



Original Article

# 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.

**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.<sup>1,2</sup> 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.<sup>3</sup>

Inhalation of ambient particulate matter, especially particulate matter with aerodynamic diameter  $\leq 2.5 \mu\text{m}$  (PM<sub>2.5</sub>), is an established trigger of AVEs occurring within hours to a few days after exposure.<sup>4,5</sup> However, long-term exposure has been recently studied in more detail and would seem to increase this risk to an even greater extent.<sup>6,7</sup> 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.<sup>6</sup> 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.<sup>7-9</sup> Elevated risks for health have also been associated with living in proximity to roadways.<sup>10,11</sup> 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.<sup>12</sup> Nitrogen oxides (NO<sub>x</sub>) and nitrogen dioxide (NO<sub>2</sub>) in particular have been used in epidemiological studies as markers of local traffic-derived air pollution with high spatial contrast.<sup>1</sup>

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.<sup>13</sup> 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.<sup>2</sup>

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.<sup>14,15</sup> This has led several study groups to investigate the combined effects of these stressors on cardiometabolic diseases in recent years, providing widely different results.<sup>16-25</sup> Fewer studies also took into account the relationship of road traffic with green space.<sup>26-28</sup> 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.<sup>29</sup> 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.<sup>30,31</sup>

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.<sup>32,33</sup> Milan is the urban core of the second largest metropolitan area in Italy after Rome. It has a total area of 181.8 km<sup>2</sup> 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.<sup>34</sup>

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<sub>2</sub> 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<sub>2.5</sub>) 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&rebuildtree=1&selnode=lr002015081100023&iddoc=lr002015081100023&testo](http://normelombardia.consiglio.regione.lombardia.it/NormeLombardia/Accessibile/main.aspx?view=showdoc&exp_coll=lr002015081100023&rebuildtree=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&idSessione=p1wyp32vyc3urymjzo5vvh45&men\\_id=00.00.00](http://80.88.164.206/ULISS-eAsl/Bacheca/coatti01.aspx?bac_codice=50&idSessione=p1wyp32vyc3urymjzo5vvh45&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  $\geq 35$  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<sup>35,36</sup>: 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 NO<sub>2</sub> exposure using estimates of annual ambient average concentrations (in  $\mu\text{g}/\text{m}^3$ ) from a land use regression (LUR) model with  $100 \times 100 \text{ m}^2$  resolution developed for 17 countries across Western Europe for the years 2005–07.<sup>37</sup> 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 NO<sub>2</sub> concentrations on a coarser resolution of  $10 \times 10 \text{ km}^2$ . We overlaid the coordinates of each address and assigned the NO<sub>2</sub> concentration of the corresponding  $100 \times 100 \text{ m}^2$  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 L<sub>den</sub> by the Municipality of Milan in 2012.<sup>38</sup> L<sub>den</sub> (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).<sup>39</sup> L<sub>den</sub> 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 L<sub>den</sub> 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 L<sub>den</sub> 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 L<sub>den</sub> within the buffer to that address. We first investigated the exposure-response relationship considering L<sub>den</sub> 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.<sup>40</sup> 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 PM<sub>2.5</sub> and surrounding greenness were included in models accounting for environmental confounding. These were assigned by using the same  $100 \times 100 \text{ m}^2$  grid as in the LUR model for NO<sub>2</sub> (Supplementary Figures S4 and S5, available as Supplementary data at *IJE* online). We derived PM<sub>2.5</sub> exposure from a similarly designed LUR model with annual ambient average concentrations (in  $\mu\text{g}/\text{m}^3$ ) developed for Europe for the year 2010.<sup>41</sup> 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  $100 \times 100 \text{ m}^2$  grid cell containing any green space.

A directed acyclic graph<sup>42</sup> 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

