



Effects of particulate matter exposure on multiple sclerosis hospital admission in Lombardy region, Italy



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ABSTRACT

Background: Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating disease of the central nervous system, characterized by recurrent relapses of inflammation that cause mild to severe disability. Exposure to airborne particulate matter (PM) has been associated with acute increases in systemic inflammatory responses and neuroinflammation. In the present study, we hypothesize that exposure to PM < 10 µm in diameter (PM₁₀) might increase the occurrence of MS-related hospitalizations.

Methods: We obtained daily concentrations of PM₁₀ from 53 monitoring sites covering the study area and we identified 8287 MS-related hospitalization through hospital admission-discharge records of the Lombardy region, Italy, between 2001 and 2009. We used a Poisson regression analysis to investigate the association between exposure to PM₁₀ and risk of hospitalization.

Results: A higher RR of hospital admission for MS relapse was associated with exposure to PM₁₀ at different time intervals. The maximum effect of PM₁₀ on MS hospitalization was found for exposure between days 0 and 7: Hospital admission for MS increased 42% (95%CI 1.39–1.45) on the days preceded by one week with PM₁₀ levels in the highest quartile. The *p*-value for trend across quartiles was < 0.001.

Conclusions: These data support the hypothesis that air pollution may have a role in determining MS occurrence and relapses. Our findings could open new avenues for determining the pathogenic mechanisms of MS and potentially be applied to other autoimmune diseases.

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1. Introduction

Multiple sclerosis (MS) is an autoimmune disease characterized by inflammatory central nervous system demyelination mediated by T cells specific for a myelin antigen (Conlon et al., 1999; Weisert, 2013).

The etiology of MS is not well understood, and pathogenesis of the disease encompasses multiple inflammatory and apoptotic processes in the central nervous system (Christensen, 2006). Genetic factors have been implicated in MS susceptibility, as several genetic loci have been associated with an increased risk of developing the disease. In particular, some alleles of HLA*DRB1 have

been associated with an up-to-threefold increase in MS risk (Sawcer et al., 2011). Exogenous (i.e., infectious), environmental, or behavioral factors can act as a trigger and cause disease onset in genetically susceptible individuals (Franklin and Nelson, 2003; Oksenberg et al., 1999). Some evidence suggests that environmental factors, such as smoking, vitamin D deficiency might play a role in the development of MS and in higher relapse frequency (Koch et al., 2013; Marrie, 2004). However, clear evidence on the possible role of MS triggers, based on epidemiological data, is lacking.

Experimental and epidemiological studies have demonstrated associations between exposure to airborne particulate matter (PM) and negative health effects, (Ritz, 2010) including neuroinflammation (Guo et al., 2012) and the accumulation of proteins associated with neurodegenerative disease (Calderon-Garciduenas et al., 2008). Moreover, exposure to PM has been associated with acute increases in systemic inflammatory responses.

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A direct connection between frequency of MS relapse and airborne particulate matter (PM) levels has been suggested by Oikonen et al. (2003), who found a fourfold-higher risk of monthly MS relapse when the concentration of PM₁₀ (PM with aerodynamic diameter $\leq 10 \mu\text{m}$) was in the highest quartile compared to the lowest (Oikonen et al., 2003).

A more recent epidemiological study conducted in Tehran, Iran, investigated the potential role of long-term exposure to air pollutants, including PM₁₀, as an environmental risk factor for MS and showed a different exposure in MS cases compared to matched controls (Heydarpour et al., 2014).

No studies have been conducted so far to investigate the hypothesis exposure to PM₁₀ might increase the occurrence of MS-related hospitalizations.

To test this hypothesis, we evaluated the association between PM₁₀ daily means and MS-related hospitalizations identified through hospital admission and discharge records of the Lombardy region in Italy, between 2001 and 2009.

2. Materials and methods

2.1. Hospital admission and discharge records

Clinical information include a primary and a secondary diagnosis fields and are coded by the International Classification of Diseases, ninth revision, Clinical Modification (ICD9-CM).

Through HADRs, we identified 8287 hospitalizations linked to MS events.

