

Full length article

Exploring the interaction between ambient air pollution and road traffic noise on stroke incidence in ten Nordic cohorts



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ABSTRACT

Introduction: Ambient air pollution and road traffic noise are stroke risk factors, but evidence on their potential joint effects remains limited. This study investigated the independent and joint associations of air pollution and road traffic noise on stroke incidence using both multiplicative and additive scales.

Methods: We followed stroke incidence in ten cohorts in Sweden, Denmark, and Finland. We modelled annual average levels of outdoor particulate matter < 2.5 µm (PM_{2.5}), nitrogen dioxide (NO₂) and road traffic noise at residential addresses. We applied Cox proportional hazards regression to evaluate their single association. We

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assessed multiplicative interaction with interaction terms in Cox models and additive interaction using the Relative Excess Risk due to Interaction method.

Results: We followed 136,897 adults for 20 years, and 8.0 % experienced stroke incidence. PM_{2.5}, NO₂ and road traffic noise were associated with higher stroke risk in single-exposure models. Multiplicative models showed higher HRs between PM_{2.5} and stroke at higher levels of noise and vice versa: HRs per 5 µg/m³ of PM_{2.5} were 1.06 (95 % CI:0.94–1.21) at 40 dB and 1.11 (95 % CI:0.85–1.44) at 80 dB of road traffic noise; HRs per 12 dB of road traffic noise were 1.06 (95 % CI:1.01–1.11) at 4 µg/m³ and 1.17 (95 % CI:0.82–1.68) at 48 µg/m³ of PM_{2.5}. Additive models showed that the combined association of PM_{2.5} and road traffic noise was 4 % (RERI = 0.04 (95 % CI:-0.05;1.12)) higher than the sum of their individual association.

Conclusion: PM_{2.5} and road traffic noise showed a non-significant synergistic association on stroke incidence.

1. Introduction

Stroke is a leading cause of death worldwide, usually ranking second after ischemic heart disease (Naghavi et al., 2024). Identifying stroke risk factors is crucial for targeting high-risk individuals, preventing disease onset (Gaziano et al., 2006), and informing policy-makers. Ambient air pollution and road traffic noise have emerged as important environmental risk factors for stroke (Argacha et al., 2019; Argacha et al., 2018; Tzoulaki et al., 2016; Ezzati et al., 2015). Previous meta-analyses have found that both air pollution and noise are independently associated with an increased risk of stroke. In two meta-analyses summarizing the evidence of 19 and 6 original studies, respectively, the risk of stroke increased 8 % (95 % confidence interval (CI): 0.89–1.32) per 5 µg per cubic meter (µg/m³) increment in concentrations of particulate matter 2.5 µm or less in diameter (PM_{2.5}) (Haddad et al., 2023) and 4.6 % (95 % CI: 1.01–1.08) per every 10 dB (dB) increment in road traffic noise (Engelmann, 2023).

Citizens are often simultaneously exposed to both air pollution and road traffic noise, as these pollutants share common sources associated with traffic (Poulsen et al., 2023). Although sharing similar sources, air pollution and road traffic noise were reported to have moderate correlations (Fecht et al., 2016). This result indicates that their effects could be explained both jointly and independently, with one partly accounting for the other's impact on health. However, most studies have focused on single-exposure models, with only a few studies having evaluated the potential confounding effect between these exposures, and even fewer studies having evaluated the potential interactive effect of between them (Eminson et al., 2023; Cole-Hunter et al., 2021; Amini et al., 2020). A meta-analysis of 15 studies examined the potential confounding effect of air pollution on the noise–stroke association and found minimal reductions or no change in the estimates after adjusting to PM_{2.5} (Eminson et al., 2023). The meta-analysis also identified only one study that evaluated interaction effects between air pollution and noise on stroke by stratification analysis and observed the strongest association between road traffic noise and stroke in the group with the highest levels of exposure to both noise and air pollution (Eminson et al., 2023). Understanding the individual and combined effects of each exposure is crucial for designing targeted interventions and shaping policies to prevent stroke in high-risk populations concerning these exposures.

To deepen the understanding of how both exposures influence health, it is important to analyze both additive and multiplicative interactions (VanderWeele and Knol, 2014). The multiplicative scale is useful for providing insights on potential underlying causal inference, and it is easy to implement in standard statistical models, while the additive scale is valuable for evaluating public health impacts, targeting interventions, and identifying mechanistic interactions (VanderWeele and Knol, 2014). However, epidemiological evidence on the interaction effects of ambient air pollution and road traffic noise on the risk of stroke, using both interaction scales, remains limited. Previous studies commonly used stratification analysis or multiplicative interaction analysis (Eminson et al., 2023; Cole-Hunter et al., 2021; Amini et al., 2020). Therefore, this paper aims to disentangle the individual and interactive associations of air pollution and road traffic noise on stroke incidence in Nordic countries at both additive and multiplicative scales.

2. Methods

2.1. Study population and study design

We pooled data from ten Swedish, Danish and Finnish cohorts included in the Nordic Studies on Occupational and Traffic Noise in Relation to Disease (NordSOUND) project (<https://www.cancer.dk/nordsound/>). The cohorts included: (1) DCH, the Diet Cancer and Health cohort, Denmark; (2) DNC, the Danish Nurse Cohort, Denmark; (3) GOT-MONICA, the Gothenburg cohort of “Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases” project, Sweden; (4) MDC, the Malmö Diet and Cancer cohort, Sweden; (5) PPS, the Primary Prevention Study cohort, Gothenburg, Sweden; (6) SDPP, the Stockholm Diabetes Preventive Program, Sweden; (7) SIXTY, The Cohort of 60-year-olds, Stockholm, Sweden; (8) SNAC-K, the Swedish National Study of Aging and Care in Kungsholmen, Stockholm, Sweden; (9) SALT, the Screening Across the Lifespan Twin Study, Stockholm, Sweden, and; (10) FINRISK, The population-based National FINRISK Study, Finland. Details of the study design of these cohorts have been described in Table S1.

We followed participants from the study baseline (1972–2001 for the different cohorts) until the first of the following events occurred: a) stroke incidence; b) death; c) emigration or loss to follow-up; d) end of follow-up (2011–2017 for the different cohorts). We included incident cases of stroke after excluding but cases of stroke occurring before the study baseline, and excluding participants who had missing data on exposure or covariate variables (Fig. S1).

2.2. Outcome assessment

Stroke incidence was estimated based on stroke hospitalizations or death recorded in the Danish, Swedish and Finnish patient and mortality registries, known for their high validity and completeness in terms of cardiovascular diagnoses (Ludvigsson et al., 2011; Schmidt et al., 2015). We identified stroke cases using International Classification of Diseases (ICD) codes (431–434, 436 for ICD-8; 431, 432, 433, 434.01, 434.11, 436 for ICD-9; I61–I64 for ICD-10) depending on the specific version in use at the time of event. A stroke-related death was defined as a recorded death with a primary diagnosis of stroke based on the ICD codes mentioned above, or as an incident stroke that resulted in death within ≤ 28 days. We estimated the date of stroke as the first record of hospitalization or death with a diagnosis of stroke. Prevalent cases were excluded by applying the same algorithms in previous years. We did not separate stroke incidence by stroke subtypes, such as hemorrhagic and ischemic stroke, because the diagnosis of stroke subtypes varies across countries, introducing potential inconsistencies (Roswall et al., 2021).