**Table 1** Characteristics of the study population, including road traffic noise ( $L_{den}$ ) and  $NO_2$  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%)	3662 (0.34%)
Age at entry (years)	Mean ( $\pm$ SD)	54 ( $\pm$ 17)	71 ( $\pm$ 13)	69 ( $\pm$ 13)	74 ( $\pm$ 12)	73 ( $\pm$ 13)
Sex	Female	582 072 (53.54%)	12 405 (45.47%)	4854 (36.77%)	5641 (54.14%)	1910 (52.16%)
Citizenship	European	927 066 (85.28%)	26 202 (96.04%)	12 615 (95.56%)	10 090 (96.84%)	3497 (95.49%)
IDI levels	1 (least deprived)	269 763 (24.81%)	6167 (22.60%)	2914 (22.07%)	2379 (22.83%)	874 (23.87%)
	2	271 105 (24.94%)	6527 (23.92%)	3145 (23.82%)	2489 (23.89%)	893 (24.39%)
	3	192 079 (17.67%)	4693 (17.20%)	2274 (17.23%)	1807 (17.34%)	612 (16.71%)
	4	158 813 (14.61%)	3957 (14.50%)	1924 (14.57%)	1501 (14.41%)	532 (14.53%)
	5 (most deprived)	195 350 (17.97%)	5938 (21.77%)	2944 (22.30%)	2243 (21.53%)	751 (20.51%)
$L_{den}$ (dBA)	<65	355 317 (32.68%)	9147 (33.53%)	4503 (34.11%)	3453 (33.14%)	1191 (32.52%)
	65–69	271 047 (24.93%)	6858 (25.14%)	3337 (25.28%)	2592 (24.88%)	929 (25.37%)
	70–74	239 584 (22.04%)	6010 (22.03%)	2858 (21.65%)	2346 (22.52%)	806 (22.01%)
	$\geq 75$	221 162 (20.34%)	5267 (19.31%)	2503 (18.96%)	2028 (19.46%)	736 (20.10%)
$NO_2$ concentration ( $\mu g/m^3$ )	Mean ( $\pm$ SD)	49.47 ( $\pm$ 4.88)	49.36 ( $\pm$ 4.95)	49.35 ( $\pm$ 5.01)	49.36 ( $\pm$ 4.91)	49.38 ( $\pm$ 4.85)
$PM_{2.5}$ concentration ( $\mu g/m^3$ )	Mean ( $\pm$ SD)	27.80 ( $\pm$ 0.88)	27.80 ( $\pm$ 0.86)	27.78 ( $\pm$ 0.87)	27.81 ( $\pm$ 0.84)	27.82 ( $\pm$ 0.85)
Surrounding greenness (%)	Mean ( $\pm$ SD)	17.2 ( $\pm$ 15.5)	18.7 ( $\pm$ 16.0)	18.9 ( $\pm$ 16.0)	18.6 ( $\pm$ 16.1)	18.7 ( $\pm$ 15.8)
Follow-up time (months)	Mean ( $\pm$ SD)	80 ( $\pm$ 28)	47 ( $\pm$ 28)	46 ( $\pm$ 28)	48 ( $\pm$ 27)	47 ( $\pm$ 28)
Age at diagnosis, for cases (years)	Mean ( $\pm$ SD)	–	75 ( $\pm$ 13)	73 ( $\pm$ 13)	78 ( $\pm$ 12)	77 ( $\pm$ 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.

(M3). 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.<sup>17,18</sup> 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  $\mu g/m^3$ , the  $NO_2$  distribution had a high mean value (49.47  $\mu g/m^3$ ) and low dispersion (standard deviation 4.88  $\mu g/m^3$ , interquartile range 5.27  $\mu g/m^3$ ) ([Supplementary Figure S8](#), available as [Supplementary data](#) at *IJE* online). Most residents were exposed to high  $L_{den}$  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 2** Single-exposure models for association of road traffic noise ( $L_{den}$ ) and  $NO_2$  with all acute vascular events and specific outcomes

		All AVEs	AMI	IS	HS
$L_{den}$ (dBA), vs <65	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)
	$\geq 75$	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	$\geq 65$	1.015 (0.989–1.041)	0.999 (0.963–1.036)	1.023 (0.982–1.066)	1.041 (0.971–1.116)
	$\geq 70$	1.025 (1.000–1.050)	1.004 (0.970–1.040)	1.043 (1.003–1.085)	1.036 (0.969–1.107)
	$\geq 75$	1.015 (0.985–1.046)	1.000 (0.957–1.044)	1.020 (0.971–1.071)	1.048 (0.966–1.137)
$NO_2$ ( $\mu g/m^3$ ), 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)
$NO_2$ ( $\mu g/m^3$ ), vs Q1: 30.10–45.89	Q2: 45.90–48.53	1.004 (0.967–1.042)	0.997 (0.945–1.053)	0.998 (0.939–1.061)	1.028 (0.927–1.141)
	Q3: 48.54–50.32	1.021 (0.983–1.061)	0.992 (0.940–1.048)	1.032 (0.971–1.097)	1.076 (0.970–1.193)
	Q4: 50.33–52.70	1.009 (0.971–1.048)	1.008 (0.955–1.064)	1.006 (0.946–1.069)	1.008 (0.907–1.120)
	Q5: 52.71–80.89	1.013 (0.976–1.052)	1.022 (0.968–1.078)	0.993 (0.934–1.055)	1.022 (0.921–1.134)

