5 $\pm$ 8.1	13.5 $\pm$ 8.1	15.1 $\pm$ 10.1	<0.001
	23	12.4 $\pm$ 6.5	12.4 $\pm$ 6.4	13.4 $\pm$ 7.8	0.004
L <sub>den</sub> , dB	1	52.7 $\pm$ 8.1	52.6 $\pm$ 8.1	54.2 $\pm$ 7.9	<0.001
	3	52.6 $\pm$ 8.0	52.6 $\pm$ 8.0	54.2 $\pm$ 7.9	<0.001
	23	52.2 $\pm$ 6.8	52.2 $\pm$ 6.8	53.2 $\pm$ 7.1	0.002

PM<sub>2.5</sub>: particulate matter with a diameter < 2.5  $\mu\text{m}$ ; NO<sub>2</sub>: nitrogen dioxide; L<sub>den</sub>: 24-hour weighted average road traffic noise level

<sup>§</sup>P-value for differences of exposure levels by HF status (incident versus no incident HF)



**Table S4. Hazard ratios of incident heart failure (HF) associated with an interquartile range (IQR) increase in three-year mean exposures to PM<sub>2.5</sub>, NO<sub>2</sub>, and L<sub>den</sub> in the Danish Nurse Cohort (N = 22,189): with adjustment of calendar year**

Exposure	Crude model	Fully adjusted model	Two-pollutant model			Three-pollutant model
	Model 1	Model 2	Model 2 + PM <sub>2.5</sub>	Model 2 + NO <sub>2</sub>	Model 2 + L <sub>den</sub>	Model 2 + PM <sub>2.5</sub> , NO <sub>2</sub> , and L <sub>den</sub>
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
PM <sub>2.5</sub>	1.45 (1.19, 1.76)*	1.35 (1.09, 1.67)*	-	1.44 (1.06, 1.95)*	1.30 (1.04, 1.64)*	1.44 (1.06, 1.96)*
NO <sub>2</sub>	1.15 (1.05, 1.26)*	1.09 (0.98, 1.22)	0.96 (0.82, 1.12)	-	1.05 (0.92, 1.20)	0.92 (0.77, 1.09)
L <sub>den</sub>	1.18 (1.05, 1.32)*	1.11 (0.99, 1.26)#	1.05 (0.93, 1.20)	1.08 (0.94, 1.25)	-	1.09 (0.94, 1.25)

PM<sub>2.5</sub>: particulate matter with a diameter < 2.5 µm (IQR: 5.1 µg/m<sup>3</sup>); NO<sub>2</sub>: nitrogen dioxide (IQR: 8.6 µg/m<sup>3</sup>); L<sub>den</sub>: 24-hour weighted average road traffic noise level (9.3 dB)

Model 1 adjusting for age (underlying time), a strata term of year of cohort entry (1993/1999), and a penalty spline term of calendar year

Model 2 adjusting for individual- and area-level covariates in addition to the covariates in Model 1

\*: P-value < 0.05; #: P-value < 0.1

**Table S5. Inverse probability weight (IPW)-adjusted hazard ratios of incident heart failure associated with an interquartile range (IQR) increase in 3-year exposure to air pollution and road traffic noise in the Danish Nurse Cohort study (N = 22,189)**

Exposure	Crude model	Fully adjusted model	Two-pollutant model			Three-pollutant model
	Model 1	Model 2	Model 2 + PM <sub>2.5</sub>	Model 2 + NO <sub>2</sub>	Model 2 + L <sub>den</sub>	Model 2 + PM <sub>2.5</sub> , NO <sub>2</sub> , and L <sub>den</sub>
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
PM <sub>2.5</sub>	1.36 (1.22, 1.50)*	1.18 (1.05, 1.33)*	-	1.15 (0.99, 1.34)	1.15 (1.02, 1.30)#	1.17 (1.00, 1.36)
NO <sub>2</sub>	1.17 (1.09, 1.26)*	1.10 (1.01, 1.19)#	1.03 (0.92, 1.15)	-	1.05 (0.95, 1.17)	0.98 (0.86, 1.11)
L <sub>den</sub>	1.18 (1.08, 1.30)*	1.12 (1.02, 1.24)#	1.09 (0.98, 1.21)	1.09 (0.97, 1.23)	-	1.10 (0.98, 1.24)

PM<sub>2.5</sub>: particulate matter with a diameter < 2.5 µm (IQR: 5.1 µg/m<sup>3</sup>); NO<sub>2</sub>: nitrogen dioxide (IQR: 8.6 µg/m<sup>3</sup>); L<sub>den</sub>: 24-hour weighted average road traffic noise level (9.3 dB)

