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Short-term exposure to traffic-related air pollution and ischemic stroke onset in 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).

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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

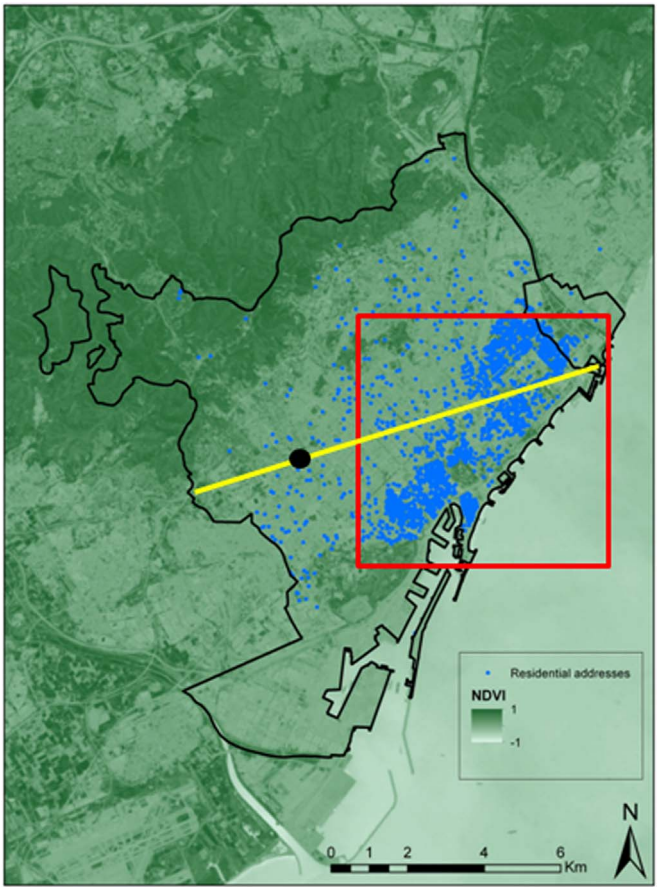

Fig. 1. Map of the city of Barcelona. Intensity of green color depicts Normalized Difference Vegetation Index concentration. Blue dots represent cases. The red square outlines the two districts assessed. Black dots indicate the $PM_{2.5}$ and BC stations. The yellow line represents Diagonal Avenue (a major Barcelona thoroughfare). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

unmeasured stroke risk factors that change slowly over time, as well as seasonal and other time trends.

We used conditional logistic regression to estimate the odds ratios (ORs) and 95% confidence intervals (CI) relating $PM_{2.5}$ and BC to risk of stroke symptom onset. All analyses were adjusted for apparent temperature (Anderson et al., 2013), modeled as a nonlinear variable using natural cubic splines. $PM_{2.5}$ and BC were initially modeled as linear continuous variables and subsequently as quartiles to relax the assumption of a linear exposure-response function.

Stratified models were fitted to evaluate whether the association between pollutants and risk of stroke symptom onset differed by the presumed stroke etiology, residential NDVI (above versus below median) and residential traffic noise (above versus below the median). A two-sided p-value < 0.05 was considered to indicate statistical significance. All analyses were performed using STATA v.12 statistical package (StataCorpCollege Station, TX).

2.4. Ethical consideration

The information used in this study was collected from the prospective BASICMAR register, with the approval of our local ethics committee. All patients (or their proxies) gave their informed consent prior to their inclusion in the study.

3. Results

During the study period, 3311 patients admitted for AIS/TIA met the inclusion criteria for this study. Of these, 2742 (83%) had a known time of stroke symptoms onset (2269AIS and 473 TIAs). Fig. S1 shows the flowchart of patient selection (Supplemental Data). The characteristics of these patients are shown in Table 1.

Approximately half of the patients were women, and the mean (SD) age was 75.0 (12.6) years. The most frequent cardiovascular risk factor was hypertension (76.5%). Cardioembolism was the most common IS etiology (33.7%).

In 2133 (77.8%) participants, the date of symptom onset was the same as the date of admission. The mean time difference between symptom onset and hospital admission was 1 h 27 min (ranging from less than 5 min to 20 h).

