Long-term exposure to road traffic noise and incident myocardial infarction

A Danish Nurse Cohort study

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Background: Evidence of nonauditory health effects of road traffic noise exposure is growing. This prospective cohort study aimed to estimate the association between long-term exposure to road traffic noise above a threshold and incident myocardial infarction (MI) in Denmark.

Methods: In the Danish Nurse Cohort study, we used data of 22,378 women, at recruitment in 1993 and 1999, who reported information on MI risk factors. The participants’ first hospital contact or out-of-hospital death due to MI were followed-up until 2014. We investigated a relationship between residential exposures to road traffic noise levels ($L_{den}$) up to 23 years and incident MI (overall, nonfatal, and fatal) using time-varying Cox regression models adjusting for potential confounders and air pollutants. We estimated thresholds of road traffic noise (53, 56, and 58 dB) associated with incident MI in a piece-wise linear regression model.

Results: Of the 22,378 participants, 633 developed MI, 502 of which were nonfatal. We observed a non-linear relationship between the 23-year running mean of $L_{den}$ and incident MI with a threshold level of 56 dB, above which hazard ratios (95% confidence intervals) were 1.30 (0.97, 1.75) for overall and 1.46 (1.05, 2.03) for nonfatal MI per 10 dB. The association with nonfatal MI attenuated slightly to 1.34 (0.95, 1.90) after adjustment for fine particles.

Conclusions: We found that long-term exposure to road traffic noise above 56 dB may increase the risk of MI. The study findings suggest that road traffic noise above 56 dB may need regulation in addition to the regulation of ambient pollutants.

Keywords: Cohort study; Incidence; Myocardial infarction; Noise; Survival analysis; Threshold limit values

Introduction

Early studies suggesting physiological responses (increased blood pressure and altered heart muscle) to noise in animal experiments\textsuperscript{1,2} have set the scene for a surge in epidemiological studies investigating the effects of noise in humans,\textsuperscript{3} particularly with a focus on coronary syndrome including myocardial infarction (MI). The World Health Organization (WHO) has...
What this study adds
This study examines threshold levels of road traffic noise associated with the increased risk of myocardial infarction, using historical data of exposure to noise for up to 23 years, longest in literature so far, and adjusts in detail for relevant air pollutants (NO\textsubscript{2} and PM\textsubscript{2.5}). This study found that a 10 dB increase in long-term exposure to road traffic noise above 56 dB is associated with 30% and 46% increases in overall and nonfatal myocardial infarction incidence. The study findings suggest that road traffic noise above 56 dB may need regulation in addition to the regulation of ambient pollutants.

concluded that there is convincing evidence of increased risk of MI associated with road traffic noise in Europe\textsuperscript{4} based on recent reviews,\textsuperscript{5,6} yet several uncertainties remain. While the majority of prospective cohort studies observed an increased risk of MI associated with long-term exposure to road traffic noise,\textsuperscript{7-10} some reported no associations\textsuperscript{11,12} (Supplementary Material, Table S1; http://links.lww.com/EE/A134). Furthermore, the WHO report concluded that the association between road traffic noise and MI is observed only above a threshold of 53 dB, with no adverse conclusions that the association between road traffic noise and MI may need regulation in addition to the regulation of ambient pollutants.

Outcome definitions
Incident MI was determined by linking the cohort participants to the Danish Register of Causes of Death (DRCD) and the Danish National Patient Register (DNPR), available until 2013 and 2014, respectively.\textsuperscript{29,30} In this study, incident MI events were defined as a first-ever hospital contact (in-, outpatient, or emergency room) for MI in DNPR since 1977, which resulted in a primary diagnosis of MI (International Classification of Diseases, 8th Revision (ICD-8) before 1994: I21 or I22, 10th Revision (ICD-10) after 1994: I21 or I22). In a previous study, the proportion of patients registered with MI in DNPR as a primary discharge diagnosis who truly had MI, determined from medical record reviews and using discharge summaries as the reference standard, was reported as very high (\textgreek{g98.0\%}).\textsuperscript{20} In addition to hospital contacts due to MI, we included out-of-hospital deaths due to MI, defined in DRCD as death with the underlying cause with ICD-10 code: I21 (acute MI), I22 (subsequent MI), and I46 (sudden death), according to definitions in previous related studies (acute and subsequent MI in Vienneau et al.\textsuperscript{20} and sudden death in Roswall et al.\textsuperscript{21}) Fatal MI events were defined as out-of-hospital deaths as defined by the DRCD, and MI events resulting in death within 28 days following a hospital contact for a first-ever MI in DNPR; otherwise, MI cases were nonfatal.

