Environmental Risk Factors

Residential exposure to traffic-borne pollution as a risk factor for acute cardiocerebrovascular events: a population-based retrospective cohort study in a highly urbanized area

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Abstract

Background: Long-term exposure to traffic-borne noise and air pollution has been variably associated with incidence of acute vascular events, namely acute myocardial infarction, ischaemic stroke and haemorrhagic stroke. This study aims at exploring this association within a highly urbanized city.

Methods: This is a population-based retrospective dynamic cohort study including all residents aged \( \geq 35 \) years in the municipality of Milan over the years 2011–18 (1 087 110 inhabitants). Residential exposure to road traffic noise (day-evening-night levels) and nitrogen dioxide was estimated using a noise predictive model and a land use regression model, respectively. Cox proportional hazards regression analyses were performed to assess the incidence of acute vascular events and specific outcomes in single-exposure and two-exposure models including adjustment for sociodemographic confounders, fine particulate matter and surrounding greenness.

Results: A total of 27 282 subjects (2.5%) had an acute vascular event. Models using nitrogen dioxide produced inconsistent results. The strongest effect was observed for noise, with an optimal cut-off for dichotomization set at 70 dBA (hazard ratio 1.025, 95% confidence interval 1.000–1.050). This association was observed specifically for ischaemic and haemorrhagic stroke. When stratifying by age group and sex, a remarkable effect was found for haemorrhagic stroke in men aged <60 years (hazard ratio 1.439, 95% confidence interval 1.156–1.792).

Conclusions: Living by roads with a day-evening-night noise level above 70 dBA exerts a small but tangible independent effect on the risks of both ischaemic and haemorrhagic stroke. It is urgent to propose mitigation measures against pollution and noise originating from vehicular traffic in order to reduce their impact, especially in the population younger than 60 years.

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Key words: Traffic, air pollution, noise, greenness, acute vascular events, cardiovascular disease, acute myocardial infarction, stroke, urban health, environmental health

Key Messages

- Traffic-borne noise and air pollution are ubiquitous in modern society and both have been studied as environmental risk factors for cardiovascular disease.
- In a metropolitan area, residential proximity to roads with high traffic intensity (mean traffic noise level above 70 dBA) is a risk factor for ischaemic and haemorrhagic stroke.
- Further interventions aimed at reducing traffic intensity in highly urbanized cities may be justified in order to reduce morbidity and mortality from stroke.

Introduction

Noise and air pollution are both acknowledged environmental stressors contributing to cardiovascular disease, which is the leading cause of morbidity and mortality worldwide.1,2 Acute vascular events (AVEs) such as acute myocardial infarction (AMI), ischaemic stroke (IS) and haemorrhagic stroke (HS), pose the highest burden, with 32.4 million cases and 15.2 million deaths every year.3 Inhalation of ambient particulate matter, especially particulate matter with aerodynamic diameter ≤2.5 μm (PM2.5), is an established trigger of AVEs occurring within hours to a few days after exposure.4,5 However, long-term exposure has been recently studied in more detail and would seem to increase this risk to an even greater extent.6,7 Differentiating cardiovascular outcomes, especially stroke subtypes, heavily affects study findings and their interpretation. The relation between air pollution and ischaemic heart disease has been reported in many cohort studies, with similar degrees of association.6 Instead, the evidence for the association with stroke is less consistent, with contrasting results, variable risk estimates and a somewhat greater role for IS rather than HS.7–9 Elevated risks for health have also been associated with living in proximity to roadways.10,11 These risks are unlikely to be explained by PM, which has a long atmospheric lifetime and tends to spread over broad areas, and may be attributable to specific components with higher concentrations near roads.12 Nitrogen oxides (NOx) and nitrogen dioxide (NO2) in particular have been used in epidemiological studies as markers of local traffic-derived air pollution with high spatial contrast.1

The connection between noise and cardiovascular outcomes is complex and mediated by direct and indirect effects. These include sleep disturbance and stress reactions affecting the autonomic nervous system and the endocrine system.13 Furthermore, different sources (road traffic, railway, aircraft noise) need to be taken into account. However, there seems to be a specific and independent role of road traffic noise. In Europe, a 10-dBA increase was found to be associated with an 8% increased incidence of ischaemic heart disease and 14% increased incidence of stroke.2 As road traffic is a source of chronic exposure to both air pollutants and noise, the specific effects of each may be hard to disentangle due to issues of collinearity and/or mutual confounding.14,15 This has led several study groups to investigate the combined effects of these stressors on cardiometabolic diseases in recent years, providing widely different results.16–25 Fewer studies also took into account the relationship of road traffic with green space.26–28 Together with reduction of psychological stress and promotion of physical activity and social interactions, attenuation of air pollution and noise is a postulated mechanism for the beneficial effect of residential surrounding greenness on health.29 On the other hand, the presence of road traffic should be reduced in greener areas, thus indicating a common source (or lack thereof) between these variables. Therefore, the effects of noise and air pollutants may be at least partly explained by their role as confounders and/or mediators in the relationship between greenness and health outcomes. This becomes of particular interest if we consider that traffic is one of the most severe and widespread problems of modern societies. Despite recent regulatory efforts, a considerable proportion of the European urban population is still exposed to noise and air pollution levels above recommended safety thresholds.30,31 Lombardy Region in Northern Italy ranks among the most polluted areas in Europe and has already been
targeted by studies linking pollution to health outcomes.\textsuperscript{32,33} Milan is the urban core of the second largest metropolitan area in Italy after Rome. It has a total area of 181.8 km\textsuperscript{2} and a road network extending for about 2000 km, with more than 940 000 circulating vehicles and a well-developed public transport system (Supplementary Figure S1, available as Supplementary data at IJE online). Therefore, vehicular traffic is the main contributor to both the total amount of air pollutants and overall noise levels throughout the year.\textsuperscript{34}