Median concentrations of pollutants during the study time period were 17.5 $\mu g/m^3$ (IQR 12–25.2) for $PM_{2.5}$, which is below the annual European air quality limit value for $PM_{2.5}$ (25 $\mu g/m^3$ according to 2008/50/CE), but quite above the equivalent WHO air quality guideline (10 $\mu g/m^3$) (WHO Air quality guidelines). BC data were available starting in 2007. Median concentration reached 1.4 $\mu g/m^3$ (IQR 0.9–2.4). No air quality standards are available for BC. The two pollutants were moderately correlated ($\rho = 0.59$, $P < 0.05$)

We found no evidence of an association between $PM_{2.5}$or BC and

Table 1
Characteristics of the study cohort.

	All N = 2742	AIS N = 2269	TIA N = 473	P-value
Sex, female n (%)	1386 (50.55)	1158 (51.04)	228 (48.20)	0.262
Age, mean (sd)	75.02 (12.56)	75.42 (12.41)	73.13(13.08)	< 0.001
TOAST n(%)				< 0.001
Large-artery atherosclerosis	313 (11.42)	245 (10.80)	68 (14.38)	
Cardioembolism	923 (33.66)	795 (35.04)	128 (27.06)	
Small-vessel occlusion	581 (21.19)	484 (21.33)	97 (20.51)	
Other etiology	65 (2.37)	59 (2.60)	6 (1.27)	
Undetermined etiology	670 (24.44)	524 (23.1)	146 (30.87)	
Two or more causes identified	137 (5)	130 (5.73)	7 (1.48)	
Negative evaluation	365 (13.31)	274 (12.08)	91 (19.24)	
Incomplete evaluation	168 (6.13)	120 (5.29)	48 (10.15)	
NK	190 (6.93)	162(7.14)	28 (5.92)	
Cardiovascular risk factors				
Smoking	666 (20.11)	570 (20.46)	96 (18.29)	0.250
Hypertension	2098 (76.51)	1741 (76.73)	357 (75.48)	0.737
Diabetes Mellitus	908 (33.11)	773 (34.07)	135 (28.54)	0.023
Dyslipidemia	1273 (46.43)	1038 (45.75)	235 (49.68)	0.122

AIS = acute ischemic stroke; TIA = transient ischemic stroke; NK = not known.
P values correspond to comparisons between AIS and TIA groups.

Table 2
Associations between exposure to air pollutants and the risk of AIS/TIA per lag periods studied and by stroke subtype per every lag period studied.

	PM 2.5		BC	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
AIS/TIA				
Lag 0–23	0.989 (0.928–1.053)	0.731	1.047 (0.968–1.129)	0.254
Lag 24–47	0.983 (0.922–1.047)	0.589	0.981 (0.909–1.061)	0.644
Lag 48–72	1.001 (0.940–1.067)	0.996	1.031 (0.956–1.112)	0.431
TOAST subtype				
Large-artery atherosclerosis				
Lag 0–23	0.996 (0.817–1.214)	0.967	1.160 (0.930–1.444)	0.189
Lag 24–47	0.980 (0.810–1.187)	0.839	**1.251 (1.001–1.552)**	**0.042**
Lag 48–72	1.048 (0.868–1.264)	0.628	**1.211 (0.988–1.484)**	**0.065**
Small-vessel occlusion				
Lag 0–23	0.872 (0.758–1.002)	0.054	1.045 (0.887–1.227)	0.544
Lag 24–47	0.905 (0.788–1.040)	0.161	0.945 (0.800–1.115)	0.502
Lag 48–72	0.936 (0.815–1.076)	0.352	1.063 (0.894–1.264)	0.488
Cardioembolism				
Lag 0–23	1.000 (0.903–1.115)	0.950	0.959 (0.831–1.107)	0.572
Lag 24–47	1.029 (0.952–1.144)	0.598	0.970 (0.843–1.115)	0.668
Lag 48–72	1.037 (0.933–1.152)	0.503	0.979 (0.848–1.130)	0.770
Other cause				
Lag 0–23	1.104 (0.730–1.694)	0.649	1.390 (0.804–2.403)	0.238
Lag 24–47	0.986 (0.685–1.419)	0.940	0.611 (0.322–1.159)	0.132
Lag 48–72	0.770 (0498–1.189)	0.238	1.021 (0.569–1.803)	0.966
Undetermined				
Lag 0–23	1.041 (0.906–1.197)	0.570	1.155 (0.965–1.382)	0.116
Lag 24–47	1.004 (0.869–1.159)	0.959	1.053 (0.885–1.252)	0.561
Lag 48–72	1.034 (0.894–1.209)	0.612	1.075 (0.914–1.265)	0.381
Undetermined (two causes)				
Lag 0–23	1.066 (0.811–1.400)	0.647	0.953 (0.673–1.351)	0.789
Lag 24–47	0.912 (0.685–1.214)	0.529	0.977 (0.689–1.385)	0.895
Lag 48–72	0.944 (0.974–1.02)	0.668	0.932 (0.668–1.301)	0.682