2.3. Exposure assessment

We used time-varying annual mean exposure variables in our study from baseline to the end of follow-up. For each 3-month follow-up period, we estimated the 5-year time-weighted running average concentrations for air pollution and road traffic noise at the participants' residential addresses during that time. We considered all changes in

participants' addresses during follow-up. We measured air pollutant concentration annually in all cohorts, whereas we measured road traffic noise annually in Gothenburg cohorts, every five years in Danish and Stockholm cohorts and every 10 years in the Malmö cohort (Pyko et al., 2023). Noise levels for years without direct estimates were determined using linear interpolation or other approximation methods (Pyko et al., 2023).

2.3.1. Ambient air pollution

We estimated address-specific outdoor concentrations of particulate matter (PM) with an aerodynamic diameter of $\leq 2.5 \mu\text{m}$ ($\text{PM}_{2.5}$) and nitrogen dioxide (NO_2). Detailed information on the exposure assessment in each cohort can be found in the [supplementary materials Table S2](#). In brief, we estimated $\text{PM}_{2.5}$ and NO_2 by dispersion models including an integrated high-resolution air pollution modelling system (DEHM-UBM-AirGIS system) in Danish cohorts with a $2 \text{ m} \times 2 \text{ m}$ resolution from street-level model and a $1 \text{ km} \times 1 \text{ km}$ resolution from background model (Brandt et al., 2012; Brandt et al., 2001; Khan et al., 2019), a Gaussian dispersion model (AERMOD) in Swedish cohorts (Ljungman et al., 2019; Carlsen et al., 2022) at a $50 \text{ m} \times 50 \text{ m}$ resolution and an urban dispersion model, Contaminants in the Air from a Road, Finnish Meteorological Institute (CAR-FMI model) with the distances between the receptor points varied from $25 \text{ m} \times 25 \text{ m}$ near the roads to a $100 \text{ m} \times 100 \text{ m}$ resolution in rural areas in the Finnish cohort (Kukkonen et al., 2001). These models incorporated factors such as traffic and non-traffic emissions, urban background levels, and long-range transport of air pollution at the regional and hemispheric background (Brandt et al., 2012; Brandt et al., 2001; Khan et al., 2019; Ljungman et al., 2019; Carlsen et al., 2022; Segerström et al., 2017). These models are known for their high accuracy. For example, the DEHM-UBM-AirGIS model revealed temporal variation correlations (single location time series, such as annual and daily concentrations) of 0.91 and 0.45, and spatial variation correlations of 0.80 and 0.92 for $\text{PM}_{2.5}$ and NO_2 respectively, compared to ground measurements (Khan et al., 2019). AERMOD's and CAR-FMI's modeled annual average concentrations showed a high correlation with measurements from monitoring stations (0.65 and 0.57 for $\text{PM}_{2.5}$ and NO_2 respectively in AERMOD model) (Segerström et al., 2017; Aarnio et al., 2018).

2.3.2. Road traffic noise

We assessed road traffic noise as day-evening-night noise level (Lden) (Lau et al., 2004). Detailed information on the exposure assessment in each cohort can be found in the [supplementary materials Table S3](#). In summary, we used a Nordic prediction method to measure Lden, accounting for noise reflection and shielding based on building density, 3D terrain data, road networks, traffic flows, speed limits, and heavy vehicle percentages (Ögren and Barregård, 2016). The Danish, Malmö and Finnish cohorts used the Nordic prediction method in SoundPLAN (version 8.0) (Plovsing and Kragh, 1849) and Gothenburg and Stockholm cohorts used a modified Nordic prediction method, accounting for more types of traffic flows, speed limits, and heavy vehicle (Ögren and Barregård, 2016). Time-weighted exposure to road traffic noise was calculated using energy-based weighting. All time-weighted road traffic noise values $< 40 \text{ dB}$ were set to 40 dB because of the high risk of imprecision of low-level noise estimates (Pyko et al., 2023).

2.4. Covariates

We included sociodemographic and lifestyle factors as covariates by applying a directed acyclic graph based on previous literature (Sørensen et al., 2014; Münzel et al., 2017) and availability across cohorts (Fig. S2). The covariates were collected through baseline questionnaires across all cohorts. Sociodemographic information included age at baseline, educational level ("low" as primary school or less, "medium" as up to secondary school or equivalent, or "high" as university degree or more) and marital status (categorized as "single" for widowed or never

married individuals, or "married," which also included those cohabitating with a partner). Area-level income data were obtained from national registries (0–24 % as the most deprived, 25–49 %, 50–74 % and 75–100 % as the least deprived). Lifestyle factors included smoking status (categorized as never, former, or current), and leisure-time physical activity (classified as "low" for activities occurring once a month or less than one hour per week, "medium" for activities about once a week or approximately one hour per week, and "high" for activities occurring three times a week or more or exceeding two hours per week).

2.5. Statistical analysis

Data from the ten cohorts were harmonized according to a common protocol. The data from each country was harmonized and pooled into one dataset, which was used in the analyses. All analyses were performed with R 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

To estimate single exposure associations between air pollution, road traffic noise and stroke incidence, we applied Cox proportional hazards models with time-varying air pollution and road traffic noise exposures. We estimated the hazard ratios (HRs) per interquartile range (IQR) increment of each exposure. We evaluated the proportional hazards (PH) assumption by the Schoenfeld residuals test for covariates, and we added strata terms for those variables which violated the test (Kuitunen et al., 2021). We analysed the association between stroke incidence and each of the three exposures using models with increasing adjustment: Model 1 included age (underlying time scale), cohort indicator, sex, and calendar year (5-y categories); Model 2 further included educational level, marital status, area-level income; Model 3 further included smoking status and physical activity. Model 3 was considered our main model and was used for further analysis. We evaluated the exposure-response relationship between exposures and outcome through natural cubic splines with four degrees of freedom. We further applied two exposure models to evaluate the independent association between air pollution and road traffic noise on stroke incidence. We evaluated generalized variance inflation factors (VIFs) to quantify multicollinearity between the covariates (Fox and Monette, 1992). Covariates with VIF values less than 10 were included in the analysis (Akinwande et al., 2015).

We evaluated the interaction of air pollution and road traffic noise on stroke incidence using both multiplicative and additive scale models. For the multiplicative scale, we incorporated an interaction term between air pollution and noise in 2 steps. First, we modeled the interaction between two continuous linear variables, followed by a second stage where we analyzed the interaction between two binary variables. For the first step, we applied the mean centering method to reduce the multicollinearity of both continuous exposures in the model (Shieh, 2011). This involves subtracting the mean of each continuous variable from its original values, thereby reducing correlation between the multiplicative interaction terms and improving the stability of the model estimates (Shieh, 2011). We calculated the interaction p-value by testing the null hypothesis of no effect modification or interaction, using ANOVA models with and without interaction terms (Brown, 1975). ANOVA was chosen because it effectively tests whether the inclusion of interaction terms significantly improves model fit, making it an appropriate method for our nested model comparison (Brown, 1975). At a continuous scale, the interaction term allowed us to evaluate the associations of an IQR increase in air pollution with increasing levels of road traffic noise in every 5 dB from 40 to 85 dB. The model also estimated the change of an IQR increase in road traffic noise with increasing levels of air pollution (from 4 to $48 \mu\text{g}/\text{m}^3$ for every $2 \mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$ and from 2 to $85 \mu\text{g}/\text{m}^3$ for every $5 \mu\text{g}/\text{m}^3$ NO_2). The ranges were defined as the exposure distribution across the cohorts: road traffic noise (40–85 dB), $\text{PM}_{2.5}$ (4–48 $\mu\text{g}/\text{m}^3$), and NO_2 (2–85 $\mu\text{g}/\text{m}^3$). We used the Delta method to calculate the 95 % confidence intervals for these slopes (Cox, 2005).

