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Short-term exposure to traffic-related air pollution and ischemic stroke onset in Barcelona, Spain

Rosa Maria Vivanco-Hidalgo[a,*,1], Gregory Wellenius[b], Xavier Basagaña[c,d,1], Marta Cirach[c], Alejandra Gómez González[a], Pablo de Ceballos[a], Ana Zabalza[a], Jordi Jiménez-Conde[a], Carolina Soriano-Tarraga[a], Eva Giralt-Steinhauer[a], Andrés Alastuey[e], Xavier Querol[e], Jordi Sunyer[c,d], Jaume Roquer[a]

[a] Hospital del Mar Medical Research Institute, Barcelona, Spain
[b] Brown University School of Public Health, Providence, Rhode Island, USA
[c] Barcelona Institute for Global Health (ISGlobal), Barcelona, Spain
[d] Universitat Pompeu Fabra (UPF), Barcelona, Spain; CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain
[e] Institute of Environmental Assessment and Water Research, IDAEA-CSIC, Barcelona, Spain

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ABSTRACT

Objective: To assess the relationship between short-term exposure to outdoor ambient air pollutants (fine particulate matter [$PM_{2.5}$] and black carbon [BC]), ischemic stroke (IS) and its different subtypes, and the potential modifying effect of neighborhood greenspace and noise.

Methods: This time-stratified case-crossover study was based on IS and transient ischemic attacks (TIA) recorded in a hospital-based prospective stroke register (BASICMAR 2005–2014) in Barcelona (Catalonia, Spain). Daily and hourly pollutant concentrations and meteorological data were obtained from monitoring stations in the city. Time-lags (from previous 72 h to acute stroke onset) were analyzed. Greenness and noise were determined from the Normalized Difference Vegetation Index (NDVI) and daily average noise level at the street nearest to residential address, respectively.

Results: The 2742 cases with known onset date and time, living in the study area, were analyzed. After adjusting for temperature, no statistically significant association between pollutants exposure and overall stroke risk was found. In subtype analysis, an association was detected between BC exposure at 24–47 h (odds ratio, 1.251; 95% confidence interval [CI], 1.001–1.552; $P = 0.042$) and 48–72 h (1.211; 95% CI, 0.988–1.484; $P = 0.065$) time-lag prior to stroke onset and large-artery atherosclerosis subtype. No clear modifying effect of greenness or noise was observed.

Conclusions: Overall, no association was found between $PM_{2.5}$ and BC exposure and acute IS risk. By stroke subtype, large-artery atherosclerotic stroke could be triggered by daily increases in BC, a diesel fuel-related pollutant in the study area.

1. Introduction

Ischemic stroke (IS) remains one of the leading causes of death and disability worldwide (Feigin et al., 2015). Ambient air pollution is a well-documented cardiovascular risk factor, especially ambient fine particulate matter ($PM_{2.5}$) and the products of incomplete fuel combustion, measured as black carbon (BC). $PM_{2.5}$ has been identified as a leading risk factor for stroke, accounting for an estimated 17% of the global stroke burden (Feigin et al., 2016). Postulated mechanistic pathways linking air pollution to cardiovascular disease include systemic inflammatory responses, systemic oxidative stress, predisposition to cardiac arrhythmias, vascular endothelial cell injury, and a prothrombotic state, acute arterial vasoconstriction, and atherosclerotic progression (Brook et al., 2010), manifesting as increased risk of either IS or transient ischemic attack (TIA).

* Correspondence to: Hospital del Mar Medical Research Institute, C/Doctor Aiguader 88, 08003 Barcelona, Spain.
E-mail addresses: rvivanco@imim.es (R.M. Vivanco-Hidalgo), Gregory_Wellenius@brown.edu (G. Wellenius), xavier.basagana@isglobal.org (X. Basagaña), marta.cirach@isglobal.org (M. Cirach), Alejandra.gomez.glez@gmail.com (A.G. González), pablo.ceballos4@gmail.com (P.d. Ceballos), anazabalza@gmail.com (A. Zabalza), jjimenez@imim.es (J. Jiménez-Conde), csoriano@imim.es (C. Soriano-Tarraga), egiralt@imim.es (E. Giralt-Steinhauer), andres.alastuey@idaea.csic.es (A. Alastuey), xavier.querol@idaea.csic.es (X. Querol), jordi.sunyer@isglobal.org (J. Sunyer), jroquer@parcdesalutmar.cat (J. Roquer).
[1] Statistical analysis performed by: Xavier Basagaña and Rosa Maria Vivanco-Hidalgo.

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Studies of the association between air pollution exposures and stroke risk typically consider separately the risks associated with long-term exposure (over the course of months to years) and short-term exposures (over the course of hours to days). While a growing number of studies have evaluated the association between short-term pollutant exposures and stroke risk, the results remain heterogeneous, as exemplified by the differing conclusions of recent meta-analyses and reviews of this topic (Wang et al., 2014; Shah et al., 2015; Maheswaran, 2016). Some of this heterogeneity in results may be due to differences across studies in populations studied, pollution sources and constituents, quality of the data, or relative rates of underlying stroke etiologies in the population (Lokken et al., 2009; Wellenius et al., 2012; Maheswaran et al., 2016; Chung et al., 2017; Henrotin et al., 2007).

Given the continued public health burden of stroke and nearly ubiquitous exposure to ambient air pollutants around the world, a better understanding of the association between ambient air pollution and stroke risk, including its different etiologic subtypes, is essential.