Model 1 adjusting for age (underlying time) and a strata term of year of cohort entry (1993/1999)

Model 2 adjusting for individual- and area-level covariates in addition to the covariates in Model 1

\*: P-value < 0.05; #: P-value < 0.1

**Table S6. Hazard ratios of incident heart failure associated with an interquartile range (IQR) increase in 1- or 23-year exposure to air pollution and road traffic noise in the Danish Nurse Cohort study (N = 22,189)**

		Crude model	Fully adjusted model	Two-pollutant model			Three-pollutant model
		Model 1	Model 2	Model 2 + PM <sub>2.5</sub>	Model 2 + NO <sub>2</sub>	Model 2 + L <sub>den</sub>	Model 2 +
							PM <sub>2.5</sub> , NO <sub>2</sub> , and L <sub>den</sub>
Exposure		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
1-year	PM <sub>2.5</sub>	1.33 (1.15, 1.53)*	1.12 (0.95, 1.32)	-	1.07 (0.88, 1.30)	1.09 (0.92, 1.28)	1.08 (0.89, 1.33)
	NO <sub>2</sub>	1.16 (1.07, 1.27)*	1.08 (0.98, 1.20)	1.06 (0.93, 1.20)	-	1.04 (0.92, 1.17)	1.00 (0.86, 1.16)
	L <sub>den</sub>	1.19 (1.06, 1.33)*	1.12 (0.99, 1.27)#	1.11 (0.98, 1.25)	1.10 (0.95, 1.27)	-	1.11 (0.96, 1.28)
23-year	PM <sub>2.5</sub>	-	-	-	-	-	-
	NO <sub>2</sub>	1.14 (1.05, 1.23)*	1.07 (0.97, 1.18)	0.95 (0.83, 1.08)	-	1.02 (0.91, 1.15)	0.90 (0.78, 1.04)
	L <sub>den</sub>	1.17 (1.06, 1.30)*	1.12 (1.00, 1.25)#	1.06 (0.94, 1.19)	1.10 (0.96, 1.25)	-	1.11 (0.97, 1.26)

PM<sub>2.5</sub>: particulate matter with a diameter < 2.5 µm (IQR: 6.0 µg/m<sup>3</sup>); NO<sub>2</sub>: nitrogen dioxide (IQR: 8.2 and 7.5 µg/m<sup>3</sup> for 1- and 23-year running means); L<sub>den</sub>: 24-hour weighted average road traffic noise level (IQR: 9.3 and 7.7.dB 1- and 23-year running means)

-: no results; \*: P-value < 0.05; #: P-value < 0.1

Model 1 adjusting for age (underlying time) and a strata term of year of cohort entry (1993/1999)

Model 2 adjusting for individual- and area-level covariates in addition to the covariates in Model 1

Model 3 adjusting for a 3- year running mean of PM<sub>2.5</sub>, NO<sub>2</sub>, or L<sub>den</sub> in addition to the covariates in Model 2

\*: P-value < 0.05

**Table S7. Multiplicative effect modification of single- and two-co-exposures on the association between three-year exposure to PM<sub>2.5</sub> and incident heart failure**

Co-exposure	Level	Hazard ratio (95% Confidence intervals) per IQR (5.1 µg/m <sup>3</sup> ) increase in PM <sub>2.5</sub>	P-value <sup>§</sup>
<b>Single co-exposure</b>			
NO <sub>2</sub>	Low	1.20 (0.96, 1.50)	0.45
	High	1.04 (0.80, 1.36)	
L <sub>den</sub>	Low	1.12 (0.91, 1.38)	0.83
	High	1.13 (0.90, 1.42)	
<b>Two co-exposure</b>			
NO <sub>2</sub> ×L <sub>den</sub>	Low NO <sub>2</sub> – Low L <sub>den</sub>	1.10 (0.86, 1.40)	0.43
	Low NO <sub>2</sub> – High L <sub>den</sub>	2.10 (1.19, 3.68)*	
	High NO <sub>2</sub> – Low L <sub>den</sub>	1.05 (0.56, 1.95)	
	High NO <sub>2</sub> – High L <sub>den</sub>	1.06 (0.79, 1.43)	

Model adjusting for age (underlying time), a strata term of year of cohort entry (1993/1999), and individual- and area-level covariates