In the second step, we created binary variables for air pollution and road traffic noise using cohort-specific cut-off points at the median value. We added an interaction term between the two dummy variables in the regression model and extrapolated the effects of each exposure across strata of the other, as well as the effect when both exposures were above the median, versus both being below.

For the additive scale, we used the Relative Excess Risk due to Interaction (RERI), the Attributable Proportion (AP) of the interaction, and the synergy index (S) using the binary exposure variable (Knol et al., 2011). The 95 % CIs were estimated using the Hosmer and Lemeshow approach (Hosmer and Lemeshow, 1992).

To evaluate the robustness of the primary analysis results, we performed multiple sensitivity analyses. First, single models were conducted separately for Denmark, Sweden and Finland due to differences in exposure assessments and exposure levels between the three countries. Second, we compared the effects of 1-year and 5-year time-weighted averages in the main models to assess any variations in impact over different time window intervals. In addition, to account for the spatial variability of exposures, we evaluated the potential confounding of urbanization in the single association between air pollution, road traffic noise and stroke incidence. We compared single models with and without adjusting for degrees of urbanization. We measured degrees of urbanization at parish levels for each participant at their baseline addresses. Degrees of urbanization are classified as Urban area (over 1,500 inhabitants/km² and 50,000 total population), Sub-urban area (300–1,500 inhabitants/km² and 5,000 total population), and Rural areas (under 300 inhabitants/km² and generally under 5,000 population) (Commission TE, Programme UNHS. OECD Regional Development Studies Applying the Degree of Urbanisation A Methodological Manual to Define Cities, Towns and Rural Areas for International Comparisons: A Methodological Manual to Define Cities, Towns and Rural Areas for International Comparisons: OECD Publishing, 2021). Fourth, to increase the robustness of the interaction analysis, we evaluated the interactive association of air pollution and road traffic noise on stroke incidence, both multiplicative and additive models, for two binary exposures using cut-off points set at the 75 percentile of exposure levels. The new cut-off point allowed us to capture the potential interaction effects in individuals exposed to high to very high levels compared to those with lower exposure levels. Finally, we assessed the multiplicative and additive interactions between air pollution and road traffic noise on stroke incidence in each cohort, to determine whether the observed associations were driven by specific cohorts or consistent across all cohorts.

3. Results

3.1. Descriptive data analysis

Our study followed 136,897 participants over a mean period of 20.6 years. We identified 10,988 incident stroke cases (8.0 %) after excluding 1,436 prevalent stroke cases (0.9 %), 14,214 individuals with missing covariate data (8.9 %), and 7,012 with missing exposure data (4.4 %) (Fig. S1). The highest cumulative incidence was observed in the PPS and SNACK-K cohorts (21.0 % and 15.0 %, respectively) (Table 1). The PPS cohort had the longest follow-up, spanning 31.0 years, and the SNACK-K cohort included the oldest participants at baseline (median age 72.4 years).

The median age at the study baseline was 54.2 years. In the total population, most participants were female (62 %), married (73 %), had a moderate level of education (50 %), were current or former smokers (63 %), engaged in low levels of physical activity during leisure time (42 %), and resided in areas with low to medium income at baseline (33 % lived in the poorest quartile, and 29 % in the second poorest quartile). The PPS cohort consisted only of male participants, while the DNC cohort included only women.

The median 5-year time-weighted mean concentration of PM_{2.5} at

baseline across ten cohorts was 13.3 µg/m³ (IQR: 10.3–16.0) (Table 1). The Danish and Swedish cohorts had higher concentrations of PM_{2.5} compared to the Finnish cohort. The median concentration of NO₂ at baseline across ten cohorts was 18.5 µg/m³ (IQR: 12.3–24.8). NO₂ levels were higher in DCH, MDC, PPS, GOT-MONICA, and SNACK-K cohorts (median values greater than 20 µg/m³) compared to DNC, SDPP, Finrisk and SALT cohorts (median values lower than 16 µg/m³). Median exposure to road traffic noise at baseline was 55.2 dB (IQR: 49.6–61.1), with medians ranging from 44.3 dB in SDPP to 62.2 dB in SNACK-K. In general, there were low to moderate correlations between the different exposures (Table S4). In the pooled dataset, the strongest correlation observed was 0.60 between road traffic noise and NO₂, followed by the correlation between PM_{2.5} and NO₂ (0.40), as well as PM_{2.5} and road traffic noise (0.28).

3.2. Single and adjusted associations

In single exposure models, long term exposure to PM_{2.5}, NO₂ and road traffic noise were associated with increased stroke incidence (Fig. 1, Table S5). An IQR increment of 5 µg/m³ of PM_{2.5}, 12 µg/m³ of NO₂, and 11 dB of road traffic noise was associated with HRs of stroke incidence of 1.09 (95 % CI: 1.01, 1.17), 1.07 (95 % CI: 1.03, 1.11) and 1.06 (95 % CI: 1.03, 1.09), respectively. The estimated for NO₂ and road traffic noise slightly attenuated in two-exposure models. When adjusted for road traffic noise, PM_{2.5} did not statistically significantly increase the incidence of stroke. The exposure–response functions of PM_{2.5}, NO₂ and road traffic noise suggested that linear functions could be used to estimate associations (Fig. S3).

3.3. Multiplicative interaction between air pollution and noise on stroke incidence

We did not find a significant interaction on the multiplicative scale between PM_{2.5} and road traffic noise (*p*-value = 0.55) (Fig. 2). However, our results indicated a small positive multiplicative interaction as we observed that the HR per 5 µg/m³ in PM_{2.5} was 1.06 (95 % CI: 0.94 – 1.21) at 40 dB and 1.11 (95 % CI: 0.86–1.41) at 80 dB of road traffic noise (Fig. 2 and Table S6). Similarly, we found higher HRs between road traffic noise and stroke incidence at higher PM_{2.5} concentration levels. The HRs per 12 dB road traffic noise and stroke incidence increased from 1.06 (95 % CI: 1.01–1.11) at 4 µg/m³ of PM_{2.5} concentration to 1.17 (95 % CI: 0.82–1.68) at 48 µg/m³ of PM_{2.5} concentration. When exposures were modelled with dummy variables (below/above the median), high levels of both PM_{2.5} and road traffic noise were associated with a 1.13 times higher stroke incidence (95 % CI: 1.06–1.20) compared to low levels of both exposures (Table 2). As in the continuous case, we found no evidence of a multiplicative interaction between two dummy exposures (HR = 1.04, 95 % CI: 0.96, 1.13; *p*-value = 0.41). We observed no interaction on the multiplicative scale between NO₂ and road traffic noise (Fig. 2, Table 3 and Table S6). However, when exposures were modelled with dummy variables (below/above the median), high levels of both NO₂ and road traffic noise were associated with a 1.11 times higher stroke incidence (95 % CI: 1.06–1.16) compared to low levels of both exposures (Table 3).