Exposure
Road traffic noise
Road traffic noise levels were estimated using the validated model system, Nord2000,\textsuperscript{22} and traffic data from a national road and traffic database. The Nord2000 calculated noise contribution from roads within a 3-km radius from the participants’ residential addresses. Input data of the Nord2000 include address, geocodes, apartment height above street level, road lines with information on annual average daily traffic volume, composition, speed, road type, and properties (e.g., motorway, rural highway, roads wider than 6 m, and other roads), and building polygons for all surrounding buildings. In addition, meteorological information, including wind speed and direction, air temperature, and cloud cover, was used in the Nord2000 model. The Nord2000 method has been validated by 544 propagation cases, including nine cases with the calculation of the annual mean of A-weighted 24-hour noise mean levels from a road, covering propagation distances up to 300 m. The validation study showed that the difference between modeled and measured values of the road traffic noise was less than 0.5 dB and had a standard uncertainty of <1 dB.\textsuperscript{22}

We calculated the annual average road traffic noise levels for the participants’ residential addresses from 1970 to 2014. For the year that participants changed the address, we calculated annual road traffic noise levels at the year of an address change as the mean of levels at two addresses (the old address and the new one). Estimated as the equivalent continuous A-weighted sound pressure level (L\textsubscript{Aeq})
at the most exposed façade of the dwelling, annual road traffic noise levels were estimated for the day ($L_d$, from 07:00 hours to 19:00 hours), evening ($L_e$, from 19:00 hours to 22:00 hours), and night ($L_n$, from 22:00 hours to 07:00 hours). Weights of 5 and 10 dB for the evening and night hours, respectively, were given when we calculated a weighted mean of 24-hour noise levels ($L_{eq}$). As we had data on noise exposure from 1970 to 2014 and intended to link the noise exposure to the year before the end of follow-up, we considered maximum exposure length up to 23 years. We calculated 1-, 3-, and 23-year running means of the noise levels to explore distinguished associations of incident MI with different exposure windows and assigned the multyear residential exposure to road traffic noise in a yearly time interval between the baseline year and last year of follow-up (Supplementary Material, Figure S2; http://links.lww.com/EE/A134). We chose three exposure windows: 1-year running mean to explore the effect of most recent and acute exposure to noise preceding year of MI diagnosis; 23-year mean, which is the longest available mean level (road traffic noise available since 1970), to examine the effect of chronic exposure to noise over many years, as a proxy of lifetime exposure to noise; and 3-year mean, which is the longest available mean exposure for PM$_{2.5}$ (available since 1990), which we consider as an important confounder. In addition, various exposure times of day for road traffic noise ($L_{d}$, $L_{e}$, $L_{n}$, and $L_{eq}$) were also considered separately.

### Air pollution

We estimated annual mean concentrations of NO$_2$ and PM$_{2.5}$ based on the participants’ residential addresses using the Danish air pollution modeling system, Danish Eulerian Hemispheric Model/Urban Background Model/AirGIS (https://au.dk/ AirGIS), which comprises three air pollution models. The three models included the Danish Eulerian Hemispheric Model to estimate the long-range transport, the Urban Background Model to calculate the local background on a 1-km² resolution grid overlaying Denmark, and the Operational Street Pollution Model to estimate the air pollution concentrations at the front door of the address. Due to the availability of necessary input data for the model system, we obtained annual mean concentrations of NO, between 1970 and 2014 and PM$_{2.5}$ between 1990 and 2014, and assigned the 3-year running mean of air pollution to the participants based on the residential address in a yearly time interval during the follow-up.

### Covariates

We used information on individual characteristics collected at the cohort recruitment including smoking status (never, previous, or current), alcohol consumption (never: no alcohol drink; moderate: 1–14 units per week; or heavy: ≥15 units per week), leisure-time physical activity (low, medium, or high), marital status (married, separated, divorced, single, or widowed), parity (none or one child), employment status (working, home-maker, retired, unemployed/rehabilitation, or other), use of oral contraceptives (never or ever), and hormone-replacement-therapy (never, previous, or current). We also categorized participants into three job strain categories (low, high, or unemployed) by combining three items: workload, busyness, and control of work. Based on the municipality of the residential address, the level of urbanization was defined: urban (cities—densely populated areas: at least 50% of the population lives in urban centers), suburban (town and suburbs—intermediate density areas: less than 50% of the population lives in rural grid cells and less than 50% of the population lives in urban centers), and rural ( thinly populated areas: more than 50% of the population lives in rural grid cells).