Low and high categories were determined based on the cutoff level of 75% (NO<sub>2</sub>: 16.8 µg/m<sup>3</sup>; L<sub>den</sub>: 57.8 dB)

<sup>§</sup> difference of estimates between subgroups; \*: P-value < 0.05

**Table S8. Risk of heart failure (HF) associated with multiple exposures to PM<sub>2.5</sub>, NO<sub>2</sub>, and L<sub>den</sub>**

Cutoff level	Exposure to 3-year running mean of PM <sub>2.5</sub> , NO <sub>2</sub> , and L <sub>den</sub>	Person-years	Incident HF	Hazard ratio (95% confidence intervals)
25%	Low-low-low	31,623	29	1.00 (reference)
	One or two high	153,222	172	1.20 (0.80, 1.78)
	High-high-high	223,932	283	1.33 (0.89, 1.99)
50%	Low-low-low	101,993	105	1.00 (reference)
	One or two high	202,169	236	1.12 (0.88, 1.42)
	High-high-high	104,615	143	1.32 (0.98, 1.77) <sup>#</sup>
75%	Low-low-low	223,309	244	1.00 (reference)
	One or two high	153,485	188	1.15 (0.94, 1.41)
	High-high-high	31,983	52	1.43 (1.02, 1.99) <sup>*</sup>

PM<sub>2.5</sub>: particulate matter with a diameter < 2.5 μm; NO<sub>2</sub>: nitrogen dioxide; L<sub>den</sub>: 24-hour weighted average road traffic noise level

Models adjusting for age (underlying time), a strata term of year of cohort entry (1993/1999), and individual- and area-level covariates.

Low and high categories were determined based on the various cutoff levels for 25% (PM<sub>2.5</sub>: 18.5 μg/m<sup>3</sup>; NO<sub>2</sub>: 8.2 μg/m<sup>3</sup>; L<sub>den</sub>: 48.6 dB); 50% (PM<sub>2.5</sub>: 20.8 μg/m<sup>3</sup>; NO<sub>2</sub>: 11.1 μg/m<sup>3</sup>; L<sub>den</sub>: 53.0 dB); and 75% (PM<sub>2.5</sub>: 23.6 μg/m<sup>3</sup>; NO<sub>2</sub>: 16.8 μg/m<sup>3</sup>; L<sub>den</sub>: 57.8 dB)

\*: P-value < 0.05; #: P-value < 0.1

**Table S9. Effect modification on the association between three-year exposure to PM<sub>2.5</sub> and incident heart failure (HF) in the Danish Nurse Cohort study (N = 22,189)**

	Effect modifiers	Hazard ratio (95% confidence intervals) per 5.1 µg/m <sup>3</sup> in PM <sub>2.5</sub>	P-value <sup>§</sup>
Age at baseline	< 65 years	1.21 (0.93, 1.57)	0.89
	≥ 65 years	1.43 (1.05, 1.93) *	
Obesity (<30 kg/m <sup>2</sup> )	No	1.16 (0.95, 1.42)	0.07
	Yes	1.29 (0.77, 2.15)	
Smoking	Never	1.04 (0.73, 1.49)	0.04
	Former	1.72 (1.25, 2.36) *	
	Current	0.96 (0.72, 1.29)	
Alcohol consumption	Never (0 drinks per week)	0.97 (0.67, 1.41)	0.72
	Moderate (1 - 14 drinks per week)	1.21 (0.95, 1.56)	
	Heavy (> 15 drinks per week)	1.34 (0.90, 2.00)	
Physical activity	Low	1.08 (0.67, 1.72)	0.70
	Medium	1.23 (0.99, 1.54) #	
	High	1.12 (0.68, 1.84)	
Shift work	Day	1.12 (0.75, 1.67)	0.34
	Evening	1.25 (0.59, 2.64)	
	Night	2.20 (0.97, 4.97) #	
	Rotating	0.81 (0.32, 2.08)	
Hypertension	No	1.01 (0.81, 1.28)	0.02
	Yes	1.41 (1.02, 1.93) *	
Diabetes	No	1.14 (0.94, 1.38)	0.29
	Yes	1.52 (0.74, 3.12)	
Urbanicity	Urban	1.27 (0.97, 1.67) #	0.07
	Suburban	0.86 (0.51, 1.44)	
	Rural	1.12 (0.83, 1.50)	

PM<sub>2.5</sub>: particulate matter with a diameter < 2.5 µm; NO<sub>2</sub>

Models adjusting for age (underlying time), a strata term of year of cohort entry (1993/1999), individual- and area-level covariates, and a 3-year running mean of L<sub>den</sub>