3.4. Additive interaction between air pollution and noise on stroke incidence

We did not observe significant additive interactions between the air pollutants and noise. However, as in the multiplicative scale, there was a non-significant positive additive interaction between binary variables of PM_{2.5} and road traffic noise (Table 2). The RERI was 0.04 (95 % CI: –0.05;1.12) suggesting that the hazard of stroke incidence was 4 % higher among individuals exposed to a high level of PM_{2.5} and road traffic noise than the sum of the hazards of stroke incidence among those exposed to PM_{2.5} and road traffic noise individually. The AP was 0.03

Table 1
Baseline characteristics of the included study population across ten cohorts at study baseline.

Characteristics	Denmark		Malmö		Gothenburg		Stockholm		Finland		TOTAL
	DCH	DNC	MDC	PPS	Go-MON	SDPP	SIXTY	SNAC-K	SALT	Finrisk	
	N = 53,664	N = 25,902	N = 23,424	N = 4,464	N = 693	N = 7,562	N = 3,888	N = 2,510	N = 6,394	N = 8,496	N = 136,897
Follow-up period (year)	1994–2016	1993–2016	1992–2017	1972–2011	1985–2011	1992–2011	1997–2017	2001–2016	1998–2016	1997–2015	1975–2017
Length of follow-up (year) ^a	20.5 (19.8–21.2)	21.7 (15.8–27.7)	21.6 (18.3–23.3)	31.0 (25.2–36.5)	18.1 (16.5–21.5)	21.3 (20.7–24.1)	19.6 (19.1–19.9)	14.3 (11.4–15.3)	16.6 (15.6–17.8)	13.9 (8.9–18.8)	20.6 (18.0–21.7)
Stroke incidence ^b	5,060 (9.4 %)	1,266 (4.9 %)	1,920 (8.2 %)	941 (21.0 %)	29 (4.2 %)	147 (1.9 %)	319 (8.2 %)	381 (15.0 %)	600 (9.4 %)	325 (3.8 %)	10,988 (8.0 %)
Sex ^b											
Female	27,741 (52 %)	25,902 (100 %)	14,893 (64 %)	0*	368 (53 %)	4,584 (61 %)	2,037 (52 %)	1,556 (62 %)	3,529 (55 %)	4,526 (53 %)	85,136 (62 %)
Male	25,823 (48 %)	0*	8,531 (36 %)	4,464 (100 %)	325 (47 %)	2,978 (39 %)	1,851 (48 %)	954 (38 %)	2,865 (45 %)	3,970 (47 %)	51,761 (38 %)
Age at baseline ^a	56.3 (51.9–60.4)	50.2 (47.2–57.8)	56.2 (50.5–62.5)	51.5 (50.1–53.3)	47.0 (36.9–55.9)	48.0 (44.0–50.9)	60.4 (60.3–60.8)	72.4 (61.4–78.5)	56.00 (50.0–65.0)	51.1 (38.3–31.4)	54.2 (50.0–56.1)
Marital status ^b											
Single	12,357 (23 %)	7,625 (29 %)	8,198 (35 %)	610 (14 %)	218 (31 %)	1,248 (17 %)	1,003 (26 %)	1,307 (52 %)	2,088 (33 %)	2,750 (32 %)	37,404(27 %)
Married	41,207 (77 %)	18,277 (71 %)	15,226 (65 %)	3,854 (86 %)	475 (69 %)	6,314 (83 %)	2,885 (74 %)	1,203 (48 %)	4,306 (67 %)	5,746 (68 %)	99,493 (73 %)
Education level ^b											
Low	16,432 (31 %)	0*	15,487 (66 %)	3,038 (68 %)	141 (20 %)	2,379 (31 %)	1,551 (40 %)	599 (24 %)	1,737 (27 %)	2,090 (25 %)	43,454(32 %)
Medium	25,255 (47 %)	25,902 (100 %)	4,311 (18 %)	911 (20 %)	348 (51 %)	2,919 (39 %)	1,253 (32 %)	1,001 (40 %)	2,338 (37 %)	4,589 (54 %)	68,827 (50 %)
High	11,877 (22 %)	0*	3,626 (15 %)	515 (12 %)	204 (29 %)	2,264 (30 %)	1,084 (28 %)	910 (36 %)	2,319 (36 %)	1,817 (21 %)	24,616 (18 %)
Smoking Status ^b											
Current	19,488 (36 %)	9,070 (35 %)	6,535 (28 %)	1,727 (39 %)	197 (28 %)	1,993 (26 %)	821 (21 %)	375(15 %)	1,303 (20 %)	2,298 (27 %)	43,807 (32 %)
Former	15,079 (28 %)	7,925 (31 %)	7,859 (34 %)	1,478 (33 %)	147 (21 %)	2,749 (36 %)	1,503 (39 %)	1,008 (40 %)	2,298 (36 %)	2,444 (29 %)	42,490 (31 %)
Never smoker	18,997 (35 %)	8,907 (34 %)	9,030 (39 %)	1,259 (28 %)	349 (50 %)	2,820 (37 %)	1,564 (40 %)	1,127 (45 %)	2,793 (44 %)	3,754 (44 %)	50,600 (37 %)
Physical activity during leisure time ^b											
Low	27,787 (52 %)	1,753 (6.8 %)	11,925 (51 %)	1,114 (25 %)	103 (16 %)	4,976 (66 %)	2,693 (69 %)	1,886 (75 %)	3,514 (55 %)	1,496 (18 %)	57,248 (42 %)
Medium	10,396 (19 %)	17,231 (67 %)	4,945 (21 %)	2,642 (59 %)	453 (65 %)	2,006 (27 %)	906 (23 %)	458 (18 %)	2,301 (36 %)	2,728 (32 %)	44,066 (32 %)
High	15,381 (29 %)	6,918 (27 %)	6,554 (28 %)	708 (16 %)	137 (20 %)	580 (7 %)	289 (8 %)	166 (6.6 %)	578 (9 %)	4,272 (50 %)	35,583 (26 %)
Area income (Quartile) ^b											
0–24 %	17,663 (33 %)	8,560 (33 %)	9,959 (43 %)	1,146 (26 %)	143 (21 %)	2,930 (39 %)	1,906 (49 %)	0*	353 (5.5 %)	1,671 (20 %)	44,331 (32 %)
25–49 %	12,030 (22 %)	6,867 (27 %)	12,377 (53 %)	988 (22 %)	114 (16 %)	3,480 (46 %)	1,043 (27 %)	0*	705 (11 %)	2,213 (26 %)	39,817 (29 %)
50–74 %	9,095 (17 %)	6,373 (25 %)	1,088 (4.6 %)	1,094 (24 %)	162 (23 %)	1,152 (15 %)	758 (19 %)	421(17 %)	2,786 (44 %)	2,255 (27 %)	25,184 (18 %)
75–100 %	14,776 (28 %)	4,102 (16 %)	0*	1,236 (28 %)	274 (40 %)	0*	181 (5 %)	2,089 (83 %)	2,550 (40 %)	2,357 (28 %)	27,565 (20 %)
PM _{2.5} (µg/m ³) ^a	19.3 (18.9–20.1)	20.6 (18.4–23.5)	11.1 (10.5–11.7)	10.1 (9.5–11.0)	10.0 (9.7–10.7)	7.6 (7.2–8.0)	8.1 (7.5–8.7)	8.3 (8.1–8.6)	7.8 (7.2–8.3)	7.4 (7.1–8.0)	13.3 (10.3–16.0)
NO ₂ (µg/m ³) ^a	27.4 (24.4–32.0)	10.6 (8.0–16.4)	24.3 (20.1–29.0)	32.0 (27.5–36.3)	27.3 (23.1–32.6)	8.6 (6.8–10.4)	12.9 (9.5–18.0)	20.4 (18.9–22.4)	13.1 (9.6–18.3)	15.3 (13.2–18.6)	18.5 (12.3–24.8)
Road traffic noise (dB) ^a	56.6 (51.9–62.0)	53.6 (47.6–59.8)	54.6 (49.4–60.5)	57.9 (53.8–63.5)	55.7 (50.4–61.0)	44.3 (34.3–50.5)	50.6 (44.3–56.9)	62.2 (58.3–67.0)	51.7 (44.9–57.7)	54.1 (48.5–60.2)	55.2 (49.6–61.0)