$PM_{2.5}$ 2.5 μ particulate matter;BC = black carbon; AIS/TIA = acute ischemic stroke / transient ischemic stroke.
Lag periods expressed in hours. OR and 95% CI expressed per IQR change (0.9–2.4 μg/m^3).

risk of stroke symptom onset in the subsequent 72 h when considering all IS etiologies together (Table 2).

However, in analyses stratified by presumed stroke etiology, BC levels in two lag periods, 24–47 and 48–72 h, were associated specifically with IS presumed to arise from large-artery atherosclerosis (OR, 1.25; 95% CI, 1.01–1.55; $P = 0.042$; OR, 1.21; 95% confidence interval, 0.98–1.48; $P = 0.065$). Results showing pollutants as quartiles are presented as Supplemental data (Table S2). We also evaluated whether the association between $PM_{2.5}$ and BC and the risk of large-artery strokes varied by levels of residential green space and traffic noise, but found no evidence to indicate relevant differences (Table 3).

Table 3
Effect modification of greenness and noise in large artery atherosclerosis ischemic stroke subtype for black carbon exposure.

	Lag 24–47 h		Lag 48–72 h	
	OR (CI 95%)	P value	OR (CI 95%)	P value
NDVI 100				
Lower	1.243 (0.930–1.662)	0.141	1.165 (0.906–1.498)	0.233
Higher	1.211 (0.867–1.692)	0.262	1.389 (0.932–2.070.983)	0.107
NDVI 300				
Lower	1.154 (0.856–1.554)	0.347	1.247 (0.968–1.607)	0.088
Higher	1.301 (0.948–1.809)	0.102	1.176 (0.805–1.718)	0.401
NDVI 500				
Lower	1.160 (0.872–1.541)	0.308	1.121 (0.870–1.442)	0.376
Higher	1.365 (0.973–1.915)	0.072	1.492 (1.018–2.186)	0.040
Noise				
Lower	1.298(0.967–1.744)	0.082	1.174(0.920–1.498)	0.197
Higher	1.227 (0.887–1.698)	0.216	1.211 (0.832–1.761)	0.316

NDVI = Normalized Difference Vegetation Index.
Lag periods expressed in hours. OR and 95% CI expressed per IQR change (0.9–2.4 μg/m^3).

4. Discussion

Ambient air pollution, particularly in an urban setting, may be associated with higher risk of acute cerebrovascular ischemic events but the evidence remains heterogeneous. To address this knowledge gap, we evaluated the association between short-term changes in $PM_{2.5}$ levels and risk of AIS/TIA symptom onset in an urban population. In contrast to several past studies, we found no evidence to suggest that daily changes in $PM_{2.5}$ levels are associated with higher risk of stroke symptom onset, either overall or for specific presumed IS etiologies. We also evaluated the association between daily changes in ambient BC (a marker of diesel vehicle exhaust in our study area) and risk of stroke symptom onset. We found no association overall, but did find that BC was associated with higher risk of symptom onset for IS presumed to be due to large artery atherosclerosis.

We did not observe an overall short-term association between $PM_{2.5}$ and risk of stroke symptom onset. Prior studies have attempted to elucidate the relationship between air pollutants exposure and the risk of IS, with conflicting results. Two recent systematic reviews and a meta-analysis showed contradictory conclusions (Wang et al., 2014; Shah et al., 2015; Maheswaran, 2016) about the most-studied pollutant, $PM_{2.5}$. Diverse explanations have been proposed to explain these results, among them a possible misclassification of stroke diagnosis and time symptom onset depending on the source used to obtain the data (Lokken et al., 2009). In our case, every stroke episode registered in BASICMAR was diagnosed by a vascular neurologist and the symptoms

onset was checked with the patient and family; those with unknown date and hour of stroke symptom onset were excluded. This approach is likely to have ensured the analysis of reliable cases and obtained robust results. Another explanation could be related to the differing sources of air pollution in the cities studied.