### Statistical analysis

Survival analyses were performed using time-varying Cox regression models with age as the underlying time scale. We visualized the shape of an association between exposure to road traffic noise and incident MI in a residual plot, by fitting the following hazard function $λ(t)$:

$$d(t) = λ_0(t) \exp\left[γ_1 \times X_1 + γ_2 \times (X_1 - ξ) + S(Year, df = 3) + \text{strata(cohort)} + \text{covariates}\right]$$

Here, $λ(t)$ is the baseline hazard function where $S(X, df = 3)$ is a spline term for road traffic noise levels, $X$, with three degrees of freedom (df), $S(Year, df = 3)$ is a spline term of calendar year, and strata(cohort) is stratification by the year of cohort entry (1993 or 1999). The df for the spline term of road traffic noise was selected based on the lowest Akaike Information Criteria (AIC) among various dfs (between 2 and 6) (Supplementary Material, Figure S3; http://links.lww.com/EE/A134). Y-axis in the residual plot indicated hazard ratios (HRs) at certain $L_{eq}$ levels (ranges between 0 and 80 dB) compared to the risk at 56 dB of $L_{eq}$. Gray vertical lines in the residual plots were drawn at 53 dB (a solid line), 56 dB (a dashed line), and 58 dB (a dotted line) of road traffic noise.

When the residual plot showed a nonlinear relationship between road traffic noise and incident MI with a significant deviation from linearity using a likelihood ratio test, we incorporated a piece-wise linear regression model into a survival analysis to estimate the effect at or above the threshold level ($ξ$). The hazard function, $λ(t)$, can be written as:

$$d(t) = λ_0(t) \exp(γ_1 \times X_1 + γ_2 \times (X_1 - ξ) + S(Year, df = 3) + \text{strata(cohort)} + \text{covariates})$$

Here, $γ_1$ and $γ_2$ are constant coefficients of $X_1$ and $(X_1 - ξ)$, respectively. We adjusted for a spline term of calendar year [$S(Year, df = 3)$], stratification by the year of cohort entry (1993 or 1999) [strata(cohort)], and covariates. $X_1 - ξ$ is determined as $X_1 - ξ$ if $X_1$ is at or above $ξ$, where $ξ$ is a threshold level of road traffic noise. If $X_1$ is less than $ξ$, $(X_1 - ξ)$ equals 0. We fitted models by applying various threshold levels ($ξ$) of road traffic noise between 41 and 60 dB with 1 dB interval (e.g., 41, 42, 43, ..., 58, 59, and 60) and compared AIC values derived from models. We used the lowest AIC value as criteria for the best-fit. An association between incident MI and road traffic noise levels at or above the threshold $ξ$ was expressed as an HR of $\exp(γ_1 + γ_2 \times ξ)$ with 95% confidence intervals (CI) of $\exp(γ_1 + γ_2 \times ξ) \pm 1.96 \times \text{pooled standard error}$, where the pooled standard error was calculated by taking a squared root of $\left[\var(γ_1) + \var(γ_2) + 2 \times \text{cov}(γ_1, γ_2)\right]$. In addition to threshold levels derived from the piece-wise linear regression models, we also considered associations at or above the WHO threshold levels and Danish government recommended limit levels (53 and 58 dB, respectively). Spearman’s rank correlation coefficients ($ρ$) among 1-year running means of road traffic noise and air pollutants at baseline were computed.

Four piece-wise linear regression models were incorporated into survival analyses. In model 1, we examined associations between road traffic noise exposure ($L_{eq}$, $L_d$, $L_e$, and $L_n$) and incident MI after adjusting for calendar year and the year of cohort entry. In model 2, we additionally controlled for the individual potential confounders, including BMI, smoking status, alcohol consumption, leisure-time physical activity, marital status, parity, employment status, use of oral contraceptives, hormone replacement therapy, job strain, and the level of urbanization. In models 3, we controlled for either 3-year running means of NO$_2$ [model 3 (a)] or PM$_{2.5}$ [model 3 (b)] to examine the unconfounded effects of road traffic noise on incident MI. Potential effect modifiers of the association between road traffic noise and incident MI were explored in the form of...
binary responses. These included age (< or ≥65 years), marital status (married or unmarried), obesity (BMI≥ or ≥30 kg/m²), ever-smoking (no or yes), regular alcohol consumption (never or moderate/heavy), physical activity (low or medium/high), regular vegetable consumption (rarely or a few/several times a week), actively working (no or yes), shift work (day or night/evening shift), history of self-reported diagnosis or medications use for hypertension and diabetes (no or yes), urbanization (urban or rural/suburban), 1-year mean levels of NO₂ and PM₂.5 (< or ≥median levels, 10.5 and 19.2 µg/m³, respectively) at baseline.