The present study aims at evaluating the role of residential exposure to traffic-borne pollution as a risk factor for AVEs in the population living in Milan. First, in an attempt to differentiate specific effects, we chose to assess the individual roles and mutual influence of estimated NO\textsubscript{2} concentration and road traffic noise level. Second, we performed subanalyses for three outcomes with different risk profiles and underlying pathogenetic mechanisms (AMI, IS, HS). Third, we accounted for potential confounding by spatially homogeneous air pollution (PM\textsubscript{2.5}) and residential surrounding greenness. Last, in order to identify subsets of the population at higher susceptibility, we investigated potential effect modification by sex and age.

Methods

This is an observational study based on data routinely collected by the Agency for Health Protection (ATS) of Milan, a public body of the Regional Health Service of Lombardy Region. The institutional functions of the ATS include the government of the care pathway at the individual level in the regional social and health care system, the evaluation of provided services, and the outcomes of patients residing in the covered area. In particular, the evaluation of the health status of the population is deemed as a priority in the Regional Council Deliberation no. 7600 of 20 December 2017, p. 75.

According to the function attributed to the ATS by the Regional Law no. 23 of 11 August 2015 [http://normelombardia.consiglio.regione.lombardia.it/NormeLombardia/Accessibile/main.aspx?view=showdoc&exp_coll=lr002015081100023&treedelta=1&selnode=lr002015081100023&iddoc=lr002015081100023&testo], ethical approval was not deemed necessary. This study is also ethically compliant with Italian national regulation (Legislative Decree no. 101 of 10 August 2018 [https://www.gazzettaufficiale.it/eli/id/2018/09/04/18G00129/sg]) and the General Authorisation to Process Personal Data for Scientific Research Purposes (nos. 8/2016 and 9/2016, referred to in the Data Protection Authority action of 13 December 2018 [https://www.garanteprivacy.it/home/docweb/-/docweb-display/docweb/9068972]). Administrative permission to perform the study was granted by the General Direction of the ATS of Milan with Resolution no. 36 of 16 January 2018 [http://80.88.164.206/ULISS-eAsl/Bacheca/coatti01.aspx?bac_codice=50&cidSessione=p1wy3vyc3uryjmz05vvh45&men_id=00.00.00]. Individuals were masked by anonymization according to the standard ISO 25237:201. Their unique identification numbers (fiscal codes) were transcoded into strings by the Information System of the ATS, which had no role in analysing the data.

Our study is population-based and used administrative health databases with routinely collected data. We retrospectively investigated a dynamic cohort of all residents in the municipality of Milan between 1 January 2011 and 31 December 2018 (the number of inhabitants per year rose up to 1 378 689 over this time span). The inclusion criteria were as follows: age ≥35 years on 1 January 2011 or reached during follow-up; no past history of any of the investigated outcomes (AMI, IS, HS); full information available about exposures and covariates of interest. We right-censored observations at the time of occurrence of one of the three possible outcomes (fatal and non-fatal cases being considered alike), death from other causes, emigration or end of follow-up (31 December 2018), whichever came first.

We also identified a subset of the population for sensitivity analyses using specific selection criteria. We defined a static cohort of residents registered in the data warehouse systems on 1 January 2011 and followed it up until event occurrence (either fatal or non-fatal), death from other causes, emigration, change of residence or 31 December 2018, whichever came first (subjects with event occurrence after a change of residence were considered as non-cases).

Outcome definition

Our algorithm for the identification of outcomes was based on record linkage between the above-defined cohort and the database of hospitalizations currently held by the data warehouse systems of the Agency for Health Protection of Milan. The database gathers all hospital discharge records (Schede di Dimissione Ospedaliera, SDO) with one main and five secondary diagnoses coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). AVEs of interest were identified according to the following codes, as is validated in the literature\textsuperscript{35,36}: 410 (AMI); 433.x1, 434.x1, 436 (IS); 430–432 (HS). Newly occurring cases of specified outcomes were detected by searching for their respective codes among principal and/or secondary causes of hospital admission.
Exposure assessment

The coordinates of each subject’s residential address were obtained from the Registry Office of Milan. In case of subjects moving from one address to another during the study period, we retained the most recent observation. Georeferenced data management and calculations were conducted using Quantum Geographical Information System (QGIS) 3.10.4 (QGIS Development Team, 2019) [http://qgis.osgeo.org].

