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Association between environmental factors and emergency hospital admissions due to Alzheimer's disease in Madrid

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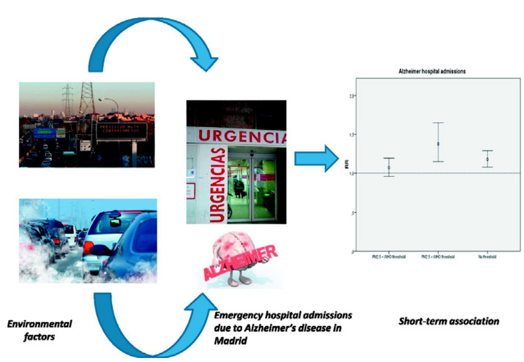
HIGHLIGHTS

- Alzheimer's disease (AD) is the most common cause of dementia among older adults
- Air pollutants may be risk factors regarding the decompensation of AD
- $PM_{2.5}$ concentrations are associated with the development and the exacerbation of AD
- Heat waves can exacerbate Alzheimer's hospital admissions
- More epidemiologic studies will be needed to confirm the relation between AD and environmental factors

GRAPHICAL ABSTRACT



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ABSTRACT

Introduction: There are scarce studies of time series that analysed the short-term association between emergency hospital admissions due to Alzheimer's disease (AD) and environmental factors. The objective is to analyse the effect of heat waves, noise and air pollutants on urgent hospital admissions due to AD in Madrid.
Methods: Longitudinal ecological time series study was performed. The dependent variable was the emergency AD hospital admissions occurred in Madrid during the period 2001–2009. Independent variables were: Daily mean concentrations (μg/m3) of air pollutants ($PM_{2.5}$ and PM_{10}; O3 and NO2); maximum daily temperature (°C) and daily and night noise levels (dB(A)). Relative Risk (RR) for an increment in interquartile range, and Attributable Risk (AR) values were calculated through GLM with Poisson link.
Results: Our findings indicated that only $PM_{2.5}$ concentrations at lag 2 with a RR: 1.38 (95% CI: 1.15–1.65); AR 27.5% (95% CI: 13.0–39.4); and heat wave days at lag 3 with a RR: 1.30 (95% CI: 1.12–1.52); AR 23.1% (95% CI: 10.7–34.2) were associated with AD hospital admissions.
Conclusion: A reduction in AD patients' exposure levels to $PM_{2.5}$ and special care of such patients during heat wave periods could result in a decrease in both emergency AD admissions and the related health care costs.

1. Introduction

Alzheimer's disease (AD) is not only the most common cause of dementia among older adults, but is also a disease which is becoming increasingly important, in that a new case of dementia is identified

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every 4 s in the world and the number of cases of dementia doubles every 20 years (WHO, 2012). Indeed, AD is the leading dementia in the USA and was ranked as the fifth leading cause of death among older adults in 2010 (Murphy et al., 2013). It has been estimated that >1.5 million persons are affected by AD in Spain, based on prevalence indices which show that around 7% of all persons over the age of 65 years are affected, a percentage that rises to 50% among the over-80 age group (Aulestia, 2016). Total expenditure (public and private) on dementias in Spain could be in the region of 8200 million euros or more, accounting for 10% of the entire health care budget for the country as a whole (Prieto et al., 2016).

The aetiology of AD is still under study. Development of AD has been attributed to a number of probable causes. From a genetic aetiology standpoint, the pre-existence of the apolipoprotein E (APOE)-ε4 allele is considered to be an important cause (Coon et al., 2007); on the other hand, many studies have confirmed the relationship between family history of AD and subsequent development of the disease (Van Djuin et al., 1991). Exposure to certain chemical agents via food has likewise been regarded as a cause of the disease (Calderon-Garciduenas et al., 2004). Thus, a diet which possibly includes the ingestion of some metals, e.g., aluminium in water, has been strongly linked to the aetiology of AD.

Exposure to prolonged environmental pollution has recently been proposed as a risk factor for AD in cities such as Mexico City (Calderón-Garcidueñas et al., 2015), in view of the fact that particulate matter (PM) present in the atmosphere and nanoparticles have been identified as risk factors for neurodegeneration and neuro-inflammation (Levesque et al., 2011a, 2011b; Levesque et al., 2013). Similarly, exposure to different sizes and compositions of PM is associated with the production and deposit of aggregate clusters of proteins (amyloid, alpha-synuclein, tau hyperphosphorylation) that are linked to AD. It has been shown in animal models that PM can be transferred from the upper part of the respiratory tract to the brain, causing inflammation at a cerebral level, something that amounts to important anatomopathological evidence of dementia (Block and Calderon-Garciduenas, 2009; Calderon-Garciduenas et al., 2004). Some papers have implicated $PM_{2.5}$ or finer particles as a cause of AD and other neurodegenerative diseases (Yegambaram et al., 2015). Moreover, an increase in AD-related amyloid β-40 and β-42 levels has been identified in rats exposed to air pollution models (Kim et al., 2012). Even so, some epidemiological studies have observed a higher prevalence of AD in rural than in urban settings (Shibayama et al., 1986; Jean et al., 1996), though this higher prevalence has not been statistically associated with the presence of pesticides (Gauthier et al., 2001). The controversy surrounding the influence of the environmental factor thus remains unresolved.