Estimated effects of the associations between long-term exposure to road traffic noise on overall, nonfatal, and fatal incident MI were expressed as HRs with 95% CI per 10 dB increase in road traffic noise levels. When the risk of incident MI was non-linearly associated with increases in noise levels, HRs of incident MI were expressed with 95% CI per 10 dB increase in road traffic noise ≥ threshold levels (53, 56, and 58 dB). However, when the linear assumption was met (e.g., fatal MI), only linear estimates of HRs with 95% CI per 10 dB increase in road traffic noise levels were presented. The Cox proportional hazard assumption was checked using a statistical test based on the scaled Schoenfeld residuals and a Kaplan–Meier curve for 23-year mean levels of Lden (< or ≥median, 53.4 dB). All analyses were conducted using the R 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Of 22,378 included participants, a total of 633 developed MI during 404,802 person-years or 18.1 years of follow-up, and of these, 502 (79.3%) were nonfatal (mean age 69.8 years at the onset of MI) and 131 (20.7%) were fatal (mean age 75.3 years at the onset of MI). Those who developed MI were more likely to have a self-reported diagnosis or medication use for hypertension or diabetes and less likely to use oral contraceptives at baseline, compared to those who never had MI during the follow-up (Table 1). Less than a third of cohort participants lived in urban areas at baseline. Kaplan–Meier curves based on the scaled Schoenfeld residuals and a Kaplan–Meier curve for 1-year mean levels of NO₂ and PM₂.5 (< or ≥median levels, 53.4 dB) are shown in Table 1. Nonfatal MI was slightly greater with exposure to road traffic noise in the evening compared to the other time of day (day- and nighttime hours) (Supplementary Material, Table S5; http://links.lww.com/EE/A134). An association with nonfatal MI was slightly greater with exposure to road traffic noise above this threshold during the evening compared to the other time of day (day- and nighttime hours) (Supplementary Material, Table S5; http://links.lww.com/EE/A134).

We observed that the adjustment for a 3-year running mean of PM₂.5 [model 3 (b)]: HRs for overall and nonfatal incident MI: 1.23 [95% CI = 0.90, 1.69] and 1.34 [95% CI = 0.95, 1.90] per 10 dB, respectively (Table 3). Different thresholds (53 or 58 dB) (Table 3) and exposure windows (1- and 3-year) (Supplementary Material, Table S5; http://links.lww.com/EE/A134) resulted in similar findings, whereas more attenuated associations after adjustment for PM₂.5 were observed compared to the adjustment for NO₂ (Supplementary Material, Figure S7; http://links.lww.com/EE/A134). An association with nonfatal MI was slightly greater with exposure to road traffic noise in the evening compared to the other time of day (day- and nighttime hours) (Supplementary Material, Table S6; http://links.lww.com/EE/A134). We did not observe effect modification of an association between the 23-year running mean of Lden and nonfatal incident MI by any factors (Supplementary Material, Table S7; http://links.lww.com/EE/A134).

Discussion

In this cohort of Danish nurses aged 44 years and above, we detected a nonlinear association between long-term exposure to road traffic noise and MI incidence, and identified a threshold at 56 dB. We found that women who were exposed to high levels of road traffic noise (≥56 dB) were more likely to be diagnosed with MI. In women living in areas with road traffic noise levels higher than 56 dB, the risk of overall and nonfatal MI incidence increased by 30% and 46% for each 10 dB increase in 23-year mean road traffic noise. The associations remained significant even after taking into account the residential air pollution levels. The results of the present study are in line with the general WHO consensus that road traffic noise leads to negative auditory health effects.¹⁴ However, the directions of the associations differ by study areas, the definition of MI (prevalent vs. incident), and sex. A previous cohort study based in Stockholm County, Sweden, reported that incident MI among women was associated with 5-year mean exposure to road traffic noise with an HR of 1.17 [95% CI = 1.03, 1.34] per 10 dB of Lden, whereas a negative association was detected in men with an HR of 0.84 [95% CI = 0.74, 0.94].¹⁵ In contrast, Roswall et al observed stronger associations of overall MI with road traffic noise in men (HR: 1.16 [95% CI = 1.08, 1.25]) than in women (HR:
1.08 [95% CI = 0.97, 1.21]) in the Greater Copenhagen and Aarhus, Denmark. The inconsistent findings may come from a failure of disentangling the impact of biological sex from that of gender. Other studies have likewise reported significant associations, including a Swiss national cohort study of 4.35 million residents (3% increased risk of MI deaths per 10 dB increments in traffic noise) and a Germany case-control study of 0.85 million participants (OR: 1.03 [95% CI = 1.01, 1.05]), whilst other case-control studies found no associations. However, after including those without hearing impairment and other noise exposures or those living at the same residential address longer than 10 years, they observed stronger associations.