We assessed NO2 exposure using estimates of annual ambient average concentrations (in μg/m3) from a land use regression (LUR) model with 100 × 100 m2 resolution developed for 17 countries across Western Europe for the years 2005–07.37 The model is based on more than 1500 EuroAirnet monitoring sites and incorporates GIS-derived land use, road network and topographical data (population density, length of major and minor roads in zones from 0.1 km to 10 km, altitude, distance to the sea) as well as satellite-derived estimates of ground-level NO2 concentrations on a coarser resolution of 10 × 10 km2. We overlaid the coordinates of each address and assigned the NO2 concentration of the corresponding 100 × 100 m2 grid cell containing it. We treated the variable either as continuous or categorized into quintiles (Supplementary Figure S2, available as Supplementary data at IJE online).

We derived road traffic noise exposure from a locally developed map with mean annual estimates of Lden by the Municipality of Milan in 2012.38 Lden (day-evening-night noise level) is the current European standard for measuring environmental noise. It is defined as the A-weighted equivalent noise level over a whole day with a penalty of 5 dBA for evening hours (20.00–22.00) and 10 dBA for nighttime hours (22.00–06.00), as adapted by Italian Regulations (Legislative Decree no. 194/2005). The noise predictive model integrates the acoustic characterization of road infrastructures (traffic flow, composition and speed, and road surface type) and data representative of territory (morphology and type of land cover) and buildings (type and geometric characteristics, use, number of residents).39 Lden values at the intersection points of a square calculation grid with 10-m spacing and 4-m ground elevation are interpolated to generate polygons representative of Lden intervals (50–54, 55–59, 60–64, 65–69, 70–74, >75 dBA). Considering that almost all roads within the city of Milan reached levels of Lden above 55 dBA, leaving virtually no unexposed population, we decided to consider noise intervals starting from a higher threshold (<65, 65–69, 70–74, >75 dBA) (Supplementary Figure S3, available as Supplementary data at IJE online). In order to account for inaccuracies in the geolocalization process, we drew a 20-m circular buffer around each address and assigned the maximum value of Lden within the buffer to that address. We first investigated the exposure-response relationship considering Lden as an ordinal variable with four categories, and then used growing thresholds in search of a potential optimal cut-off for dichotomization.

Covariates

We evaluated the effect of four sociodemographic and address-specific variables as potential confounders/effect modifiers. These variables were included as fixed covariates in all statistical models: age at entry, sex, citizenship (European versus non-European) and the Italian Deprivation Index as an area-level proxy of socioeconomic status. The Italian Deprivation Index is an aggregate indicator calculated for small census sections as the sum of the standardized values of five variables: percentage of population with poor education; unemployment; occupied dwellings for rent; percentage of single parents with dependent children; population density.40 The index is then categorized into five levels according to the quintiles of the distribution of the territory covered by the Agency for Health Protection of Milan.

Residential values of PM2.5 and surrounding greenness were included in models accounting for environmental confounding. These were assigned by using the same 100 × 100 m2 grid as in the LUR model for NO2 (Supplementary Figures S4 and S5, available as Supplementary data at IJE online). We derived PM2.5 exposure from a similarly designed LUR model with annual ambient average concentrations (in μg/m3) developed for Europe for the year 2010.41 Residential greenness was assessed by means of a locally developed map based on land use classification data for the year 2012 by the Municipality of Milan. We defined surrounding greenness (%) as the percentage of the 100 × 100 m2 grid cell containing any green space.

A directed acyclic graph42 illustrating our model assumptions and providing justification for the choice of these covariates, as determined by the implied minimal adjustment set, can be found in Supplementary Figure S6, available as Supplementary data at IJE online.

Statistical analyses

We performed survival analyses using Cox proportional hazards regression, estimating hazard ratios (HRs) for the outcomes of interest and the corresponding Wald two-sided 95% confidence intervals (CIs). We estimated multivariable models with one proxy of exposure (M1), mutually adjusted models with both proxies (M2) and mutually adjusted models including all environmental variables
Continuous variables were included in the models either as linear terms or natural cubic splines with three degrees of freedom. We then evaluated model performances by comparing values of Akaike Information Criterion (AIC), which penalizes for the additional degrees of freedom. Effect modifications by age and sex were further assessed in stratified analyses. Age grouping was performed according to previous landmarks in the literature (<60, 60–75, >75 years) so as to favour comparability of results.17,18 All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

Out of 1 118 447 potentially eligible residents, we had to exclude 31 337 subjects (2.8%) because of missing or erroneous geolocalization or other missing covariates. Therefore, the study population included 1 087 110 residents (a flow diagram illustrating each stage of the study population selection can be found in Supplementary Figure S7, available as Supplementary data at IJE online). A detailed description of covariates, exposures and follow-up characteristics of the cohort, including differentiation by outcome, can be found in Table 1. Although values ranged from 30.1 to 80.9 µg/m³, the NO2 distribution had a high mean value (49.47 µg/m³) and low dispersion (standard deviation 4.88 µg/m³, interquartile range 5.27 µg/m³) (Supplementary Figure S8, available as Supplementary data at IJE online). Most residents were exposed to high Lden values according to our classification (67.3% above 65 dBA, 42.4% above 70 dBA, 20.3% above 75 dBA). All environmental variables showed only weak to moderate correlations (Spearman’s rank order correlation coefficients <0.40) (Supplementary Table S1, available as Supplementary data at IJE online). The mean follow-up time was approximately 81 months, for a total of 7 237 472 person-years. In total, 27 282 (2.5%) had an incident AVE after a mean follow-up time of 47 months (48.4% were AMIs and 51.6% were strokes, of which 74.0% were IS and 26.0% HS).