Hospitalizations occurred in 107 hospitals located in the Lombardy region of Italy, during the period 2001–2009 (Table 1). Hospitalizations were selected if the principal diagnosis or one of the secondary diagnoses was reported as “multiple sclerosis” (ICD-9 340), along with “injection of steroids” (9923) as pharmacologic intervention code. For each MS hospitalization, we obtained data on municipality of residence (area of residence) at the time of admission, patient gender, date of birth, date of hospital admission (index date). Finally, we linked PM₁₀ exposure data (See Section 2.2) to each event according to the area of residence, at the time of admission. Distribution of hospital admissions per area of residence, year of hospital admission, day of hospital admission, and hospital characteristics are shown in Table 1.

2.2. Air pollution and weather data

Air pollution exposure was estimated by using a methodological approach previously described and validated in other epidemiological studies on the effects of air pollution in the Lombardy region (Baccarelli et al., 2008; Baccarelli et al., 2007b).

Briefly, we obtained from the Regional Environmental Protection Agency (ARPA Lombardia) recordings of daily air pollution data measured from 2001–2009 by monitors located at 53 different sites throughout Lombardy (Fig. 1A). The 53 stations included in this study were selected by the ARPA Lombardia from the approximately 200 monitors of the Regional Air Monitoring Network on the basis of their reliability, determined by standardized quality control procedures, correlation with in situ measurements, continuity of recording, and their ability to represent local background air pollution.

Nine different study areas in the region (Fig. 1A), characterized by homogeneous within-area air pollution concentrations and temporal variations, were identified. Levels of air pollutants measured by different monitors were highly correlated within each study area. Moreover, mobile monitoring in each of the study areas during the study period showed high concordance with measurements taken by the permanent monitors in the same area

Table 1

Demographic Characteristics of subjects with at least one MS hospital admission in Lombardy from 2001 to 2009.

Variables	Lombardy Hospital Admissions 2001–2009 (n=8287(100%))
Gender	
Male	2601(31.39%)
Female	5686(68.61%)
Age (years)	
≤ 30 years	1763(21.27%)
30–50 years	4791(57.81%)
≥ 50 years	1733(20.91%)
Area of residence	
Area 1, Milan, urban area	1029(12.42%)
Area 2, Milan, suburban area	1799(21.71%)
Area 3, Bergamo and Brescia 18	737(8.89%)
Area 4, Po river valley (towns > 15,000 population)	718(8.66%)
Area 5, Po river valley (remaining territory)	2109(25.45%)
Area 6, major northern cities(Varese, Como, Lecco)	332(4.01%)
Area 7, lower Valtellina valley	40(0.48%)
Area 8, Alps	158(1.91%)
Area 9, Pre-Alpine territory	1365(16.47%)
Years of admission	
2001	545(6.58%)
2002	558(6.73%)
2003	619(7.47%)
2004	758(9.15%)
2005	828(9.99%)
2006	1030(12.43%)
2007	1242(14.99%)
2008	1359(16.40%)
2009	1348(16.27%)
Day of the week	
Sunday	118(1.42%)
Monday	2508(30.26%)
Tuesday	1508(18.20%)
Wednesday	1463(17.65%)
Thursday	1223(14.76%)
Friday	1168(14.09%)
Saturday	299(3.61%)
Hospital characteristics	
Reference Center for MS	7368(88.91%)
Hospital (with generic Neurology Department)	370(4.46%)
Others	549(6.62%)

(ARPA Lombardia, 2006).

Mean daily concentrations of PM with an aerodiameter equal to or less than $10 \mu\text{m}$ (PM₁₀) were averaged, within each study area, using an algorithm that combined levels reported by multiple monitoring (Schwartz, 2000).

The Southern part of Pavia province (Fig. 1A) was excluded, because this area had no local monitoring stations and showed pollution patterns in repeated point mobile recordings that differed from those measured by stationary monitors located in neighboring areas.

All subjects were assigned to one of nine geographic areas (1: Milan urban area; 2: Milan suburban area; 3: Bergamo/Brescia; 4: Po River Valley (towns > 15,000 population); 5: Po river valley (remaining territory); 6: Varese/Como/Lecco; 7: Lower Valtellina Valley; 8: Alps; 9: Pre-Alpine territory), based on the municipality of residence at the date of hospital admission (Fig. 1A).

Most air pollution stations also record data on weather, allowing us to collect data on daily average of air temperature. We used data from the nearest Regional Weather Service surface station of the ARPA Lombardia network for stations that did not measure meteorologic variables.

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