Roswall et al. and the present study examined the relationship between long-term exposure to road traffic noise and

| Table 1. Descriptive statistics for participants from the Danish Nurse Cohort at the year of cohort entry in 1993 or 1999. |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Variables       | Total N = 22,378 | No incident myocardial infarction (MI) N = 21,745 | Incident MI N = 633 | Nonfatal MI N = 502 (79.3%) | Fatal MI N = 131 (20.7%) |
| Total time at risk, sum (mean) | 404,802.0 (18.1) | 404,802.0 (18.1) | 404,802.0 (18.1) | 504,467.5 (18.3) |
| Age at baseline, mean ± SD | 52.5 ± 7.6 | 52.3 ± 7.5 | 51.0 ± 9.4 | 57.7 ± 8.6 | 64.2 ± 10.4 |
| Age at incident MI | 71.0 ± 10.1 | 69.8 ± 9.7 | 75.3 ± 10.6 |
| Marital status, n (%) | Married 15,801 (70.6) | 15,405 (70.8) | 396 (62.6) | 332 (66.1) | 64 (48.9) |
| Divorced 2,645 (11.8) | 2,576 (11.8) | 69 (10.9) | 55 (11.0) | 14 (10.7) |
| Widowed 1,323 (5.9) | 1,241 (5.7) | 82 (13.0) | 59 (11.8) | 23 (17.6) |
| BMI (kg/m²), mean ± SD | 23.7 ± 3.5 | 23.7 ± 3.5 | 24.3 ± 3.8 | 24.3 ± 3.9 | 24.0 ± 3.4 |
| BMI (kg/m²), n (%) | Underweight (<18.5) 550 (2.5) | 530 (2.4) | 20 (3.2) | 14 (2.8) | 6 (4.6) |
| Normal weight (18.5–25) 15,511 (69.3) | 15,128 (69.6) | 383 (60.5) | 307 (61.2) | 76 (58.0) |
| Overweight (25–30) 5,060 (22.6) | 4,881 (22.4) | 179 (28.3) | 138 (27.5) | 41 (31.3) |
| Obese (≥30) 1,257 (5.6) | 1,206 (5.5) | 51 (8.1) | 43 (8.6) | 8 (6.1) |
| Smoking status, n (%) | Never 7,793 (34.8) | 7,647 (35.2) | 146 (23.1) | 119 (23.7) | 27 (20.6) |
| Current 7,799 (34.9) | 7,472 (34.4) | 252 (40.2) | 57 (53.7) | 8 (6.1) |
| Alcohol consumption, n (%) | None (0 drinks/week) 3,358 (15.0) | 3,215 (14.8) | 143 (22.6) | 113 (22.5) | 30 (22.9) |
| Moderate (1–15 drinks/week) 13,850 (61.9) | 13,491 (62.0) | 359 (56.7) | 286 (57.0) | 73 (55.7) |
| Heavy (>15 drinks/week) 5,170 (23.1) | 5,039 (23.2) | 131 (20.7) | 103 (20.5) | 28 (21.4) |
| Physical activity, n (%) | Low 1,454 (6.5) | 1,384 (6.4) | 70 (11.1) | 44 (8.8) | 26 (19.8) |
| Medium 14,918 (66.7) | 14,495 (66.7) | 423 (66.8) | 338 (67.3) | 85 (64.9) |
| High 6,006 (26.8) | 5,866 (27.0) | 140 (22.1) | 120 (23.9) | 20 (15.3) |
| Diagnosis or medication—hypertension, n (%) | No 19,632 (87.7) | 19,173 (88.2) | 459 (72.5) | 370 (73.7) | 89 (67.9) |
| Yes 2,718 (12.1) | 2,547 (11.7) | 171 (27.0) | 130 (25.9) | 41 (31.3) |
| Diagnosis or medication—diabetes, n (%) | No 21,968 (98.2) | 21,362 (98.2) | 606 (95.7) | 484 (96.4) | 122 (93.1) |
| Yes 248 (1.1) | 229 (1.1) | 19 (3.0) | 11 (2.2) | 8 (6.1) |
| Hormone therapy use, n (%) | Never 16,421 (73.4) | 16,024 (73.7) | 397 (62.7) | 312 (62.2) | 85 (64.9) |
| Past 2,134 (9.5) | 2,025 (9.3) | 109 (17.2) | 84 (16.7) | 25 (19.1) |
| Current 3,823 (17.1) | 3,696 (17.0) | 127 (20.1) | 106 (21.1) | 21 (16.0) |
| Oral contraceptive use, n (%) | Never 8,673 (38.8) | 8,296 (38.2) | 377 (59.6) | 275 (54.8) | 102 (77.9) |
| Ever 13,705 (61.2) | 13,449 (61.8) | 256 (40.4) | 227 (45.2) | 29 (22.1) |
| Parity | None 3,174 (14.2) | 3,060 (14.1) | 114 (18.0) | 73 (14.5) | 41 (31.3) |
| >One child 19,204 (85.8) | 18,685 (85.9) | 519 (82.0) | 429 (85.5) | 90 (68.7) |
| Employment status, n (%) | Actively working 18,151 (81.1) | 17,802 (81.9) | 349 (55.1) | 299 (59.6) | 50 (38.2) |
| Home-maker 382 (1.7) | 370 (1.7) | 12 (1.9) | 9 (1.8) | 3 (2.3) |
| Retired 3,211 (15.7) | 3,245 (14.9) | 266 (42.0) | 189 (37.6) | 77 (58.8) |
| Unemployed/rehabilitation 145 (0.6) | 142 (0.7) | 3 (0.5) | 2 (0.4) | 0 (0.0) |
| Other 189 (0.8) | 186 (0.9) | 3 (0.5) | 3 (0.6) | 0 (0.0) |
| Job strain | Low 17,390 (77.7) | 17,059 (78.5) | 331 (52.3) | 285 (56.8) | 46 (35.1) |
| High 811 (3.6) | 791 (3.6) | 20 (3.2) | 16 (3.2) | 4 (3.1) |
| Not working 4,177 (18.7) | 3,895 (17.9) | 282 (44.5) | 201 (40.0) | 81 (61.8) |
| Urbanization level, n (%) | Urban 6,898 (30.8) | 6,728 (30.9) | 170 (26.9) | 134 (26.7) | 36 (27.5) |
| Suburban 5,158 (23.0) | 5,023 (23.1) | 135 (21.3) | 106 (21.1) | 29 (22.1) |
| Rural 10,322 (46.1) | 9,904 (46.0) | 228 (35.8) | 262 (52.2) | 66 (50.4) |
incident MI in Denmark, but the two studies suggest different exposure-response functions (linear and nonlinear associations, respectively). Although both studies used the MI incidence definition based on hospital contacts due to MI that is reported as reliable (>98% of positive predicted value), several factors may be accountable for the discrepancy between the two studies. In essence, the present study had longer follow-up periods (mean follow-up: 14.5 years in Roswall et al’s study vs. 18.1 years in the present study), younger participants at baseline (mean age at baseline: 57.5 years vs. 52.5 years), different distribution of sex (53.5% women vs. 100% women), urban setting (two metropolitan areas vs. all areas in Denmark), lower road traffic noise and NO2 levels at baseline (57.1 dB and 15.7 µg/m3 vs. 52.7 dB and 12.9 µg/m3), and a lower percentage of incident MI (2,403 [4.7%] vs. 633 [2.8%]) (Supplementary Material, Table S8; http://links.lww.com/EE/A134).