Models are adjusted for age, sex, citizenship and Italian Deprivation Index (IDI). 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 3** Mutually adjusted, two-exposure models for association of road traffic noise ( $L_{den}$ ) and  $NO_2$  with all acute vascular events and specific outcomes

		All AVEs	AMI	IS	HS
$L_{den}$ (dBA), vs <65	65–69	1.000 (0.969–1.032)	0.991 (0.948–1.037)	0.998 (0.948–1.050)	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)
	$\geq 75$	1.022 (0.985–1.061)	0.985 (0.934–1.040)	1.045 (0.984–1.110)	1.089 (0.985–1.205)
$L_{den}$ (dBA), cut-offs	$\geq 65$	1.013 (0.987–1.041)	0.992 (0.955–1.030)	1.027 (0.984–1.072)	1.049 (0.976–1.128)
	$\geq 70$	1.025 (0.998–1.052)	0.996 (0.959–1.034)	1.052 (1.009–1.097)	1.046 (0.975–1.124)
	$\geq 75$	1.013 (0.981–1.046)	0.989 (0.944–1.036)	1.025 (0.973–1.080)	1.061 (0.973–1.158)
$NO_2$ ( $\mu g/m^3$ ), continuous	per 10 increase	1.000 (0.974–1.027)	1.026 (0.988–1.066)	0.977 (0.936–1.021)	0.963 (0.895–1.037)
$NO_2$ ( $\mu g/m^3$ ), vs Q1: 30.10–45.89	Q2: 45.90–48.53	0.999 (0.962–1.038)	0.998 (0.945–1.054)	0.989 (0.930–1.052)	1.019 (0.918–1.131)
	Q3: 48.54–50.32	1.017 (0.979–1.056)	0.994 (0.940–1.050)	1.023 (0.962–1.088)	1.065 (0.959–1.183)
	Q4: 50.33–52.70	1.002 (0.964–1.042)	1.010 (0.955–1.067)	0.992 (0.931–1.056)	0.991 (0.890–1.104)
	Q5: 52.71–80.89	1.001 (0.961–1.042)	1.025 (0.967–1.087)	0.968 (0.907–1.035)	0.991 (0.886–1.109)

All models are adjusted for age, sex, citizenship and Italian Deprivation Index (IDI).  $L_{den}$  models are adjusted for  $NO_2$  as a continuous variable.  $NO_2$  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.

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  $NO_2$  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  $NO_2$  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  $NO_2$  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  $PM_{2.5}$  and greenness (M3); considering these as natural cubic splines ([Table 4](#)) instead of linear terms ([Supplementary Table S3](#), available as

**Table 4** Mutually adjusted, two-exposure models for association of road traffic noise ( $L_{den}$ ) and  $NO_2$  with all acute vascular events and specific outcomes including  $PM_{2.5}$  and surrounding greenness as potential confounders

		All AVEs	AMI	IS	HS
$L_{den}$ (dBA), vs <65	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)
	$\geq 75$	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	$\geq 65$	1.007 (0.980–1.034)	0.988 (0.951–1.027)	1.019 (0.975–1.064)	1.037 (0.963–1.117)
	$\geq 70$	1.020 (0.993–1.047)	0.993 (0.956–1.032)	1.047 (1.003–1.093)	1.036 (0.964–1.114)
	$\geq 75$	1.007 (0.975–1.040)	0.984 (0.938–1.032)	1.020 (0.968–1.076)	1.053 (0.964–1.150)
$NO_2$ ( $\mu g/m^3$ ), continuous	per 10 increase	0.992 (0.964–1.021)	1.024 (0.982–1.067)	0.957 (0.913–1.003)	0.972 (0.898–1.052)
$NO_2$ ( $\mu g/m^3$ ), vs Q1: 30.10–45.89	Q2: 45.90–48.53	0.992 (0.954–1.031)	0.998 (0.944–1.056)	0.970 (0.911–1.033)	1.022 (0.918–1.137)
	Q3: 48.54–50.32	1.007 (0.967–1.047)	0.993 (0.938–1.052)	0.992 (0.930–1.058)	1.083 (0.971–1.207)
	Q4: 50.33–52.70	0.993 (0.953–1.034)	1.009 (0.952–1.070)	0.961 (0.900–1.027)	1.016 (0.907–1.137)
	Q5: 52.71–80.89	0.992 (0.951–1.035)	1.019 (0.959–1.083)	0.949 (0.886–1.016)	1.012 (0.900–1.137)