A direct relationship between BC exposure and risk of IS has been reported (Wellenius et al., 2012). In our case, IQR increases showed a positive but nonsignificant trend toward higher risk of AIS in almost every time lag analyzed. By etiology, there was a 20% increased risk of having a large-vessel atherosclerosis stroke for every IQR increase of BC exposure at 24–47 and 48–72 h prior to symptoms onset. Recently, the pro-oxidant and pro-inflammatory effects of $PM_{2.5}$ and traffic-related air pollutant concentrations have been found to contribute to the risk of developing atherosclerosis (Bai and Sun, 2016; Kaufman et al., 2016). We speculate that exposure to BC-bearing soot particles could have destabilized the pre-existing atheromatous plaque or led to vessel occlusion through activation of the inflammatory response and oxidative stress in the previous 48–72 h in those individuals with pre-existing atherosclerotic disease (Nichols et al., 2013). Recently, an association has been described between BC exposure and increased plasma levels of myeloperoxidase, which is involved in lipid peroxidation (Li et al., 2016). The products generated by this reaction (reactive oxygen and nitrogen species) can promote either endothelial dysfunction or disruption of vulnerable plaques in people with atherosclerosis. Other mechanisms, like an increase in blood viscosity that could lead to arterial thrombosis, have also been reported to be associated with exposure to traffic-related pollutants (Park et al., 2008).

We assessed the possible modifying effect of green space and noise in the association between exposure to air pollution and stroke. Greenness is associated with improved health, but there is little knowledge about the potential mechanisms underlying this association (Dadvand et al., 2016). A recent study performed in Spain observed that greenness had a protective effect on mortality only in areas with low socioeconomic status (de Keijzer et al., 2017). We observed contradictory results regarding NDVI exposure, the measure of greenness selected for our study. On average, however, the whole population of our study is exposed to low levels of greenness, which could provide a possible explanation for these findings. Further studies are needed with different populations exposed to a higher density of green space to test the effect of this possible modifier.

Similarly, long-term noise residential noise levels did not modify the associations between pollutants and IS. Recent studies have linked long-term exposure to traffic noise to hypertension and increased hospital admissions and mortality, mainly related to IS in the elderly (Halonen et al., 2015). We found no reports testing noise as an acute modifier in the association between air pollution and IS. We hypothesize that a possible detrimental modifier effect of noise could be found in a larger cohort with more variability in the levels of exposure to noise.

It has been suggested that the adverse health effects of BC (a component of $PM_{2.5}$) are more robust than those of $PM_{2.5}$ mass (Janssen et al., 2011). In our case, BC accounts for 10% of the $PM_{2.5}$ mass, and the latter is mostly (> 60%) made up by soluble ammonium nitrate, ammonium sulfate and soluble organic matter (Rivas et al., 2016). Also, most of the BC-bearing particles fall in the range of ultrafine particles (finer than 0.1 μm), as demonstrated by the 0.03–0.04 μm mode determined for traffic-related ultrafine particle number concentration in Barcelona, Rome, and Madrid (Brines et al., 2015), from which a proportion is able to translocate lung, while most of the $PM_{2.5}$ mass is made of particles that are too large to translocate. The MED-PARTICLES study concluded that acute BC exposure was related to an increased risk for all mortalities, especially for cardiovascular causes (Ostro et al., 2015). BC is considered the best indicator of traffic pollution in Barcelona (Reche et al., 2011; Brines et al., 2015). The mean BC concentration found in this study is close to average urban background exposure levels. Thus, mean annual BC levels for 2009 (included within our study period) of 1.7–1.9 $\mu g/m^3$ have been reported for Barcelona, London, and Lugano urban background sites, 3.5–7.8 $\mu g/m^3$ for traffic sites in Bern and London, and 0.7–0.8 $\mu g/m^3$ for the urban background in smaller cities influenced by industrial emissions (Huelva and Santa Cruz de Tenerife, Spain) (Reche et al., 2011).