We hereby report results of survival models restricted to hazard ratios (HRs) for the exposures. As for sociodemographic covariates, increasing age, male sex, European citizenship and higher Italian Deprivation Index all stood out

| Table 1 Characteristics of the study population, including road traffic noise (L_{den}) and NO2 exposure at the residential address |
| Whole cohort | All AVEs | AMI | IS | HS |
|--------------|---------|-----|----|----|
| N (%) | 1 087 110 | 27 282 (2.51%) | 13 201 (1.21%) | 10 419 (0.96%) | 3 612 (0.34%) |
| Age at entry (years) | Mean (± SD) | 54 (± 17) | 71 (± 13) | 69 (± 13) | 74 (± 12) | 73 (± 13) |
| Sex | Female | 582 072 (53.54%) | 12 405 (45.47%) | 4 854 (36.77%) | 5 641 (54.14%) | 1 910 (52.16%) |
| Citizenship | European | 927 066 (85.28%) | 26 202 (96.04%) | 12 615 (95.56%) | 10 090 (96.84%) | 3 497 (95.49%) |
| IDI levels | | | | | | |
| 1 (least deprived) | 269 763 (24.81%) | 6 167 (22.60%) | 3 145 (23.82%) | 2 489 (23.89%) | 893 (24.39%) |
| 2 | 271 105 (24.94%) | 6 527 (23.92%) | 3 415 (25.28%) | 2 849 (23.89%) | 939 (25.37%) |
| 3 | 192 079 (17.67%) | 4 693 (17.20%) | 2 274 (17.23%) | 1 807 (17.34%) | 612 (16.71%) |
| 4 | 158 813 (14.61%) | 3 957 (14.50%) | 1 924 (14.57%) | 1 501 (14.41%) | 532 (14.53%) |
| 5 (most deprived) | 195 350 (17.97%) | 5 938 (21.77%) | 2 944 (22.30%) | 2 243 (21.53%) | 751 (20.51%) |
| L_{den} (dBA) | | | | | | |
| <65 | 355 317 (32.68%) | 9 147 (33.53%) | 4 503 (34.11%) | 3 453 (33.14%) | 1 191 (32.52%) |
| 65–69 | 271 047 (24.93%) | 6 858 (25.14%) | 3 337 (25.28%) | 2 592 (24.88%) | 929 (25.37%) |
| 70–74 | 239 584 (22.04%) | 6 010 (22.03%) | 2 858 (21.65%) | 2 346 (22.52%) | 806 (22.01%) |
| ≥75 | 221 162 (20.34%) | 5 267 (19.31%) | 2 503 (18.96%) | 2 028 (19.46%) | 736 (20.10%) |
| NO2 concentration (µg/m³) | Mean (± SD) | 49.47 (± 4.88) | 49.36 (± 4.95) | 49.35 (± 5.01) | 49.36 (± 4.91) | 49.38 (± 4.85) |
| PM2.5 concentration (µg/m³) | Mean (± SD) | 27.80 (± 0.88) | 27.80 (± 0.86) | 27.78 (± 0.87) | 27.81 (± 0.84) | 27.82 (± 0.85) |
| Surrounding greenness (%) | Mean (± SD) | 17.2 (± 15.5) | 18.7 (± 16.0) | 18.9 (± 16.0) | 18.6 (± 16.1) | 18.7 (± 15.8) |
| Follow-up time (months) | Mean (± SD) | 80 (± 28) | 47 (± 28) | 46 (± 28) | 48 (± 27) | 47 (± 28) |
| Age at diagnosis, for cases (years) | Mean (± SD) | – | 75 (± 13) | 73 (± 13) | 78 (± 12) | 77 (± 12) |

