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Emergency multiple sclerosis hospital admissions attributable to chemical and acoustic pollution: Madrid (Spain), 2001–2009

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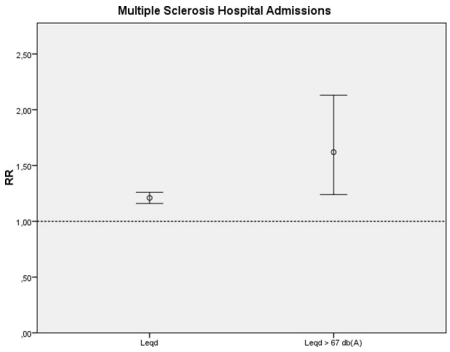
HIGHLIGHTS

- Multiple sclerosis (MS) is the most prevalent neurological disease among young adults in Spain.
- No has been detected association between chemical pollutants caused by traffic and MS admissions.
- The relationship is linear and without threshold. The effect is more pronounced above 67 dB (A).
- The results indicate that traffic noise can exacerbate MS symptoms, leading to hospital admissions due to this cause

GRAPHICAL ABSTRACT



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ABSTRACT

Introduction: Multiple sclerosis (MS) is the most prevalent neurological disease among young adults in Spain. A number of recent studies have linked traffic-related pollution, both chemical and acoustic, to the aetiology and exacerbation of neurodegenerative diseases.
Objective: To analyse the existence of a significant short-term association between daily emergency MS hospital admissions and chemical and acoustic pollution caused by traffic in Madrid.
Methodology: We conducted a longitudinal ecological time series study, in which the dependent variable was the number of daily emergency MS hospital admissions (ICD-9: 340) registered in Madrid from 1 January 2001 to 31 December 2009. The independent variables were daily mean concentrations ($\mu g/m^3$) of $PM_{2.5}$, PM_{10}, O_3 and NO_2. Equivalent diurnal (Leqd), nocturnal (Leqn) and daily equivalent noise levels (Leq24) were also considered. In addition, we controlled for linear trends, seasonality and the autoregressive nature of the series itself. Day of the week was also added as a covariate. Significant environmental variables were determined using Poisson GLM models. Relative risk (RR) and attributable risk (AR) values were calculated for increases of 10 $\mu g/m^3$ in the case of chemical pollutants and 1 dB(A) in noise levels.
Results: While there was no association between chemical pollutants caused by traffic and MS admissions, such an association was in evidence for Leqd at lag zero. This association is linear without a threshold, with there being a level above 67 dB(A) from which this effect is more pronounced. The RRs were as follows: for all Leqd values, 1.21 (95% CI: 1.16, 1.26); and for Leqd >67 dB(A), 1.62 (95% CI: 1.24, 2.13).
Conclusion: The above results indicate that traffic noise can exacerbate MS symptoms, leading to hospital admissions due to this cause.

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1. Introduction

Multiple sclerosis (MS) is the most prevalent neurological disease among young adults in Spain (IMSERSO and MTAS, 2007), with an estimated 45 to 120 cases per 100,000 population, which yields a figure of over 40,000 cases with a rising trend over time (Ayuso, 2014). The economic burden of the disease is fundamentally related to the progression of disability, cost associated with MS outbreaks, and acquisition of treatments used for its management. According to estimates, the total cost per patient in Spain is €30,000, with an annual MS-related cost of close on 1400 million euros (Ayuso, 2014), 8% of which is attributable to hospital admissions (Kolasa, 2013).

The principal cause of MS is believed to be an autoimmune reaction of T lymphocytes, which damages the myelin sheath and causes neuroinflammation and neurodegeneration in the central nervous system. The most notable signs of disease progression are demyelination, oligodendrocyte cell death, activation of immune cells in the brain (microglia and astrocytes), and damage to the neuroaxonal unit. Rapid activation of microglia and astrocytes is associated with an increase in oxidative stress. Oxidative stress occurs when metabolic processes or the action of external toxins result in an excess of oxidants over antioxidants, which can lead to cell death (Ohl et al., 2016).

A number of recent studies have linked traffic-related pollution, both chemical and acoustic, to neurodegenerative diseases (Block et al., 2012; Tzivian et al., 2015). These studies indicate that vehicles, mainly diesel-powered, can cause oxidative stress and neuroinflammation (Calderón-Garciduenas et al., 2008) and activate the microglia (Block et al., 2004). Furthermore, some studies have related chemical pollution caused by traffic to incidence of dementia in Sweden (Oudin et al., 2016), deterioration in cognitive function among elderly persons (Ranft et al., 2009; Power et al., 2011; Wellenius et al., 2012; Tzivian et al., 2016), Parkinson's disease (Ritz et al., 2016) and Alzheimer's disease (Jung et al., 2015).