Note: 0*, no data; DGH, the Danish Diet Cancer and Health cohort; DK, Denmark; DNC, the Danish Nurse Cohort; GOT-MONICA, the Gothenburg cohort of “Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases” (MONICA) project, Sweden; MDC, the Malmö Diet and Cancer cohort, Sweden; PPS, the Primary Prevention Study cohort, Gothenburg, Sweden; SDPP, the Stockholm Diabetes Preventive Program, Sweden; SE, Sweden; SIXTY, the 60-Years cohort, Stockholm, Sweden; SNAC-K, the Swedish National Study of Aging and Care in Kungsholmen, Stockholm, Sweden; NO₂, nitrogen dioxide; PM_{2.5}, particulate matter with an aerodynamic diameter ≤ 2.5 µm (fine particulate matter).

^a Median and 25th–75th percentiles.

^b Frequency (%).

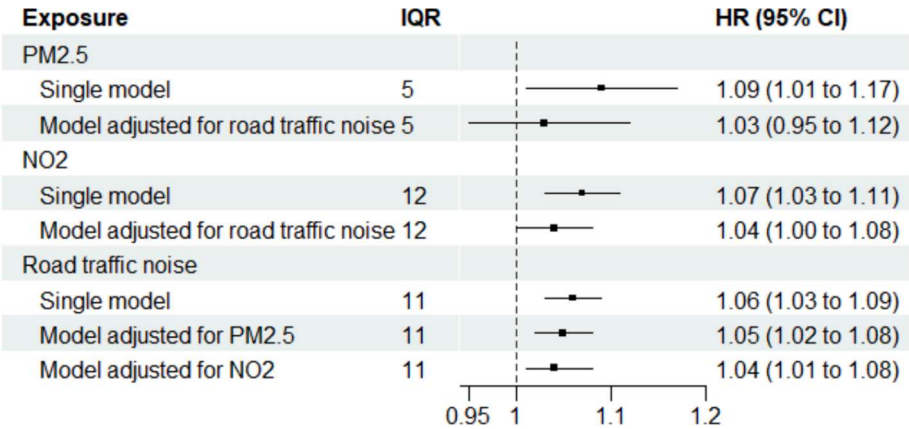


Fig. 1. Multivariable-adjusted association between air pollution, road traffic noise and stroke incidence in single exposure models and two exposure models in pooled data of ten cohorts, expressed as Hazard Ratios (HR) and 95% Confidence Intervals (CI).

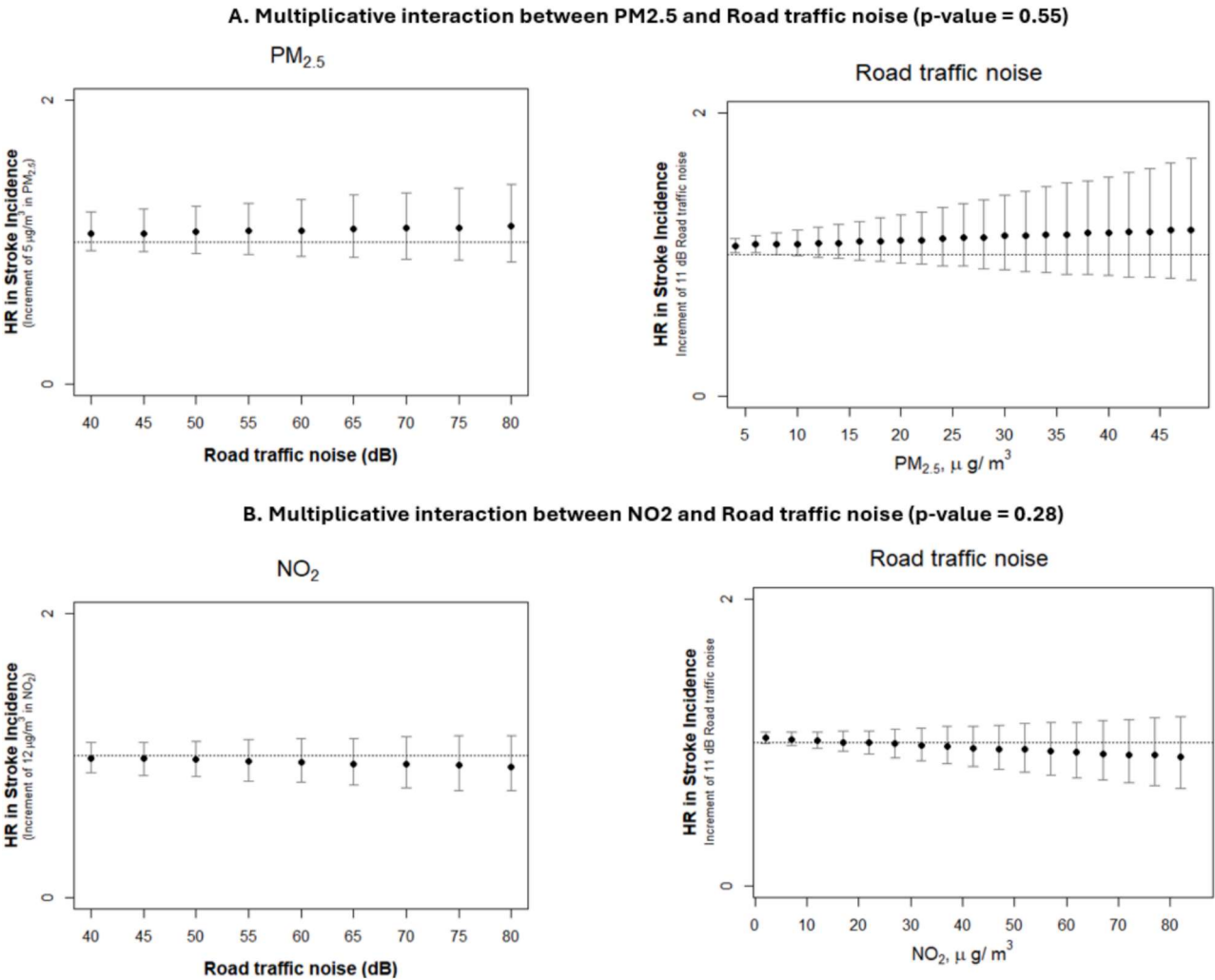


Fig. 2. Hazard ratios and 95% confidence interval for stroke in relation to modification effects of air pollution and road traffic noise using multiplicative scale for two continuous exposure variables.