AMI, acute myocardial infarction; AVE, acute vascular event; HS, haemorrhagic stroke; IDI, Italian Deprivation Index; IS, ischaemic stroke; L_{den}, A-weighted equivalent day-evening-night noise level; SD, standard deviation.
as the most impactful variables on all outcomes (their HRs can be found in Supplementary Table S2, available as Supplementary data at IJE online). In single-exposure models (M1) we found modest positive associations with all AVEs for both exposures, although all confidence intervals (CIs) included 1 (Table 2). There was no evident trend for increases in risk with increasing L den intervals or NO2 quintiles. The strongest effect on the risk of AVEs was observed for L den, with an optimal cut-off for dichotomization set at 70 dBA (HR 1.025, 95% CI 1.000–1.050). Subanalyses for specific outcomes showed that most of these associations were attenuated towards the null for AMI. As for IS and HS, stronger associations were found with L den, whereas NO2 models yielded inconsistent results. An optimal cut-off for dichotomization of L den was found at 70 dBA for IS (HR 1.043, 95% CI 1.003–1.085) and at 75 dBA for HS (HR 1.048, 95% CI 0.966–1.137). In mutually adjusted models (M2), we found that NO2 still performed poorly and only changed estimates for L den slightly upward for both IS and HS (Table 3). Although part of the effect was removed, similar estimates remained even after adjustment for PM2.5 and greenness (M3); considering these as natural cubic splines (Table 4) instead of linear terms (Supplementary Table S3, available as Table 2 Single-exposure models for association of road traffic noise (L den) and NO2 with all acute vascular events and specific outcomes

| L den (dBA), vs <65 | All AVEs | AMI       | IS        | HS        |
|---------------------|----------|-----------|-----------|-----------|
| 65–69               | 1.000 (0.969–1.032) | 0.994 (0.951–1.040) | 0.995 (0.946–1.047) | 1.029 (0.945–1.122) |
| 70–74               | 1.026 (0.993–1.061) | 1.005 (0.958–1.053) | 1.048 (0.994–1.105) | 1.033 (0.944–1.130) |
| ≥75                 | 1.022 (0.988–1.058) | 0.999 (0.951–1.050) | 1.032 (0.976–1.091) | 1.068 (0.973–1.172) |
| L den (dBA), cut-offs |         |           |           |           |
| ≥65                 | 1.015 (0.989–1.041) | 0.999 (0.963–1.036) | 1.023 (0.982–1.066) | 1.041 (0.971–1.116) |
| ≥70                 | 1.025 (1.000–1.050) | 1.004 (0.970–1.040) | 1.043 (1.003–1.085) | 1.036 (0.969–1.107) |
| ≥75                 | 1.013 (0.985–1.046) | 1.000 (0.957–1.044) | 1.020 (0.971–1.071) | 1.048 (0.966–1.137) |
| NO2 (µg/m³), continuous |         |           |           |           |
| per 10 increase | 1.008 (0.984–1.033) | 1.022 (0.987–1.059) | 0.994 (0.955–1.034) | 0.987 (0.923–1.056) |

Models are adjusted for age, sex, citizenship and Italian Deprivation Index (IDI). Reported values are hazard ratios with 95% confidence intervals in brackets.

AMl, acute myocardial infarction; AVE, acute vascular event; HS, haemorrhagic stroke; IS, ischaemic stroke; L den, A-weighted equivalent day-evening-night noise level; Q, quintile.

Table 3 Mutually adjusted, two-exposure models for association of road traffic noise (L den) and NO2 with all acute vascular events and specific outcomes

| L den (dBA), vs <65 | All AVEs | AMI       | IS        | HS        |
|---------------------|----------|-----------|-----------|-----------|
| 65–69               | 1.000 (0.969–1.032) | 0.991 (0.948–1.037) | 0.998 (0.948–1.105) | 1.034 (0.949–1.127) |
| 70–74               | 1.026 (0.992–1.062) | 0.997 (0.950–1.046) | 1.055 (1.000–1.114) | 1.044 (0.952–1.145) |
| ≥75                 | 1.022 (0.985–1.061) | 0.985 (0.934–1.040) | 1.045 (0.984–1.110) | 1.089 (0.985–1.203) |
| L den (dBA), cut-offs |         |           |           |           |
| ≥65                 | 1.013 (0.987–1.041) | 0.992 (0.955–1.030) | 1.027 (0.984–1.072) | 1.049 (0.976–1.128) |
| ≥70                 | 1.025 (0.998–1.052) | 0.996 (0.959–1.034) | 1.052 (1.009–1.097) | 1.046 (0.975–1.124) |
| ≥75                 | 1.013 (0.981–1.046) | 0.989 (0.944–1.036) | 1.025 (0.973–1.080) | 1.061 (0.973–1.158) |
| NO2 (µg/m³), continuous |         |           |           |           |
| per 10 increase | 1.000 (0.974–1.027) | 1.026 (0.986–1.078) | 0.977 (0.936–1.021) | 0.963 (0.895–1.037) |

All models are adjusted for age, sex, citizenship and Italian Deprivation Index (IDI). L den models are adjusted for NO2 as a continuous variable. NO2 models are adjusted for L den as an ordinal variable with four categories. Reported values are hazard ratios with 95% confidence intervals in brackets.