All models are adjusted for age, sex, citizenship, Italian Deprivation Index (IDI) plus  $PM_{2.5}$  concentration and surrounding greenness (both specified as natural cubic splines with three degrees of freedom).  $L_{den}$  models are adjusted for  $NO_2$  as a continuous variable.  $NO_2$  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	Age group 1 (<60 years)	Age group 2 (60–74 years)	Age group 3 ( $\geq 75$ years)
All AVEs	Women	$\geq 65$	0.935 (0.834–1.050)	0.993 (0.927–1.064)	1.016 (0.967–1.066)
		$\geq 70$	0.971 (0.867–1.088)	1.027 (0.960–1.099)	0.999 (0.954–1.046)
		$\geq 75$	0.963 (0.835–1.111)	0.953 (0.874–1.039)	1.022 (0.966–1.082)
	Men	$\geq 65$	0.994 (0.931–1.060)	0.985 (0.921–1.055)	1.010 (0.952–1.071)
		$\geq 70$	1.072 (1.007–1.141)	1.005 (0.952–1.060)	1.033 (0.976–1.093)
		$\geq 75$	1.067 (0.989–1.151)	1.040 (0.984–1.099)	1.021 (0.952–1.095)
AMI	Women	$\geq 65$	1.007 (0.853–1.188)	0.950 (0.856–1.055)	1.009 (0.930–1.095)
		$\geq 70$	1.018 (0.866–1.197)	1.002 (0.903–1.111)	0.984 (0.911–1.064)
		$\geq 75$	0.988 (0.805–1.213)	0.982 (0.861–1.120)	1.039 (0.946–1.143)
	Men	$\geq 65$	0.957 (0.885–1.034)	1.045 (0.971–1.126)	0.974 (0.893–1.062)
		$\geq 70$	1.028 (0.954–1.108)	0.989 (0.921–1.063)	0.987 (0.907–1.074)
		$\geq 75$	0.997 (0.909–1.094)	0.973 (0.888–1.065)	0.975 (0.877–1.083)
IS	Women	$\geq 65$	0.833 (0.687–1.011)	0.987 (0.887–1.098)	1.024 (0.955–1.099)
		$\geq 70$	0.893 (0.735–1.084)	1.051 (0.947–1.166)	1.008 (0.944–1.077)
		$\geq 75$	0.850 (0.661–1.092)	0.967 (0.848–1.104)	1.008 (0.929–1.093)
	Men	$\geq 65$	1.023 (0.891–1.174)	1.058 (0.961–1.164)	1.046 (0.952–1.151)
		$\geq 70$	1.099 (0.964–1.254)	1.061 (0.967–1.165)	1.080 (0.986–1.182)
		$\geq 75$	1.175 (1.006–1.373)	1.016 (0.904–1.142)	1.035 (0.924–1.158)
HS	Women	$\geq 65$	0.963 (0.723–1.284)	1.150 (0.959–1.380)	1.003 (0.886–1.136)
		$\geq 70$	1.007 (0.763–1.328)	1.034 (0.869–1.230)	1.002 (0.890–1.127)
		$\geq 75$	1.133 (0.815–1.575)	0.834 (0.661–1.052)	1.029 (0.891–1.188)
	Men	$\geq 65$	1.302 (1.018–1.664)	0.958 (0.809–1.133)	1.028 (0.889–1.189)
		$\geq 70$	1.439 (1.156–1.792)	0.913 (0.771–1.080)	1.052 (0.915–1.210)
		$\geq 75$	1.401 (1.094–1.794)	0.959 (0.776–1.186)	1.121 (0.947–1.327)