Furthermore, fatal MI was positively associated with exposure to road traffic noise in the Roswall et al study. In contrast, we could not confirm the association in the present study. The discrepancy could be explained by the uncertainty of causes of death registered in the DRCD, in spite of the same definition of fatal MI used in the two studies. In Denmark, due to the low autopsy rate (<10%),28 misclassification of out-of-hospital or sudden MI deaths with no prior MI diagnoses cannot be avoided. Among 131 participants with fatal MI in the present study, 86 of them were out-of-hospital deaths due to MI. Therefore, without further validation of the fatal MI, the interpretation of the result may be limited.

Typical environmental noise exposure levels are, for example, whispering (30 dB), normal conversation (60 dB), hairdresser/lawnmower (90 dB), ambulance siren (120 dB), jet engine take-off (140 dB), and rocket launch (180 dB).44 The WHO recommends limits of noise from road traffic by the time of day: day-time (<53 dB) and nighttime (<45 dB).4 The recommended noise limits for road traffic noise in Denmark are 53 dB in recreational areas in open country (e.g., areas for camping sites or holiday cottages), 58 dB in recreational areas near or in cities and residential (e.g., dwellings) and public areas (e.g., hospitals and schools), and 63 dB for commercial areas (e.g., hotels and offices).41 However, there is no regulation on road traffic noise in Europe44 and Denmark.41

This study observed an increased risk of incident MI above a threshold level at 56 dB of the 23-year running mean of Lden.

### Table 2.
Distribution of 1-year running means of road traffic noise and air pollutants at the cohort baseline in 1993 or 1999 and Spearman’s rank correlation coefficients (ρ) between the exposure levels.

|               | Mean ± SD | 5th | 25th | 50th | 75th | 95th | Lden | Ld | Le | Ln | NO2 (µg/m3) | PM2.5 (µg/m3) |
|---------------|-----------|-----|------|------|------|------|------|-----|----|----|------------|---------------|
| Lden (dB)     | 52.7 ± 8.1| 37.0| 48.6 | 53.1 | 58.0 | 64.9 | 1.000|    |    |    |           |               |
| Ld (dB)       | 50.4 ± 8.2| 35.0| 46.3 | 50.7 | 55.7 | 62.9 | 0.997| 1.000| 1.000|    |           |               |
| Le (dB)       | 48.0 ± 8.1| 33.8| 44.0 | 48.4 | 53.3 | 60.3 | 0.996| 0.998| 1.000| 0.999| 1.000| 1.000|
| Ln (dB)       | 44.5 ± 7.9| 30.6| 40.4 | 44.9 | 49.7 | 56.4 | 0.991| 0.991| 1.000| 1.000| 1.000| 1.000|
| NO2 (µg/m3)   | 12.9 ± 8.0| 5.4 | 7.8  | 10.5 | 16.0 | 27.5 | 0.613| 0.625| 0.622| 0.608| 1.000| 1.000|
| PM2.5 (µg/m3) | 19.4 ± 3.9| 13.0| 16.6 | 19.2 | 22.5 | 25.2 | 0.323| 0.327| 0.326| 0.320| 0.495| 1.000|