Aside from the above-described aetiological viewpoint of the relationship, recent studies have shown that certain environmental factors can be associated with hospital admissions due to neurological diseases, especially with large exposures to $PM_{2.5}$ concentrations(Kioumourtzoglou et al., 2016), even at the short term (Zanobetti et al., 2014). These environmental factors may be capable of exacerbating the symptoms of persons who suffer from neurodegenerative diseases such as dementia (Linares et al., 2017) or Parkinson's disease (PD) (Linares et al., 2016a, 2016b), to the point where there is an increase in hospital admissions due to this cause.

Accordingly, the aim of this study was to use time series analysis to ascertain and analyse the existence of a short-term association between emergency hospital admissions due to AD and various environmental factors such as chemical air pollution and temperature, in the city of Madrid. From a public health stance, the relevant aspect resides in the fact that, in some cases, exposure to these environmental factors is modifiable and so emergency AD admissions could be reduced by limiting exposure to such factors.

2. Material and methods

2.1. Study population

The city of Madrid is a densely populated metropolitan area situated in the central region of Spain. In the period 2001–2009, it had a mean population of 3,116,897 and of this total, 754,005 persons (24.2%) were aged 60 years or over (INE, 2015).

2.2. Study variables

2.2.1. Dependent variable

The dependent variable was the number of emergency AD hospital admissions (International Classification of Diseases 9th Revision (ICD-9): 331.0) registered at all hospitals in the city of Madrid across the period, 1 January 2001 to 31 December 2009. Data on emergency admissions were obtained from the hospital morbidity survey (HMS), compiled and defined by the National Statistics Institute (*Instituto Nacional de Estadística*/INE) as hospitalisation of any person with emergency admission diagnosis of AD.

2.2.2. Independent variables

As our main independent variables of analysis, we used the following:

1. **Chemical air pollutants**: daily mean concentrations (μg/m^3) of particulate matter <2.5 and 10 μm in diameter ($PM_{2.5}$ and PM_{10}), tropospheric ozone (O_3), and nitrogen dioxide (NO_2). All measurements were made using the gravimetric method or equivalent (beta-

01	PASEO DE RECOLETOS	CENTRO	3°41'31,00"	40°25'21,36"
03	PL. DEL CARMEN	CENTRO	3°42'11,42"	40°25'09,15"
04	PL. DE ESPAÑA	MONCLOA	3°42'44,40"	40°25'26,37"
05	BARRIO DEL PILAR	FUENCARRAL	3°42'41,55"	40°28'41,62"
06	PL. DR. MARAÑÓN	CHAMBERÍ	3°41'27,00"	40°26'15,39"
07	PL. M. SALAMANCA	SALAMANCA	3°40'49,19"	40°25'47,81"
08	ESCUELAS AGUIRRE	SALAMANCA	3°40'56,35"	40°25'17,63"
09	PL. LUCA DE TENA	ARGANZUELA	3°41'36,35"	40°24'07,68"
10	CUATRO CAMINOS	CHAMBERÍ	3°42'25,66"	40°26'43,95"
11	AV. RAMÓN Y CAJAL	CHAMARTÍN	3°40'38,47"	40°27'05,30"
12	PL. MANUEL BECERRA	SALAMANCA	3°40'06,71"	40°25'43,70"
13	VALLECAS	PUENTE VALLECAS	3°39'05,48"	40°23'17,34"
14	PL. FDEZ. LADREDA	USERA	3°42'59,71"	40°23'06,28"
15	PLAZA DE CASTILLA	TETUÁN-CHAMARTÍN	3°41'19,29"	40°28'05,73"
16	ARTURO SORIA	CIUDAD LINEAL	3°38'21,24"	40°26'24,17"
18	GENERAL RICARDOS	CARABANCHEL	3°43'54,60"	40°23'41,20"
19	ALTO EXTREMADURA	LATINA	3°44'30,83"	40°24'28,29"
20	AV. DE MORATALAZ	MORATALAZ	3°38'43,03"	40°24'28,64"
21	ISAAC PERAL	MONCLOA	3°43'04,54"	40°26'24,51"
22	PASEO DE PONTONES	ARGANZUELA	3°42'46,56"	40°24'22,95"
23	C/ ALCALÁ (Final)	SAN BLAS	3°36'34,62"	40°26'55,44"
24	CASA DE CAMPO	MONCLOA	3°44'50,44"	40°25'09,68"
25	SANTA EUGENIA	VILLA VALLECAS	3°36'09,18"	40°22'44,48"
26	URB. EMBAJADA	BARAJAS	3°34'48,42"	40°27'33,56"
27	BARAJAS PUEBLO	BARAJAS	3°34'48,10"	40°28'36,94"

Fig. 1. Madrid Municipal Air Quality Monitoring Grid.