AMI, acute myocardial infarction; AVE, acute vascular event; HS, haemorrhagic stroke; IS, ischaemic stroke; L den, A-weighted equivalent day-evening-night noise level; Q, quintile.
Table 4 Mutually adjusted, two-exposure models for association of road traffic noise (L_{den}) and NO₂ with all acute vascular events and specific outcomes including PM₂.₅ and surrounding greenness as potential confounders

| L_{den} (dBA), vs <65 | AMI | IS | HS |
|-----------------------|-----|----|----|
| 65–69                 | 0.995 (0.964–1.027) | 0.989 (0.945–1.035) | 0.991 (0.941–1.044) | 1.025 (0.940–1.119) |
| 70–74                 | 1.020 (0.986–1.056) | 0.995 (0.947–1.045) | 1.048 (0.992–1.107) | 1.031 (0.939–1.133) |
| ≥75                   | 1.013 (0.975–1.052) | 0.978 (0.926–1.034) | 1.036 (0.974–1.102) | 1.074 (0.968–1.191) |

| L_{den} (dBA), cut-offs | AMI | IS | HS |
|-------------------------|-----|----|----|
| ≥65                     | 1.007 (0.980–1.034) | 0.988 (0.951–1.027) | 1.019 (0.973–1.064) | 1.037 (0.963–1.117) |
| ≥70                     | 1.020 (0.993–1.047) | 0.993 (0.956–1.032) | 1.047 (1.003–1.093) | 1.036 (0.964–1.114) |
| ≥75                     | 1.007 (0.975–1.040) | 0.984 (0.938–1.032) | 1.020 (0.968–1.076) | 1.053 (0.964–1.150) |

| NO₂ (µg/m³), continuous per 10 increase | AMI | IS | HS |
|----------------------------------------|-----|----|----|
| 0.992 (0.964–1.021)                   | 1.024 (0.982–1.067) | 0.957 (0.913–1.003) | 0.972 (0.898–1.052) |

All models are adjusted for age, sex, citizenship, Italian Deprivation Index (IDI) plus PM₂.₅ concentration and surrounding greenness (both specified as natural cubic splines with three degrees of freedom). L_{den} models are adjusted for NO₂ as a continuous variable. NO₂ models are adjusted for L_{den} as an ordinal variable with four categories. Reported values are hazard ratios with 95% confidence intervals in brackets.

AMI, acute myocardial infarction; AVE, acute vascular event; HS, haemorrhagic stroke; IS, ischaemic stroke; L_{den}, A-weighted equivalent day-evening-night noise level; Q, quintile.

Table 5 Models for association between road traffic noise (L_{den}) at three different cut-offs for dichotomization and overall and specific outcomes, stratified by sex and age at baseline

| L_{den} (dBA), cut-offs | Women | Men | Women | Men | Women | Men |
|-------------------------|-------|-----|-------|-----|-------|-----|
| Age group 1 (<60 years) |       |     |       |     |       |     |
| All AVEs                |       |     |       |     |       |     |
| ≥65                     | 0.935 (0.834–1.050) | 0.971 (0.867–1.088) | 0.963 (0.835–1.111) | 0.994 (0.931–1.060) | 1.072 (1.007–1.141) | 1.067 (0.989–1.151) |
| ≥70                     | 1.018 (0.866–1.197) | 0.988 (0.803–1.213) | 0.953 (0.874–1.039) | 0.985 (0.921–1.053) | 1.050 (0.952–1.060) | 1.040 (0.984–1.099) |
| ≥75                     | 0.823 (0.687–1.011) | 0.838 (0.735–1.084) | 0.836 (0.700–1.213) | 0.897 (0.794–1.053) | 0.951 (0.809–1.109) | 0.897 (0.787–1.083) |
| AMI                     |       |     |       |     |       |     |
| ≥65                     | 0.833 (0.678–1.005) | 0.893 (0.735–1.084) | 1.018 (0.866–1.197) | 1.012 (0.861–1.213) | 0.982 (0.861–1.120) | 1.007 (0.887–1.098) |
| ≥70                     | 1.018 (0.866–1.197) | 0.988 (0.803–1.213) | 0.953 (0.874–1.039) | 0.985 (0.921–1.053) | 1.050 (0.952–1.060) | 1.040 (0.984–1.099) |
| ≥75                     | 0.823 (0.687–1.011) | 0.838 (0.735–1.084) | 0.836 (0.700–1.213) | 0.897 (0.794–1.053) | 0.951 (0.809–1.109) | 0.897 (0.787–1.083) |
| IS                      |       |     |       |     |       |     |
| ≥65                     | 0.833 (0.678–1.005) | 0.893 (0.735–1.084) | 1.018 (0.866–1.197) | 1.012 (0.861–1.213) | 0.982 (0.861–1.120) | 1.007 (0.887–1.098) |
| ≥70                     | 1.018 (0.866–1.197) | 0.988 (0.803–1.213) | 0.953 (0.874–1.039) | 0.985 (0.921–1.053) | 1.050 (0.952–1.060) | 1.040 (0.984–1.099) |
| ≥75                     | 0.823 (0.687–1.011) | 0.838 (0.735–1.084) | 0.836 (0.700–1.213) | 0.897 (0.794–1.053) | 0.951 (0.809–1.109) | 0.897 (0.787–1.083) |
| HS                      |       |     |       |     |       |     |
| ≥65                     | 0.963 (0.723–1.328) | 1.150 (0.959–1.380) | 1.007 (0.763–1.328) | 1.034 (0.869–1.230) | 1.140 (1.094–1.374) | 1.175 (1.060–1.373) |
| ≥70                     | 1.007 (0.763–1.328) | 1.150 (0.959–1.380) | 1.007 (0.763–1.328) | 1.034 (0.869–1.230) | 1.140 (1.094–1.374) | 1.175 (1.060–1.373) |
| ≥75                     | 1.133 (0.815–1.575) | 1.034 (0.869–1.230) | 1.133 (0.815–1.575) | 1.034 (0.869–1.230) | 1.140 (1.094–1.374) | 1.175 (1.060–1.373) |

Models are adjusted for age, citizenship and Italian Deprivation Index. Reported values are hazard ratios with 95% confidence intervals in brackets.