<sup>§</sup>Difference of estimates between subgroups; \*: P-value < 0.05; #: P-value < 0.05

**Table S10. Previous studies on the association between long-term exposure to PM<sub>2.5</sub>, NO<sub>2</sub>, and road traffic noise and heart failure**

Author (year)	Cohort/study, area, study period, and N	Disease definition	Exposure				Hazard ratios (95% Confidence intervals)		
			Period	Window	Variable §	Mean (5-95th percentile)	Adj†	Published	Per unit ¶
<b>Mortality</b>									
Beelen et al. (2009)	Netherlands Cohort Study on Diet and Cancer, the Netherlands, 1987-1996, N=120,852	ICD-9: 428; ICD-10: I50	1987-1996	10-year mean (1987-1996)	PM <sub>2.5</sub>	-	-	2.69 (1.37-5.27) per 10 µg/m <sup>3</sup>	1.66 (1.18-2.33)
<b>Incidence</b>									
Atkinson et al. (2013)	UK general practices cohort, UK, 2003-2007, N=810,188	ICD-10: I50	2002-2006	Previous year's annual mean	PM <sub>2.5</sub>	12.9 (SD: 1.4; min: 7.2; max: 20.2) in 2002	-	1.06 (1.01-1.11) per 1.9 µg/m <sup>3</sup>	1.17 (1.03-1.32)
					NO <sub>2</sub>	22.5 (SD: 7.4; min: 1.7; max: 60.8)	-	1.06 (1.01-1.11) per 10.7 µg/m <sup>3</sup>	1.05 (1.01-1.09)
To et al. (2015)	Canadian National Breast Screening Study, Canada, 1992-2013, N=29,549	ICD-9: 428; ICD-10: I500, I501, I509	1998-2006	9-year mean (1998-2006)	PM <sub>2.5</sub>	12.47 (SD: 2.40)	-	1.30 (1.11-1.52) per 10 µg/m <sup>3</sup>	1.14 (1.06-1.24)
Carey et al. (2016)	Greater London general practices cohort, UK, 2005-2011, N=209,215	ICD-10: I50	2004	1-year road traffic PM <sub>2.5</sub> (2004)	PM <sub>2.5</sub>	1.45 (SD: 0.52)	-	1.15 (1.02-1.30) per 1 µg/m <sup>3</sup>	2.04 (1.09-3.81)
Seidler et al. (2016)	Administrative cohort in Rhine-Main area of Germany, 2005-2010, N=654,172 control and 70,012 cases	ICD-10: I50	2005	Annual mean	Noise	(min: 40; max: 70)	-	1.01 (1.00-1.02) per 10 dB	1.01 (1.00-1.02)
Stockfelt et al. (2017)	The Primary Prevention Study, Sweden, 1990-2011, N=5,850	ICD-9: 428; ICD-10: I50, I11.0	1990-2011	5-year moving average	PM <sub>2.5</sub>	Median 9.3 (min: 6.3; max: 12)	-	1.49 (1.07-2.10) per 5 µg/m <sup>3</sup>	1.50 (1.06-2.13)
	The GOT-MONICA cohort, Sweden, 1990-2011, N=4,500	ICD-9: 428; ICD-10: I50, I11.0	1990-2011	5-year moving average	PM <sub>2.5</sub>	Median: 8.5 (min: 5.6; max: 12)	-	0.50 (0.21-1.17) per 5 µg/m <sup>3</sup>	0.49 (0.21-1.17)
Kim et al. (2017)	National Health Insurance Service – National Sample Cohort, 2007-2013, N=136,094	ICD-10: I11.0, I13.0, I13.2, I25.5, I42, I50, O90.3	2007-2013	7-year moving average	PM <sub>2.5</sub>	25.0 (SD: 14.3; min: 2.8; max: 121.2)	-	1.44 (1.29-1.61) per 1 µg/m <sup>3</sup>	6.42 (3.63-11.35)
					NO <sub>2</sub>	34.5 (SD: 12.9; min: 6.4; max: 92.4)	-	2.40 (2.02-2.85) per 18.4 ppb	1.62 (1.47-1.78)
Sørensen et al. (2017)	Danish Diet, Cancer, and Health cohort, 1993-2011, N=50,954	ICD-8: 427.0, 427.1; ICD-10: I50, I11.0, I42.0, I42.9	1993-2011		NO <sub>2</sub>	15.7 (12.2-33.5)	Noise	1.07(1.01,1.14) per 7.5 ug/m <sup>3</sup>	1.09 (1.01-1.17)