Ld indicates daytime; Lden, 24-hour weighted average road traffic noise level; Le, evening; Ln, night; NO2, nitrogen dioxide; PM2.5, particulate matter with a diameter <2.5 µm.

**Figure 1.** Relationship between (A) overall, (B) nonfatal, and (C) fatal incident MI and 23-year running mean of road traffic noise (24-hour weighted mean) in the Danish nurse cohort (N = 22,378). A relationship between 23-year exposure to road traffic noise and (A) overall, (B) nonfatal, (C) fatal incident MI in the Danish nurse cohort was expressed in a solid spline line with 95% CIs (dashed spline lines). Y-axis in the residual plot indicated HRs at certain Lden levels (ranged between 0 and 80 dB) compared to the risk at 56 dB of Lden. Gray vertical lines in the residual plots were drawn at 53 dB (a solid line), 56 dB (a dashed line), and 58 dB (a dotted line) of Lden. A histogram of the distribution of 23-year exposure to road traffic noise was drawn in light gray. Model adjusting for strata term of baseline year, a penalty spline term of calendar year, and individual- and area-level covariates.
Model 2 (adjusted model) = Model 2 + NO2
Model 3 (a) (model 2 + NO2) = Model 3 (a) adjusting for 3-year running mean of NO2 in addition to covariates in model 2.
Model 3 (b) (model 2 + PM2.5) = Model 3 (b) adjusting for 3-year running mean of PM2.5 in addition to covariates in model 2.

Table 3. HRs of incident myocardial infarction associated with 10 dB increase in 23-year exposure to road traffic noise in the Danish Nurse Cohort study (N = 22,378).

| Incident MI | ≥Threshold levels of road traffic noise | Model 1 | Model 2 (adjusted model) | Model 3 (a) (model 2 + NO2) | Model 3 (b) (model 2 + PM2.5) |
|-------------|----------------------------------------|---------|--------------------------|----------------------------|----------------------------|
|             | Overall                                 | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) |
| Overall MI  | Overall                                 | 0.91 (0.82, 1.01) | 0.90 (0.81, 1.00) | 0.90 (0.79, 1.02) | 0.87 (0.77, 0.98) |
|             | ≥53 dB                                  | 1.17 (0.94, 1.46) | 1.15 (0.92, 1.43) | 1.22 (0.93, 1.59) | 1.09 (0.86, 1.39) |
|             | ≥56 dB                                  | 1.33 (0.99, 1.79) | 1.30 (0.97, 1.75) | 1.41 (0.99, 1.99) | 1.23 (0.90, 1.69) |
|             | ≥58 dB                                  | 1.43 (0.98, 2.08) | 1.40 (0.96, 2.03) | 1.51 (1.08, 2.33) | 1.31 (0.88, 1.95) |
| Nonfatal MI | Overall                                 | 0.93 (0.82, 1.04) | 0.93 (0.82, 1.05) | 0.90 (0.78, 1.04) | 0.88 (0.77, 1.00) |
|             | ≥53 dB                                  | 1.26 (0.99, 1.61) | 1.25 (0.98, 1.60) | 1.27 (0.95, 1.71) | 1.16 (0.89, 1.51) |
|             | ≥56 dB                                  | 1.48 (1.07, 2.04) | 1.46 (1.05, 2.03) | 1.50 (1.02, 2.19) | 1.34 (0.95, 1.90) |
|             | ≥58 dB                                  | 1.59 (1.05, 2.41) | 1.58 (1.04, 2.39) | 1.59 (1.09, 2.56) | 1.42 (0.91, 2.20) |
| Fatal MI    | Overall                                 | 0.86 (0.68, 1.07) | 0.84 (0.67, 1.05) | 0.92 (0.69, 1.22) | 0.87 (0.67, 1.11) |

Model 1 adjusting for 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 covariates in model 1.
Model 3 (a) adjusting for 3-year running mean of NO2 in addition to covariates in model 2.
Model 3 (b) adjusting for 3-year running mean of PM2.5 in addition to covariates in model 2.