AMI, acute myocardial infarction; AVE, acute vascular event; HS, haemorrhagic stroke; IS, ischaemic stroke; L_{den}, A-weighted equivalent day-evening-night noise level.
Supplementary data at IJE online) improved model performance (see Supplementary Figures S9–S11, available as Supplementary data at IJE online for estimated dose-response curves).

In consideration of this, we retained $L_{\text{den}}$ as the only exposure variable for stratified analyses. Details about cohort stratification are found in Supplementary Table S4, available as Supplementary data at IJE online. We identified effect modifications by age and sex (Table 5). Specifically, we found remarkable effects for men aged <60 years, as the optimal cut-off for IS rose to 75 dBA (HR 1.175, 95% CI 1.006–1.373) and the highest increase in risk was observed for HS with the 70-dBA cut-off (HR 1.439, 95% CI 1.156–1.792).

The sensitivity analyses performed on the static cohort subset included 831 116 individuals. These analyses yielded very similar results for all models, with only minor changes to parameter estimates and no tangible impacts on highlighted trends and consequent interpretations (Supplementary Tables S5–S9, available as Supplementary data at IJE online).

**Discussion**

Our study explores the effects of traffic-borne air pollution and noise on cardiocerebrovascular outcomes in a metropolitan context with high levels of exposure. We highlight an increased risk of stroke, particularly of HS and not limited to old age.

Several cohort studies have investigated the effects of both road traffic noise and NO$_2$/NO$_x$. Most of them found no associations with incident AVEs, although comparison of results is hampered by heterogeneity in study designs, risk measures, outcome definitions and exposure assessment methods. In 2014, two twin publications stemming from the ESCAPE project pooled study-level estimates from 11 European cohorts with approximately 100 000 participants. They found no associations between residential exposure to NO$_2$ and incidence of acute coronary events and stroke (HR 1.03, 95% CI 0.97–1.08; and 0.99, 95% CI 0.89–1.11 per 10 µg/m$^3$ fixed increment, respectively). Instead, they reported positive associations with PM$_{2.5}$, which were robust after adjustment for $L_{\text{den}}$. For both outcomes they found effect modification by age, with null/protective effects at <60 years and higher effects in the 60–74 and ≥75 ranges.\textsuperscript{17,18} The Dutch GLOBE study found no associations between road traffic noise or any air pollutants (including NO$_2$) and ischaemic heart disease and stroke (considered altogether), with only marginal effect changes after mutual adjustment. For both exposures, risk estimates were slightly higher in subjects aged 65 and over.\textsuperscript{16} A Swedish prospective cohort study found no separate associations with either $L_{\text{den}}$ or nitrogen oxides (NO$_x$) in relation to incident AMI, both before and after mutual adjustment, but the average exposure levels in their setting were modest (51 dBA and 11 µg/m$^3$, respectively).\textsuperscript{20} However, null associations were also found by Carey et al.\textsuperscript{21} investigating a large cohort (N = 211 016) in Greater London, where mean values of NO$_2$ and night-time noise were considerably higher. Cai et al.\textsuperscript{23} used the same LUR model for NO$_2$ estimation as in our study, in a joint analysis of three cohorts from Norway and the UK (N = 355 732). After mutual adjustment, they found suggestive evidence of an association between annual mean $L_{\text{den}}$ and acute coronary events, whereas air pollutants (NO$_2$ and PM$_{2.5}$) were linked to incident ischaemic strokes. Andersson et al.\textsuperscript{24} investigated the individual and combined effects of $L_{\text{den}}$ and NO$_x$ on the incidence of ischaemic heart disease and stroke in a Swedish cohort of 6304 men. Their two-pollutant models yielded HRs of 1.14 (95% CI 0.96–1.36) for ischaemic heart disease and 1.07 (95% CI 0.85–1.36) for stroke for $L_{\text{den}}$ above 63 dB compared with below 53 dB. No linear positive trend across NO$_2$ quintiles was shown for either outcome. In a nationwide Danish Nurse Cohort consisting of 23 423 nurses, Amini et al.\textsuperscript{25} evaluated the effect of air pollution on hospital contacts due to stroke, with differentiation by stroke subtype. In their fully adjusted models, inclusion of $L_{\text{den}}$ as a covariate did not appreciably change the estimates for air pollutants. The 1-year running mean of PM$_{2.5}$ was associated with ischaemic stroke (HR 1.14, 95% CI 1.01–1.27 per interquartile range increase) but not haemorrhagic stroke (HR 1.06, 95% CI 0.78–1.43); NO$_2$ played a lesser role in both cases (HR 1.07, 95% CI 0.98–1.17; and 0.93, 95% CI 0.71–1.22, respectively).