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  $L_{den}$  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  $NO_x/NO_2$ . 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  $\mu g/m^3$  fixed increment, respectively). Instead, they reported positive associations with  $PM_{2.5}$ , which were robust after adjustment for  $L_{den}$ . For both outcomes they found effect modification by age, with null/‘protective’ effects at <60 years and higher effects in the 60–74 and  $\geq 75$  ranges.<sup>17,18</sup> 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.<sup>16</sup> A Swedish prospective cohort study found no

separate associations with either  $L_{den}$  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  $\mu g/m^3$ , respectively).<sup>20</sup> However, null associations were also found by Carey *et al.*<sup>21</sup> 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.*<sup>23</sup> 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  $L_{den}$  and acute coronary events, whereas air pollutants ( $NO_2$  and  $PM_{2.5}$ ) were linked to incident ischaemic strokes. Andersson *et al.*<sup>24</sup> investigated the individual and combined effects of  $L_{den}$  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  $L_{den}$  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.*<sup>25</sup> evaluated the effect of air pollution on hospital contacts due to stroke, with differentiation by stroke subtype. In their fully adjusted models, inclusion of  $L_{den}$  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.*<sup>22</sup> found 10-year average values of  $NO_2$  and  $L_{den}$  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  $L_{den}$  remained (HR 1.12, 95% CI 1.03–1.21). Similarly, in a different study by Sørensen *et al.*<sup>19</sup> 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  $\mu g/m^3$  increase and 1.16, 95% CI 1.07–1.24 per 10 dB increase in yearly exposure, respectively). In two-exposure models, only  $L_{den}$  (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) retained an effect on IS. No positive associations with HS were shown.

Compared with previous literature, our study found residential proximity to heavy traffic load proxied by high  $L_{den}$  values (above 70 dBA, choosing the most conservative cut-off) to exert a small but tangible effect on the risk of stroke. The different effects observed for  $NO_2$  and  $L_{den}$  on the three considered outcomes highlight the issue of correctly assessing the individual roles of these stressors within a highly urbanized setting.<sup>43,44</sup> Estimates were unaltered by adjustment for  $PM_{2.5}$ . However, one caveat arises since levels of  $PM_{2.5}$  are consistently and diffusely high with scarce inter-individual variability within the study area. The exposure-response relationship between  $PM_{2.5}$  and health outcomes is known to be very steep at low levels and flatten out at higher concentrations.<sup>45,46</sup> Our results point towards an independent effect of road traffic noise in further increasing the risk of cerebrovascular accidents in a polluted city. Noise and air pollution act via different organ-damaging pathways, whose effects may be complementary. Noise may act as a trigger (via vascular dysfunction and acute blood pressure elevation) accelerating or exacerbating chronic processes caused by background air pollution (endothelial dysfunction and vasoconstriction, prothrombotic and coagulant changes, progression of atherosclerosis).<sup>47,48</sup> This might also explain why our results were stronger for HS, whose risk pattern is notoriously more affected by sleep and acute blood pressure elevation compared with IS.<sup>49</sup> However, we cannot rule out the chance that noise is merely a better proxy for another risk factor more closely associated with proximity to high traffic load.

Our finding of only slightly decreased estimates after inclusion of greenness in fully adjusted models is in line with recently published literature, although a direct comparison is hampered by heterogeneity in assessing greenness exposure. In a longitudinal study of more than a million individuals in Rome, Orioli *et al.*<sup>26</sup> highlighted a protective role of residential greenness against stroke incidence, and their mediation analyses found no mediation by  $PM_{2.5}$ ,  $NO_2$  or traffic noise ( $L_{den}$ ). A cross-sectional study by Klompaker *et al.*<sup>27</sup> aimed at evaluating the associations of combined exposures to surrounding greenness, air pollution and road traffic noise with several self-reported physician-diagnosed cardiometabolic diseases as outcomes. They reported that only  $PM_{2.5}$  was associated with stroke and heart attack. The estimates remained unaffected after adjustment for greenness and traffic noise, which was consistent with the lack of associations for these variables in single-exposure models. This would indicate that the noxious effect of road traffic is at least partly independent of its role in the causal pathway from greenness to AVEs.

Stratified analyses yielded heterogeneous results in different age and sex groups. Compared with previous literature,<sup>16–18,23</sup> 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.<sup>50</sup>

The use of models with suboptimal performance to estimate values of air pollutants and noise may cause exposure to be 'spatially misaligned'.<sup>51,52</sup> The overall worse performance of  $NO_2$  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  $NO_2$  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.<sup>53</sup> 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.<sup>54,55</sup>

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<sub>2.5</sub> 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.

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

## Supplementary data

Supplementary data are available at *IJE* online.

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## Conflict of interest

None declared.

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