More recently still, a study was published which analysed the relationship between residence near a major highway and the impact on risk of suffering from dementia, Parkinson's disease and multiple sclerosis, with an association being found solely in the case of dementia (Chen et al., 2017). Although the studies by Tzivian et al. in 2015 and 2016 are the only ones to have analysed the effects of acoustic and chemical air pollution separately, the fact the environmental indicator in Chen's study was distance to highway can be assumed to mean that the effect of traffic noise on these neurodegenerative diseases was indirectly included.

The epidemiological design of these studies – which are generally of the cohort type – means that the effects of long-term exposure to the different traffic-related pollutants are analysed, thereby making it possible to draw conclusions about the aetiology of the neurodegenerative disease in question. Recently, a number of studies have been conducted in the city of Madrid, which, by means of time-series analysis, have enabled short-term associations to be established between traffic-related pollution, chemical as well as acoustic, and emergency hospital admissions due to different neurodegenerative diseases, including Alzheimer's disease (Culqui et al., 2017), Parkinson's disease (Linares et al., 2017a) and dementia (Linares et al., 2017b). It must be understood, however, that in these types of studies it is only possible to infer statistically that the above environmental factors may be associated with exacerbation of the symptoms of these diseases and any ensuing emergency hospital admissions.

Accordingly, the aim of this study was to analyse whether emergency MS admissions might be influenced, in the short term, by existing noise, $PM_{2.5}$, PM_{10}, NO_2 and O_3 levels in the city of Madrid across the period 2001–2009, by ascertaining how many of such hospital admissions were attributable to these environmental risk factors. In addition, we propose an integrative model to explain the biological mechanism whereby traffic noise could be linked to exacerbation of MS symptoms.

2. Materials 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 (INE, 2015).

2.2. Study variables

2.2.1. Dependent variable

The dependent variable was the number of emergency MS hospital admissions (ICD 9: 340) at all hospitals in the city of Madrid across the period, 1 January 2001 to 31 December 2009. Emergency admission data were drawn from the hospital morbidity survey, compiled by the National Statistics Institute (*Instituto Nacional de Estadística/INE*) as admissions of persons with emergency diagnosis of MS.

2.2.2. Independent variables

As our main independent variables of analysis, we used:

1. **Chemical air pollutants**: daily mean concentrations ($\mu g/m^3$) of particulate matter (PM) <2.5 and 10 μm in diameter ($PM_{2.5}$ and PM_{10}), tropospheric ozone (O_3), and nitrogen dioxide (NO_2). To estimate daily mean levels of chemical air pollutants, each monitor's daily level was averaged for that monitor, and a city-wide average was then calculated from all monitors for any given day. We used the data supplied by the Madrid Municipal Air Quality Monitoring Grid (http://www.mambiente.munimadrid.es/).
2. **Noise levels**: mean daily noise levels (dB(A)) for equivalent diurnal noise level 7–23 h (Leqd), equivalent nocturnal noise level 23–7 h (Leqn), and daily noise level 24 h (Leq_{24}). These data were also supplied by the Madrid Municipal Air Quality Monitoring Grid. To estimate daily mean noise levels, we averaged each monitor's daily level and then computed a city-wide average for all these monitors on any given day.

2.2.3. Control variables

Maximum daily temperatures (°C): furnished by the State Meteorological Agency (*Agencia Estatal de Meteorología/AEMET*) for the city of Madrid across the study period.

In addition, we controlled for linear trends, seasonality, and the autoregressive nature of the series itself. Day of the week was also added as a covariate.

2.3. Statistical analysis

We first performed a descriptive analysis of all the above-mentioned variables. Secondly, we proceeded to draw up scatter-plot diagrams to explore the relationship established between noise and air-pollutant levels on the one hand, and emergency MS hospital admissions on the other, by plotting the noise or air-pollutant levels on the X-axis and the mean value of emergency MS admissions on the Y-axis. We then fitted a curve through the cloud of points by type of function which proved statistically significant ($p < 0.05$), using smoothing techniques between the two variables. These graphs enabled us to form a preliminary idea of the type of functional relationship existing between the main variables of analysis, and the existence of thresholds, if any. To confirm the existence of thresholds, it is necessary to ascertain the value at which this increase occurs, without the effect of other variables that might be affecting this relationship, e.g., by using a scatterplot diagram with prewhitening of the series (Makridakis et al., 1983). To this end, we drew up a new scatterplot diagram, with the mean of the residuals for MS variables being plotted on the Y-axis and the levels of the environmental variables on the X-axis. Any deviations detected in the scatterplot correspond to genuine MS anomalies. The benefit of using