(95 % CI: −0.04; 0.10), indicating that 3 % of stroke cases in the study can be attributed to this interaction. The synergy index (SI) of 1.43 (95 % CI: 0.56; 3.64), which exceeds 1, points to a positive interaction on the additive scale, indicating that the joint exposure to PM_{2.5} and road traffic noise results in more stroke incident cases than expected from

their individual contributions. However, these findings were not statistically significant. As in the multiplicative scale, there was no additive interaction (very small non-significant negative) between binary variables of NO₂ and road traffic noise (Table 3).

Table 2
Interaction of binary variables of PM_{2.5} vs road traffic noise on stroke incidence in pooled data of ten cohorts, expressed as hazard ratios (HR) and 95% confidence intervals (CI).

	Low level noise (< median)	High level noise (≥median)	Effect of high-level vs low-level noise within the strata of PM _{2.5}
	HR (95 %CI)	HR (95 %CI)	HR (95 %CI)
Low level PM _{2.5} (< median)	1 (reference)	1.04 (0.99;1.10)	1.04 (0.99;1.10)
High level PM _{2.5} (≥median)	1.05 (0.98;1.12)	1.13 (1.06;1.20)	1.08 (1.01;1.14)
Effect of high-level vs low-level of PM _{2.5} within the strata of noise	1.05 (0.98;1.12)	1.08 (1.02;1.15)	
Multiplicative scale of two binary exposures	1.03 (0.96;1.12), p-value = 0.41		
Relative excess risk due to interaction (RERI)	0.04 (−0.05;1.12)		
The proportion attributable to interaction (AP)	0.03 (−0.04;0.1)		
The synergy index (S)	1.43 (0.56;3.64)		

Note: PM_{2.5}, particulate matter with an aerodynamic diameter ≤ 2.5 μm (fine particulate matter); Noise: Road traffic noise; The cut off point of exposure is cohort-specific cut-off points at the median value.; p-value from a testing the null hypothesis of no effect modification or interaction, using ANOVA models with and without interaction terms.

Table 3
Interaction of binary variables of NO₂ vs road traffic noise on stroke incidence in pooled data of ten cohorts, expressed as hazard ratios (HR) and 95% confidence intervals (CI).

	Low level noise	High level noise	Effect of high-level vs low-level noise within the strata of NO ₂
	HR (95 % CI)	HR (95 % CI)	HR (95 %CI)
Low level NO ₂	1 (reference)	1.05 (0.99;1.11)	1.05 (0.99;1.11)
High level NO ₂	1.07 (1.00;1.14)	1.11 (1.06;1.16)	1.04 (0.97;1.10)
Effect of high-level vs low-level NO ₂ within the strata of noise	1.07 (1.00;1.14)	1.06 (1.00;1.12)	
Multiplicative scale of two binary exposures	0.99 (0.91;1.07), p-value = 0.76		
Relative excess risk due to interaction (RERI)	−0.01 (−0.91;1.07)		
The proportion attributable to interaction (AP)	−0.01 (−0.10;0.07)		
The synergy index (S)	0.91 (0.44;1.90)		

Note: NO₂, nitrogen dioxide; Noise: Road traffic noise; The cut off point of exposure is cohort-specific cut-off points at the median value; p-value from a testing the null hypothesis of no effect modification or interaction, using ANOVA models with and without interaction terms.

3.5. Sensitivity analysis

HRs for air pollution and road traffic noise were similar between Denmark and Sweden, but not for Finland (Table S7). Exposure to PM_{2.5}, NO₂, and road traffic noise increased stroke incidence in Denmark and Sweden, but the increases were only statistically significant in Denmark. Exposure to PM_{2.5} and NO₂ did not increase stroke incidence in Finland. The associations of PM_{2.5} were slightly stronger for

the 5-year mean time-weighted exposures compared to the 1-year mean time-weighted exposures (Table S8). Adjusting for degrees of urbanization slightly attenuated the associations between air pollution, road traffic noise, and stroke incidence (Table S9). Consistent with the main results, there was a non-significant positive interaction on the additive scale between PM_{2.5} and road traffic noise with the cutoff point at the third quartile (see Table S10) and there was non-significant negative interaction on the additive scale between NO₂ and road traffic noise with the cutoff point at the third quartile, see Table S11. The multiplicative and additive interactions between air pollution and road traffic noise in relation to stroke incidence across cohorts were generally consistent with the pooled analysis including all ten cohorts (Table S12 and Fig. S4).

4. Discussion

In this multi-cohort study conducted in Denmark, Sweden and Finland with more than 135,000 participants, we examined the independent and interactive association of air pollution and road traffic noise on stroke incidence. We observed that higher levels of PM_{2.5}, NO₂ and road traffic noise were statistically significantly associated with a higher stroke incidence. Although we did not find statistically significant interactions between PM_{2.5} and noise, synergistic multiplicative and additive interactions between PM_{2.5} and road traffic noise in relation to stroke incidence cannot be entirely excluded. We further found no interactions between NO₂ and road traffic noise in relation to stroke incidence.

Long-term exposure to air pollution and road traffic noise increased the incidence of stroke. In this study, the incidence of stroke was 1.09 (95 % CI: 1.01, 1.17) times higher per each 5 μg/m³ increment in PM_{2.5} and 1.07 (95 % CI: 1.03, 1.11) times higher per each 12 μg/m³ increment in NO₂. The positive association between road traffic noise and stroke incidence in nine of the ten cohorts was published previously (Roswall et al., 2021). A recent global meta-analysis reported relative risks for stroke of 1.08 (95 % CI: 0.89–1.32) per 5 μg/m³ of PM_{2.5} and 0.98 (95 % CI: 0.92–1.05) per 10 μg/m³ of NO₂ (7), which aligns with our findings regarding PM_{2.5} but not for NO₂. Our results for NO₂ diverge from overall global evidence but are consistent with some earlier publications. A pooled analysis from Sweden, Denmark, the Netherlands, and Germany, including three same cohorts included in this pooled analysis (CEANS, DHC, DNC), found that the association between NO₂ exposure and stroke risk was 1.08 (95 % CI: 1.04–1.12) per 10 μg/m³ increase (Wolf et al., 2021), which is a comparable association with our NO₂ findings. Another study in Denmark, which used a different study population from our Danish cohorts, also showed a positive association of 1.03 (95 % CI: 1.02–1.04) per 7.15 μg/m³ increase (Poulsen et al., 2023). The inconsistency in epidemiological evidence regarding the relationship between NO₂ and stroke may be attributed to regional variations in exposure levels and correlations between exposures, dose–response relationships of NO₂ and stroke incidence as well as study and exposure assessment methodology and relevant differences between areas. Our study adds weight to the evidence by suggesting a positive association between NO₂ and stroke. Our results of the association between air pollution and stroke incidence in Finland were consistent with existing evidence. The difference in the association between air pollution and stroke incidence in Finland compared to Sweden and Denmark could be explained by the smaller sample size, lower percentage of stroke cases, and lower air pollution levels in Finland compared to the other two countries.