					Noise	57.0 (49.0–70.6)	NO <sub>2</sub>	1.08(1.00,1.16) per 9.9 dB	1.07 (1.00-1.14)
Downward et al. (2018)	The Dutch arm of this study (EPIC-NL), the Netherlands, 1993-2010, N=33,831	ICD-10: I50	2009	1-year (2009)	PM <sub>2.5</sub>	17 (SD: 0.56; min: 15.4; max: 20.95)	-	0.44 (0.16-1.20) per 5 µg/m <sup>3</sup>	0.43 (0.16-1.20)
					NO <sub>2</sub>	25 (SD: 6; min: 13; max: 62)	-	1.22 (1.01-1.48) per 10 µg/m <sup>3</sup>	1.19 (1.00-1.40)
Bai et al. (2018)	Ontario Population Health and Environment Cohort, Canada, 1996–2012, N=1,112,060	ICD-9: 428; ICD-10: I50	1996–2012	3-year moving average	NO <sub>2</sub>	21.4 (SD: 3.5; min: 9.9; max: 21.1)	PM <sub>2.5</sub>	1.05 (1.04-1.06) per 4.0 ppb	1.13 (1.10-1.16)
					Noise	NA	NO <sub>2</sub>	0.999 0.999-1.000	0.99 (0.98-1.00)
Bai et al. (2019)	Ontario Population Health and Environment Cohort, Canada, 2001-2015, N=5,062,146	ICD-9: 428; ICD-10: I50	1998-2012	3-year moving average	PM <sub>2.5</sub>	9.6 (SD: 2.8; min: 1.1; max: 20.0)	-	1.05 (1.04-1.05) per 3.5 µg/m <sup>3</sup>	1.07 (1.07-1.07)
					NO <sub>2</sub>	18.3 (SD: 8.5; min: 2.7; max: 71.4)	-	1.02 (1.01-1.04) per 13.9 ppb	1.01 (1.00-1.03)
Yazdi et al. (2019)	Medicare beneficiary cohort, USA, 2000-2012, N=11,084,660	ICD-9: 428	2000-2012	Annual mean	PM <sub>2.5</sub>	~12 (min: 7.5; max: 15)	-	1.053 (1.052–1.054) per 1 µg/m <sup>3</sup>	1.30 (1.30-1.31)
Bai et al. (2020)	Ontario Population Health and Environment Cohort, Canada, 2001-2015, N=986,295	ICD-9: 428; ICD-10: I50	2001-2015	3-year moving average	Noise	56.3 (SD: 7.1; min: 15; max: 85.3)	UFP/ NO <sub>2</sub>	1.07 (1.06-1.08) per 10.7 dB	1.06 (1.05-1.07)

§ PM<sub>2.5</sub>: particulate matter with a diameter < 2.5 µm (µg/m<sup>3</sup>); NO<sub>2</sub>: nitrogen dioxide (µg/m<sup>3</sup>); Noise: 24-hour weighted average road traffic noise level (dB)