The present study has some limitations common to this type of approach. First, air pollution levels were obtained through a fixed single station and not from individual exposure, likely leading to exposure measurement error but not likely biasing our health effects estimates, as the pattern of spatial misclassification is expected to be the same for both case days and control days. Prior studies on health effects of PM_1, $PM_{2.5}$ and PM_{10} using data from this station evidenced a clear causal relationship for mortality (Perez et al., 2008; Ostro et al., 2011), which supports the representativeness of this urban background site for health studies. We believe that the monitoring station we used represents a good indicator of the temporal variability of the city levels. This station has been used in previous studies, and represents both the pollution of the central areas due to sea breeze transport and that from one of the largest traffic arteries of the city, located about 200 m from the monitoring site (Ostro et al., 2015). In addition, not all parameters are measured at all sites. The most complete one, with BC and daily $PM_{2.5}$, is the one close to Diagonal Avenue. Second, the levels of these air pollutants decreased during the study period (Fig. 2) and thus the magnitude of the effect expected could be less than in other studies with populations exposed to higher levels of pollutants. However, other

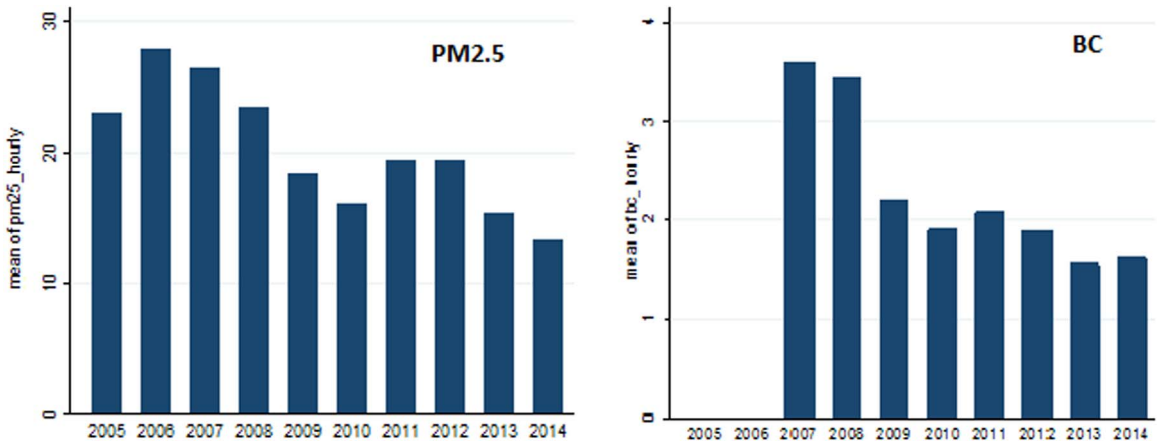

Fig. 2. Mean levels of $PM_{2.5}$ and BC during the study period.

studies performed in the US detected harmful effects even in those areas with air pollutants concentrations considered safe by the US EPA (Wellenius et al., 2012).

Because the case-crossover design stratifies the analyses by calendar month, these time trends are not expected to confound our analysis. Third, the multiple comparisons by IS subtype that we have performed could have led to a random finding of a positive association. Due to the characteristics and the lack of data on the excluded AIS patients (intrahospital strokes and patients living outside our area of reference), we could not compare them with the included cases. Finally, the study only considered one medical center that serves residents of specific neighborhoods in Barcelona, potentially limiting the generalizability of our findings to other populations.

On the other hand, this study has important strengths to be considered. A difference from previous studies, especially those that relied on administrative records, is that all participants had undergone a thorough assessment; thus, information on diagnosis, time of symptoms onset, and geocoding were reliable and misclassification was unlikely. Finally, the analysis of air pollution considered the main pollutants from sources specific to our area, an approach that we recommend future studies should take into account.

5. Conclusions

We found no evidence of an association between $PM_{2.5}$ or BC and risk of IS symptom onset in the subsequent 72 h. However, our results showed that exposure to BC, the main traffic-related air pollutant in our area, at levels comparable to most cities in Europe, is associated with a higher risk of atherosclerotic stroke. If these results are confirmed in other studies, setting BC air quality standards in the forthcoming revision of the EC Directive on air quality could have valuable health benefits.

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List of disclosures

All authors of the manuscript report no conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2017.12.024.

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