We found that adjusting for degrees of urbanization slightly attenuated the associations between air pollution, road traffic noise, and stroke incidence. This result might be due to overadjustment. Degrees of urbanization may serve as a proxy variable for air pollution and road traffic noise. Air pollutions were modeled by traffic and non-traffic emissions, urban background levels, and long-range transport of air pollution. Road traffic noise measurements are influenced by

urbanization-related factors such as building density, 3D terrain data, road networks, traffic flows, speed limits, and the percentage of heavy vehicles. These factors are highly correlated with degrees of urbanization. Adjusting analyses for this variable will reduce variation in the exposures, thereby resulting in over-adjustment of the analyses (Vatcheva et al., 2016).

Our analysis showed limited confounding between NO₂ and road traffic noise, but PM_{2.5} was slightly confounded after adjusting for road traffic noise. Our findings aligned with previous studies for road traffic noise but not for air pollution. Several review studies found that traffic noise and cardiovascular outcomes were independently associated with CVD after adjusting for air pollution (Tétreault et al., 2013; Tétreault et al., 2013). Evidence on the confounding effect of noise in the air pollution-CVD relationship is limited. One study showed that the association between air pollution (a combined variables of both PM_{2.5} and NO₂) and hypertension did not change after adjusting for road traffic noise (Klompaker et al., 2019). A further study indicated that both PM_{2.5} and NO₂ exhibited minor confounding after controlling for traffic noise in their association with stroke (Cai et al., 2018). NO₂ is considered a marker for local emissions and exhaust particles related to traffic which might have direct pathways to stroke independently with noise compared to PM_{2.5}. On the other hand, PM_{2.5} is composed by a variety of sources, including traffic, industrial activities, and natural sources. This diversity might make it more susceptible to confounding by noise. Our results indicate that future studies should account for road traffic noise in PM_{2.5} and stroke research.

We found no significant multiplicative and additive interaction of air pollution and road traffic noise. While we observed an indication of positive interaction between PM_{2.5} and road traffic noise, we observed no significant interaction between NO₂ and road traffic noise. The absence of interaction between NO₂ and road traffic noise may stem from differences in the biological pathway of NO₂ compared to PM_{2.5} leading to cardiovascular diseases. There are fewer studies on the mechanisms linking NO₂ to cardiovascular diseases compared to PM_{2.5} (de Bont et al., 2022). PM_{2.5}, a particulate pollutant, can penetrate deep into the respiratory tract, enter the bloodstream, and trigger inflammation, and atherosclerosis (Shrey et al., 2011). The mechanism linking NO₂ to cardiovascular diseases remains a topic of debate. The Committee on the Medical Effects of Air Pollutants (COMEAP) reported that adverse health effects induced by NO₂ may be attributable to other pollutants produced by the same sources (such as ultrafine particles) (COMEAP) CotMEoAP. Nitrogen dioxide: health effects of exposure, 2015). Some other studies reported that NO₂, a gaseous pollutant, might contribute to oxidative stress and disrupts endothelial integrity (de Bont et al., 2022; Frampton et al., 2002). The uncertainty in the causal relationship between NO₂ and stroke as well as these distinct mechanisms of PM_{2.5} and NO₂ and stroke suggest that road traffic noise may interact differently with gaseous and particulate pollutants at the molecular level. Road traffic noise contributes to stroke through inflammatory and oxidative stress mechanisms (Babisch, 2002; Sørensen et al., 2024), which it shares the mechanism with NO₂. A review study confirmed that differences in mechanisms could lead to interactions in health impacts (Fecht et al., 2016).

The non-significance of positive multiplicative interaction between PM_{2.5} and road traffic noise might be explained by the low or intermediate levels of the two exposures in our study compared to global levels. We have only a small population exposure to high levels of those two exposures. When exposure to air pollution or road traffic noise occurs at low or intermediate levels, as in our study, their combined health impacts may not be immediately apparent. We found no statistically significant p-value for the multiplicative interaction scale between air pollution and road traffic noise, but the stratified analysis showed significant results. Exposure to above-median levels of both PM_{2.5} and road traffic noise were associated with a 1.13 times higher stroke incidence (95 % CI: 1.06–1.20) compared to exposure to below-median levels of both exposures. Exposure to above-median levels of both NO₂ and road

traffic noise were associated with a 1.11 times higher stroke incidence (95 % CI: 1.06–1.16) compared to exposure to below-median levels of both exposures. Only a few studies have investigated the stratification analysis between air pollution and road traffic noise, and their results have been consistent with our stratification analysis results. A systematic review identified four studies from United Kingdom and Denmark that compared the association of road traffic noise with stroke across different levels of air pollution (Eminson et al., 2023). They reported the strongest association between road traffic noise and stroke in the highest NO₂ exposure tertile (Eminson et al., 2023). Another study in Massachusetts also demonstrated that combined exposure to PM_{2.5} (above median) and noise pollution (above 55 dB) statistically increases the risk for cardiovascular diseases (p-value < 0.05) (Osborne et al., 2023). However, relying solely on multiplicative interaction or stratification analysis results may lead to false positive findings, over-looking key subgroups that would benefit from interventions. While multiplicative interaction examines the relative risk increase when two factors are present, additive interaction focuses on the absolute risk increase due to combined exposures. This perspective is especially useful for public health interventions because it can reveal the actual burden of disease within the population due to combined exposures, which is essential for allocating resources and prioritizing interventions (VanderWeele and Knol, 2014).

On the additive interaction scale, previous authors have discussed that the direction of RERI is useful to draw conclusions about the public health relevance of interaction (VanderWeele and Knol, 2014). In our study, we found indications of a positive additive interaction of PM_{2.5} and road traffic noise on stroke incidence as RERI (4 %) and AP (3 %) were greater than 0. This suggests that targeting interventions at groups exposed to both high PM_{2.5} and road traffic noise could reduce stroke incidence by 4 % more than separate interventions for each exposure alone. Our findings could be valuable for designing stroke interventions targeting populations at higher risk due to PM_{2.5} and road traffic noise exposure; however, they should be interpreted with caution, as they are based on a single study, rather than multiple lines of prior evidence and the 95 % confidence interval for RERI included 0. In addition, previous epidemiologists have suggested that the magnitude of RERI, along with its confidence interval, can provide evidence of a biological interaction between two risk factors and the outcome. The combined exposure creates an additional, direct impact on disease risk, revealing outcomes that occur only when both exposures are present, rather than with either exposure alone (VanderWeele and Knol, 2014). The non-significant additive interaction between PM_{2.5} and road traffic noise may be explained by different pathways through which the two exposures enter the human body. PM_{2.5} impacts health via inhalation and bloodstream translocation (Manisalidis et al., 2020), while traffic noise induces stress and disrupts sleep (Welch et al., 2023). Because these pathways differ, the combined exposure may not produce a significant additive effect on stroke risk. To observe pronounced effects at the population level, a sufficient degree of exposure at the molecular level is necessary (Drexler and Shukla, 2021). It is important to note that this is only a hypothesis, however, for ethical reasons experimental studies to confirm these findings are unlikely to be performed.