† Mutual adjustment

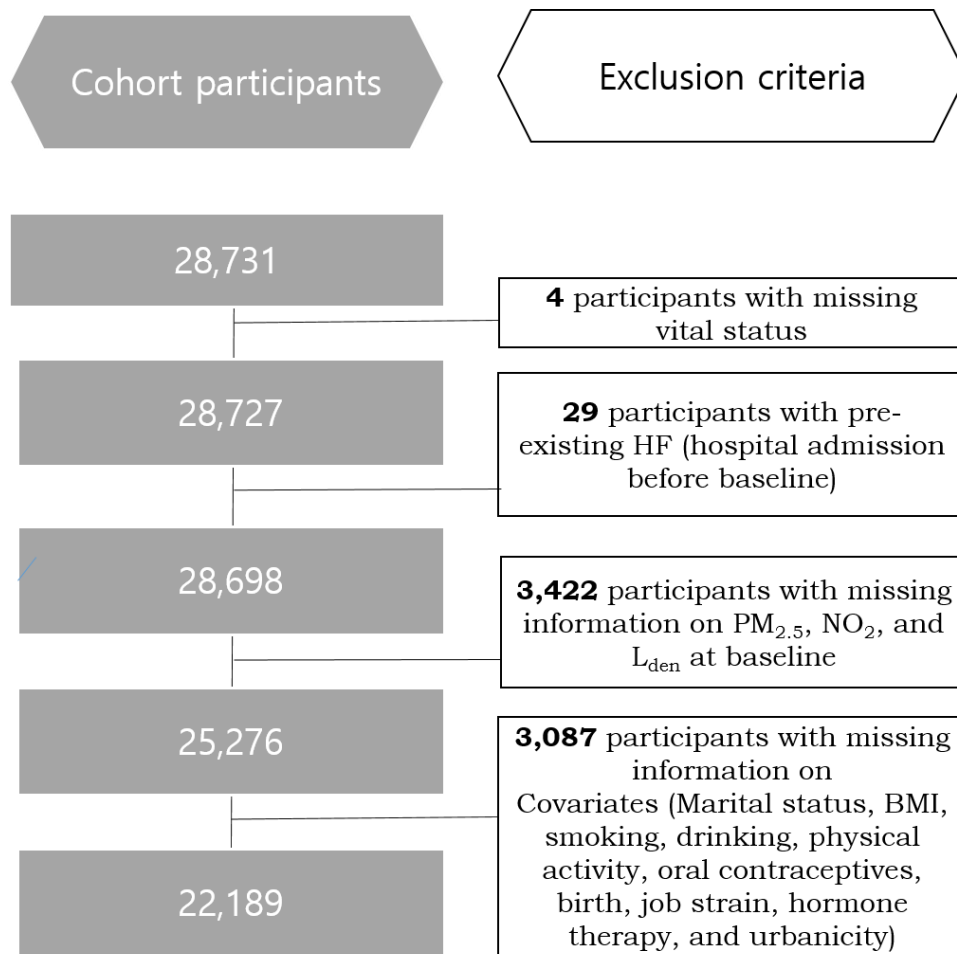
¶ PM<sub>2.5</sub>: 5.1 µg/m<sup>3</sup>; NO<sub>2</sub>: 8.6 µg/m<sup>3</sup>; Noise: 9.3 dB

ICD-8, 9, or 10: International classification of disease, 8<sup>th</sup>, 9<sup>th</sup>, or 10<sup>th</sup> version

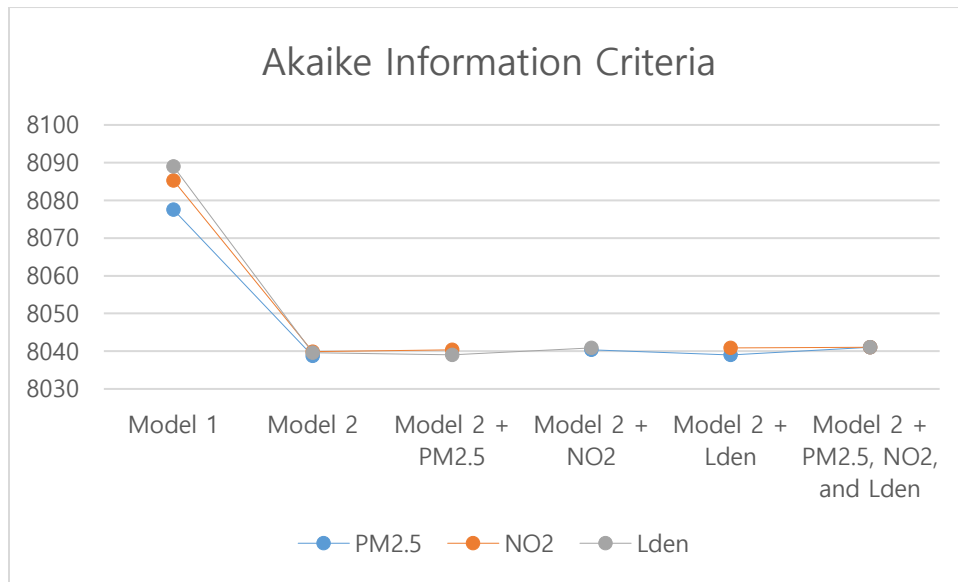
UFP: Ultrafine particle



**Figure S1. Number of participants in the study.**



**Figure S2. Akaike Information Criteria to compare models.**



PM<sub>2.5</sub>: particulate matter with a diameter < 2.5 μm; NO<sub>2</sub>: nitrogen dioxide; L<sub>den</sub>: 24-hour weighted average road traffic noise level

Model 1 adjusting for age (underlying time) and a strata term of year of cohort entry (1993/1999)

Model 2 adjusting for individual- and area-level covariates in addition to the covariates in Model 1