The present study has several strengths. First, we benefited from access to a large prospective cohort study with detailed information on confounders and MI risk factors and a neutral and validated definition of MI incidence obtained through follow-up of the participants in internationally unique population-based nationwide health registries. Second, the study also covered the entire Denmark, provided large contrast in exposure, and allowed us to examine the effects of various levels of road traffic noise. Third, we also benefited from detailed data on road traffic noise exposure over 23 years, the longest in the literature to date, showing that long-term exposure over many years is likely relevant for the development of MI. Finally, we benefited from having data on both NO2 and PM2.5 allowing us to estimate the effect of road traffic noise independently after adjustment for air pollution.

The present study also has several limitations. First, road traffic noise exposure was modeled at the most exposed façade, not taking into account the bedroom location, time spent at home, window opening habits, individual noise insulation initiatives, hearing impairment, or use of earplugs, which may affect the true exposure. The nondifferential misclassification of exposure levels in relation to the development of MI may result in the associations towards the null. Second, the exposure levels of Lden were limited to residential addresses. Exposure levels at the residence may be different from that of the workplace when they were employed. As we did not obtain information on the participants’ workplace addresses, we were not able to estimate these exposure levels. Moreover, the participants may also be exposed to indoor hazardous noise at a workplace and synergistically increased stress levels. The participants’ occupational noise exposure could be varied depending on the working environment, which was not measured in the study. However, we considered job strain in the model, which may represent a proxy of stress levels at work. In future studies, consideration of time activities (including at work) and indoor hazardous noise may improve the estimation of the sole effect of road traffic noise. Third, we did not assess the subjective experience of noise exposure, commonly referred to as annoyance (or noise sensitivity), which may help explain the relationship between road traffic noise and incident MI. Fourth, we were not able to adjust for time-variant individual characteristics (e.g., lifestyle and SES), as only a third of participants were followed-up for 10 years (2009) and not all covariates were included in the final survey round. Therefore, we cannot rule out the misclassification of covariates that were obtained at baseline. Finally, as we investigated Danish female nurses’ exposure levels and health studies suggested a dose-response relationship between 16-hour (6–22 hours) road traffic noise exposures and prevalent MI in men above 60 dB.13 Moreover, the more recent WHO provided convincing evidence of an increased risk of MI above the threshold of 53 dB.4,14 The discrepancy of threshold levels between studies may come from the participants’ characteristics (e.g., sex), study areas, and statistical models. Therefore, a generalization of the findings in the present study to other populations warrants caution.

We estimated the unconfounded association of road traffic noise with incident MI after controlling for air pollutants. With adjustment of PM2.5, we observed attenuated effect size with the marginal significance of the association between a 23-year running mean of Lden and nonfatal MI. However, the association was robust to the adjustment of NO2. We have previously documented strong associations of incident MI with PM2.5 but null associations of incident MI with NO2 which suggests that PM2.5 is the most relevant pollutant for MI development, explaining the observed phenomenon.46 Roswall et al46 observed attenuated but significant associations between incident MI and road traffic noise after controlling for NO2, in line with this study, but did not have data on PM2.5. In contrast, two large studies in Swiss and Canada found that adjustment for air pollution exposure (PM2.5 and NO2 in a Swiss study and UFP and NO2 in a Canada study) had little impact on the HR of the linear exposure-response relationship between road traffic noise and MI deaths13 and incidence, respectively. Moreover, studies with consideration of confounding effects of air pollution are warranted to investigate the role of air pollution on the relationship between road traffic noise on incident MI, as inadequate control for relevant air pollutants (PM2.5) may lead to an overestimation of the effects of road traffic noise.

Although the exact mechanism of the noise-induced MI is not well established, it has been proposed that persistent exposure to noise may elevate stress levels and dysregulate the autonomic nervous system and endocrine system.47 Animal experiments reveal that long-term exposure to noise caused permanent vascular changes and alternations in the heart muscle.1,2 In humans, long-term exposure to road traffic noise may increase stress levels, interrupt sleep patterns, increase blood pressure, alter heart rate variability, and finally develop chronic disorders, including atherosclerosis, hypertension, and ischemic heart diseases.47,48 Furthermore, an experimental study with 18 healthy subjects revealed that exposure to residential road traffic noise increased levels of gene expression biomarkers of oxidative stress and DNA repair.49

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outcomes, a generalization of the results to Danish citizens or other populations warrants caution.

**Conclusions**

In this prospective cohort study of 22,378 Danish female nurses >44 years of age, we observed a nonlinear relationship between road traffic noise and incident MI. In particular, the associations of 23-year exposure to road traffic noise with incident MI were observed at levels above 56 dB, independent of air pollution (NO₂ and PM₁₀). Our study findings strengthen the evidence base showing that road traffic noise is a risk factor for cardiovascular disease and demonstrates the need to regulate road traffic noise in addition to ambient pollution concentrations.

**Conflicts of interest statement**

The authors declare that they have no conflicts of interest with regard to the content of this report.

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