Our study has some strengths. First, our study used a large population from six major urban areas in Denmark, Sweden and Finland, with nearly complete follow-up of stroke incidence cases (age at baseline above 50 years across all cohorts and over 20 years of follow-up). Our findings are robust and generalizable across the Nordic countries. Additionally, we found that even low levels of air pollution and road traffic noise are associated with stroke incidence, highlighting the need for stricter policy thresholds of these exposures to protect public health. Our observed air pollution levels in Sweden and Finland were below the annual limit values in the new ambient air quality directive of Europe (2024/2881), which are set at 10 µg/m³ for PM_{2.5}, 20 µg/m³ for NO₂, but still above the recommended World Health Organization air quality guidelines (Beloconi and Vounatsou, 2023). Our observed road

traffic noise levels across all cohorts were approximately at the annual [World Health Organization](#) recommendation threshold of 55 dB (Lden) for the European Region ([Organization, 2018](#)). This evidence highlights the urgent need for policy updates to lower acceptable exposure limits and mitigate the burden of stroke and other health risks associated with air pollution and road traffic noise in Europe in upcoming years. Third, we used time-varying exposure data with high resolution exposure assessment, which allowed following of participants over time as they moved. Finally, our study is the first to use both multiplicative and additive interaction scales to assess the combined effects of air pollution and road traffic noise on stroke incidence. This approach offers a more accurate interpretation of evidence heterogeneity, public health intervention recommendations, and mechanistic interactions compared to traditional stratification methods ([VanderWeele and Knol, 2014](#)).

We acknowledge several limitations in our study. First, we pooled data from ten cohorts, each with varying exposure assessment models and covariate distributions. To evaluate potential bias in three exposure assessment models and population heterogeneity, we conducted sensitivity analyses comparing findings between three countries. Secondly, modeling very low noise exposure posed challenges. We set all road traffic noise exposures < 40 dB to 40 dB, which would result in exposure misclassification. Since the exposure model does not differentiate between cases and other study subjects, any misclassification is likely non-differential as towards the null. In addition, we did not have time-varying data on covariates. To minimize this potential bias, we adjusted for the calendar year, considering follow-up time. We acknowledge that we used different temporal resolutions in exposure measurement in our study, which might bring incomparable interpretation for the association between air pollution-stroke and road traffic noise-stroke. However, a previous study in Denmark reported that road traffic noise temporal resolution has remained stable during the same study period as ours ([Sørensen et al., 2024](#)). Therefore, we believe our road traffic noise estimates remain robust and allow for meaningful comparisons with air pollution measurements. Finally, we acknowledge that 0.6 % of our total study population was lost to follow-up. Participants were censored upon emigration. Given the low emigration rate, the potential bias from loss to follow-up is likely minimal. Furthermore, the lost to follow-up population is likely to present our total study population, further supporting the robustness of our findings ([Table S13](#)).

5. Conclusion

In conclusion, we observed that long-term exposure to PM_{2.5}, NO₂ and road traffic noise were associated with stroke incidence in a large, pooled Nordic cohort. We found suggestions of synergistic effects of PM_{2.5} and road traffic noise on risk of stroke incidence, with both multiplicative and additive scale. These findings could be valuable for designing stroke interventions to target simultaneous reduce in air pollution and traffic noise, and require further confirmation.

Ethics approval and consent to participate.

All cohorts was conducted in accordance with local and ethical requirements and followed the Helsinki Declaration ([Association WM. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. Bulletin of the World Health Organization., 2001](#)). The present study is conducted in a pooled cohort, consisting of 10 original cohorts. [Informed consent](#) was obtained from all participants. The Diet, Cancer and Health research project was approved by the Danish Data Protection Agency and the regional ethical committees in Copenhagen and Aarhus (File (KF)03–345/93). The Danish Nurses Cohort was approved by Den Videnskabssetiske Komité for Københavns og Frederiksberg kommuner (File (KF) 01–103/93). The [C EANS](#) cohorts (SDPP, SIXTY, SALT and SNAC-K) were approved by the Regionala etikprövningsnämnden i Stockholm. The Gothenburg Cohorts (PPS, GOT-MONICA) were approved by Göteborgs Forskningsetikkommitté. The MDC cohort was approved by Lunds

Universitet Medicinska Fakultetens Forskningsetiska Kommitté (LU 51–90. The national FINRISK study obtained permissions from the THL Ethics Committee and the Coordinating Ethics Committee of Helsinki and Uusimaa Hospital District.

Consent for publication

Not applicable.

CRediT authorship contribution statement

Huyen Nguyen Thi Khanh: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Massimo Stafoggia:** Writing – review & editing, Validation, Supervision, Methodology, Formal analysis, Conceptualization. **Mette Sørensen:** Writing – review & editing, Validation, Supervision, Software, Resources, Project administration, Methodology, Funding acquisition, Data curation. **Aslak Harbo Poulsen:** Writing – review & editing, Visualization, Software, Resources, Project administration. **Ole Raaschou-Nielsen:** Writing – review & editing, Project administration. **Jibran Khan:** Writing – review & editing, Project administration. **Jørgen Brandt:** Writing – review & editing, Project administration. **Anja Olsen:** Writing – review & editing, Project administration. **Zorana Jovanovic Andersen:** Writing – review & editing, Resources, Project administration. **Mette Kildevaeld Simonsen:** Writing – review & editing. **Youn-Hee Lim:** Writing – review & editing. **Jiawei Zhang:** Writing – review & editing. **Thomas Cole-Hunter:** Writing – review & editing. **Göran Pershagen:** Writing – review & editing, Project administration, Methodology. **Andrei Pyko:** Writing – review & editing, Project administration, Data curation. **Agneta Åkesson:** Writing – review & editing, Conceptualization. **Leonard Stockfelt:** Writing – review & editing, Project administration. **Eva M. Andersson:** Writing – review & editing, Project administration. **Mikael Ögren:** Writing – review & editing, Project administration. **David Segersson:** Writing – review & editing. **Annika Rosengren:** Writing – review & editing. **Anna Oudin:** Writing – review & editing, Project administration. **Maria Albin:** Writing – review & editing, Project administration. **Gunnar Engström:** Writing – review & editing, Project administration. **Susanna Gustafsson:** Writing – review & editing, Project administration. **Kristoffer Mattisson:** Writing – review & editing, Project administration. **Debora Rizzuto:** Writing – review & editing, Project administration. **Patrik KE Magnusson:** Writing – review & editing, Project administration. **Hrafnhildur Gudjonsdottir:** Writing – review & editing, Project administration. **Karin Leander:** Writing – review & editing, Project administration. **Timo Lanki:** Writing – review & editing, Project administration. **Pekka Tiittanen:** Writing – review & editing, Project administration. **Tarja Yli-Tuomi:** Writing – review & editing, Project administration. **Pekka Jousilahti:** Writing – review & editing, Project administration. **Petter Ljungman:** Writing – review & editing, Supervision, Methodology, Formal analysis, Conceptualization. **Jeroen de Bont:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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Authors' contributions.

HN, MS, PL, JDB, MS generated study aims and conducted the study. HN, MS, PL, JDB, MS designed the study. HN performed data analysis. JDB and MS double checked the data analysis. AHP, ORN, JK, AO provided dataset for DCH cohort. ZJA, MKS, YHL, JZ, TCH, HN provided the dataset for DNC cohort. GP, AP, AÅ, DR, PM, HG, KL, LS, EMA, DS, AR, MÖ, AO, MA, KM, SG provided the dataset from Swedish cohorts. TL, PT, TYT, PJ provided the dataset from Finnish cohorts. HN wrote the first draft of the manuscript under the supervision of MS, PL, JDB, MS. All

authors contributed to the manuscript revision, and read, and approved the submitted version.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2025.109403>.

Data availability

The data that has been used is confidential.

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