As of today, the strongest results linking NO$_2$ and noise to incidence of both AMI and stroke have been found in the Danish ‘Diet, Cancer and Health cohort’. Roswall et al.\textsuperscript{22} found 10-year average values of NO$_2$ and $L_{\text{den}}$ to be individually associated with a higher risk of AMI in single-pollutant models (HR 1.08, 95% CI 1.03–1.12; and 1.14, 95% CI 1.07–1.21 per interquartile range increase, respectively). Mutual adjustment reduced the association with NO$_2$ (HR 1.02, 95% CI 0.96–1.08), whereas the association with $L_{\text{den}}$ remained (HR 1.12, 95% CI 1.03–1.21). Similarly, in a different study by Sørensen et al.\textsuperscript{19} investigating IS and HS as outcomes in the same cohort, both variables were associated with IS in single-exposure models (incidence rate ratio 1.11, 95% CI 1.03–1.20 per 10 µg/m$^3$ increase and 1.16, 95% CI 1.07–1.24 per 10 dB increase in yearly exposure, respectively). In two-exposure models, only $L_{\text{den}}$ (incidence rate ratio 1.15, 95% CI 1.04–1.26) but not NO$_2$ (incidence rate ratio 1.02, 95% CI 0.92–1.12)
They reported that only PM2.5 was associated with stroke incidence and road traffic noise with several self-reported physiologic or comorbid conditions which may act as confounders, outcome predictors or mediators (atherosclerosis, hypertension, diabetes, dyslipidaemia), and associated use of medications; (iv) house characteristics (height from the ground, wall thickness and structure) and factors influencing true residential exposure (occupational status, commuting, time-activity patterns, air conditioning usage, window-opening habits).

Stratified analyses yielded heterogeneous results in different age and sex groups. Compared with previous literature,16-18,23 our finding of a greater risk in a younger category and restricted to men is unprecedented. In particular, a greater effect for HS in men aged <60 years might indicate an anticipation of the effects of traffic exposure in a highly exposed population. Further investigation is warranted in order to clarify whether there truly is an underlying biological mechanism at play.

Strengths and limitations

One of the major strengths of this study is the size of the investigated population. The use of administrative data limits selection bias, as these databases cover the whole population. Our use of residential addresses to assign exposure also ensures reliable information on the individual residence with freedom from recall or non-response bias. Although the positive predictive values of algorithms used to identify cases may be suboptimal, our outcomes were acute and clearly defined events associated with hospitalization. This allowed us to overcome the major limitations and inaccuracies coming from the use of administrative data to carry out research on chronic conditions.50

The use of models with suboptimal performance to estimate values of air pollutants and noise may cause exposure to be ‘spatially misaligned’.31,52 The overall worse performance of NO2 as a predictor of strokes might be explained by the coarser resolution of the LUR model, or the fact that local traffic intensity data were used to build the Milan noise predictive model but were not available for the European NO2 model, which included only road network data. Another consideration to be made is about model transferability in time. Assigning fixed levels of exposure over the whole study period does not consider regulatory actions to decrease traffic load and their effectiveness.53 However, we value spatial patterns of noise and air pollution over absolute levels, and our use of these modelled exposures assumes that intracity gradients and therefore intracohort contrasts are stable over time.54,55

Last, we cannot exclude residual confounding due to factors of individual susceptibility that were not accounted for. These mainly include: (i) family history; (ii) physiological parameters and lifestyle variables (body mass index, smoking status, menopausal status in women); (iii) chronic conditions which may act as confounders, outcome predictors or mediators (atherosclerosis, hypertension, diabetes, dyslipidaemia), and associated use of medications; (iv) house characteristics (height from the ground, wall thickness and structure) and factors influencing true residential exposure (occupational status, commuting, time-activity patterns, air conditioning usage, window-opening habits).
As the population improves in understanding and awareness, they are more likely to implement protective measures. This may lead to a spurious estimation of risk and explain the non-consistent increase in risk with increasing levels of exposure that we observed.

Conclusions

We found suggestive evidence that living close to high-traffic roads (i.e. roads with mean traffic noise level above 70 dBA) exerts a small but tangible effect on the risk of stroke, independently from exposure to high PM$_{2.5}$ levels and from the protective role of surrounding greenness. The varying degrees of association observed for specific outcomes and in different age and sex groups, with the greatest effect reported for HS in middle-aged men, are likely due to different pathogenetic mechanisms at play and warrant further investigation. The burden of cerebrovascular disease and the ubiquity of exposure in modern society bear important implications for public health policies. Our findings would justify the adoption of further risk reduction strategies in highly urbanized cities, such as reducing traffic intensity, undertaking urbanization changes to provide a greater separation between locations of residence and traffic, and empowering individuals to increase awareness and self-protective behaviours.

Supplementary data

Supplementary data are available at IJE online.

Funding

None.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Conflict of interest

None declared.

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