It can be hypothesized that exposure to the main pollutants of cities are related to the acute IS (AIS) risk and that the effects are not homogeneous and may depend on the IS subtype. To test our hypothesis, the aim of the present study was to assess the relationship of short-term $PM_{2.5}$ and BC exposure to IS, overall and by etiologic subtypes, in a cohort of well-characterized patients with AIS or TIA in a southern European city. Finally, we assessed whether these associations were modified by neighborhood green space and noise.

2. Methods

2.1. Study design and population

The BASICMAR database (Roquer et al., 2008) is an ongoing prospective register of patients with acute stroke at University Hospital del Mar, a tertiary public hospital serving a population of 339 196 in two districts (Ciutat Vella and Sant Martí) of the City of Barcelona. Data are obtained at hospital admission from patients, caregivers, relatives, and/or prior medical records. From this database, we identified 5671 patients admitted with AIS or TIA between January 1, 2005, and December 31, 2014. All patients included in the register were evaluated by a vascular neurologist, with a complete neurovascular examination including imaging studies and diagnostic tests that confirm the diagnosis of AIS or TIA (defined as acute transient episode of neurological dysfunction cause, presumably by ischemia and without acute infarction on imaging). Routinely, data are revisited every 3 months by a vascular neurologist and any patients with a stroke-mimic diagnosis are excluded from the register. Demographic data and the following vascular risk factors (based on their presence during the index admission, a prior physician diagnosis or need for medical treatment) were recorded from the BASICMAR database: arterial hypertension (evidence of at least two blood pressure measurements > 140/90 mmHg recorded on different days before stroke onset); diabetes (fasting serum glucose level ≥ 7.0 mmol/L); hyperlipidemia (serum cholesterol levels > 220 mg/dL or triglyceride levels > 200 mg/dL); atrial fibrillation (AF) confirmed by an ECG performed during admission or previous ischemic heart disease (IHD), defined as previous history of angina pectoris or myocardial infarction; smoking habit; alcohol consumption (overuse when intake was ≥ 60 g/d); and use of antiaggregant or statin treatments before stroke onset.

The attending neurologist estimated the time of stroke symptom onset based on clinical presentation and history obtained from the patient, relatives, or other witnesses, entering a classification of undetermined, woke up with symptoms, or known onset. The present analysis was limited to patients with known time of stroke symptom onset.

Patient addresses were geocoded using information from the Cartographic Institute of Catalonia (ICC). For this analysis, we excluded patients with in-hospital strokes, those living outside the reference area of the 2 districts served (n = 1707), and those with evidence of acute hemorrhage in the first CT (n = 653).

Cases were classified by the neurologist in charge in the Stroke Unit and confirmed in a 3-month follow-up visit to the outpatient clinic using the approach developed for the TRIAL of ORG 10172 in AIS Treatment (TOAST) (Adams et al., 1993): large-artery atherosclerosis, small-vessel occlusion, cardioembolism, other determined cause, or undetermined cause.

2.2. Environmental data

Hourly $PM_{2.5}$ and BC for the period 2005–2014 were recorded at an urban background research site located in southwest Barcelona (Palau Reial). $PM_{2.5}$ was measured using an optical spectrometer for $PM_{2.5}$ (GRIMM 1180) and a Multi-Angle Absorption Photometer for BC, as described elsewhere (Reche et al., 2011). We obtained hourly meteorological data from the first-order weather station at the Barcelona International Airport (National Environmental Satellite).

We evaluated whether the association between air pollutants and risk of IS symptom onset differed by levels of neighborhood green space and traffic noise. To estimate neighborhood greenness, we used the Normalized Difference Vegetation Index (NDVI) derived from the Landsat 8 Operational Land Imager (OLI) sensor data at 30 m x 30 m resolution. The Landsat image from April 16, 2013 was selected for analysis. Data were obtained from Landsat 8 OLI-TIRS, launched in 2013, instead of previous Landsat imagery (Landsat 4–5) because Landsat 8 data is atmospherically corrected whereas Landsat 4–5 is not.

In previous studies, we compared NDVI imagery for different time-windows in our study area (Barcelona) and the agreement was high (over 0.9). Surrounding greenness was quantified as the average NDVI within 100, 300, and 500 m around each participant's residential geocoded address (Fig. 1).

Noise exposure was estimated using Barcelona's strategic noise map (2012). The daily average noise level (dB) at the street nearest to each participant's residential address was registered.

2.3. Statistical analysis

A descriptive analysis of the clinical and demographic variables was performed, calculating percentages for categorical variables and mean with corresponding standard deviations for quantitative variables. A bivariate analysis, using Chi square for categorical variables and *t*-test for continuous variables, with their correspondent non-parametric test if needed, was performed to compare AIS (acute ischemic strokes) and TIA (transient ischemic attacks). P values corresponded to comparisons between AIS and TIA groups. The time-stratified case-crossover study design was used to quantify the association between $PM_{2.5}$ and BC exposure and risk of acute AIS/TIA, as previously described (Wellenius et al., 2012).

We defined the case period as 0–23, 24–47, and 48–72 h preceding estimated stroke symptom onset so that we could compare our results to previous studies; the majority of related publications have used these time-lags (Wang et al., 2014; Shah et al., 2015). The four control periods used for the analysis corresponded to the same day of the week, one week prior to the day of stroke onset, and 1, 2 and 3 weeks post-onset day. Depending on the day of the month, these control periods varied in order to remain in the same month. With that approach, we understand that classic risk factors such as high blood pressure, diabetes, dyslipidemia, and smoking that were present at the moment of the stroke episode remained stable in the control period, as we used control periods reflecting the exposure distribution while at risk for the outcome, but close enough in time that the baseline risk was similar. Most of the potential risk factors of stroke that vary within a month are unlikely to co-vary with an environmental variable such as air pollution, except for meteorological variables that were adjusted for in our analyses. This approach eliminates confounding by measured and