Published in final edited form as:

Environ Res. 2016 February ; 145: 68–73. doi:10.1016/j.envres.2015.11.017.

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.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.envres.2015.11.017>

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.

Keywords

Air pollution; PM₁₀; Multiple Sclerosis; MS hospitalization; Lombardy region

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; Weissert, 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.

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 < 10 µm) 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” (ICD9 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 (ARPA Lombardia, 2006).

Mean daily concentrations of PM with an aerodiameter equal to or less than 10 µm (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.

2.3. Statistical analysis

We used Poisson regression analysis to investigate the association between exposure to PM_{10} and risk of hospitalization for MS relapse.

Since hospital admissions are non-negative discrete numbers and, hence, are not normally distributed, we used Generalized Linear Model (GLM) of Poisson regression, considering the daily number of MS hospital admissions as dependent variable and PM_{10} concentration as the independent variable.

Exposure to PM_{10} was estimated by calculating the average level for the following time intervals before hospital admission: Days 0–1, Days 1–3, Days 0–7, Days 0–14, Days 7–14, Day 0–21, Day 0–28. We also calculated exposure quartiles for each time interval (Supplementary Table 3).

In this model, if β_i is a coefficient obtained by Poisson regression, then $\exp(\beta_i)$ represents the relative risk of occurrence of the event in second, third and fourth PM_{10} quartile compared to the first one. The results were expressed as a relative risk (RR) estimate.

Multivariable generalized linear Poisson regression models were fitted by adjusting for day of the week on the date of admission (from Monday to Saturday), seasonality (Sep–Nov, Dec–Feb, Mar–May, Jun–Aug), day-off (categorical variable with 4 categories identifying for each year the days in which hospital admission is less probable, with 0 being more probable and 3 being less probable), resident population in each area (Fig. 1B), and smoothing spline functions for time trend and temperature. We incorporated a smoothed spline function of time, which can accommodate nonlinear and non-monotonic patterns between time and outcome, diminishing short-term fluctuations in the data, thereby helping to reduce the degree of serial correlation.

Based on previous findings reported in the literature and on data simulations, the basic model included a smoothing spline for time with 7 degrees of freedom (df) per year of data. This number of degrees of freedom reduces and often eliminates autocorrelation. Other covariates, such as day of the week and smoothing splines of 3-day lags of average

temperature with 3 df, were also included in the model because they may be associated with daily MS hospitalization and are likely to vary over time in concert with air pollution levels.

Statistical tests were conducted using an α level of .05 and 95% CIs were used to measure precision.

All statistical analysis were performed in SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Characteristics of the study population

Table 1 shows the main demographic characteristics of subjects experiencing MS hospital admission in Lombardy from 2001–2009, as well as their distribution among the nine Lombardy areas. In the 9-year study period, 8287 MS hospital admissions were recorded in the study areas. The highest percentage of hospital admissions were recorded in area 5 (Po river valley – remaining territories, 25.45%), area 1 (Milan urban area, 12.42%) and area 2 (Milan Suburban area, 21.71%). Those areas recorded the higher mean population in the study period (Table 2). The number of admissions, as expected, was higher in females (68.61%) than males (31.39%). More than half of the subjects (57.81%) were aged between 30 and 50 years. The highest percentage of admissions takes place in working days and especially on Monday (30.26%).

3.2. Study subject exposure characterization

Recorded average PM₁₀ levels in the study period was below the levels of action used for the general population (50 µg/m³ for PM₁₀, EU directive 50/2008) from March to November, and higher from December to February, with a wide gradient of exposures (Table 3). The distribution of mean PM₁₀ for the period 2001–2009 across areas (supplementary table 2) showed higher levels of PM₁₀ in Area 5 (Po river valley, remaining territory, 52.5 µg/m³), Area 1 (Milan, urban area, 50.8 µg/m³), and Area 2 (Milan, suburban area, 46.8 µg/m³). As evidences indicated a possible relationship between temperature and MS-related hospital admissions, we also reported temperature distribution in Table 3.

3.3. Air pollution increases the relative risk of MS relapse

A higher risk of hospital admission for MS relapse was associated with exposure to PM₁₀ at different time intervals (Table 4). Supplementary Table 3 presents the quartiles of the mean PM₁₀ level measured in the area of residence for each time interval. Analysis were adjusted for day of the week, season, day-off, resident population in each area and with spline smoothers of temperature and time trend. The maximum effect of PM₁₀ on MS hospitalization was found for exposure between days 0 and 7. An increase in PM₁₀ level from the first reference PM₁₀ quartile to the second quartile was associated with an adjusted relative risk (RR) of 1.21 (95%CI 1.16–1.26; p value_{adj} < 0.001), corresponding to a 21% increase in hospital admissions for MS relapse; an increase from the third to the first quartile was associated with an adjusted RR of 1.36 (95%CI 1.30–1.42; p value_{adj} < 0.001) corresponding to a 36% increase in hospital admissions for MS relapse; and an increase from the fourth to the first quartile was associated with an adjusted RR of 1.42 (95%CI

1.39–1.45; p value_{adj} < 0.001) corresponding to a 42% increase in hospital admissions for MS relapse. We also found a significant dose-response increase in the number of hospital admissions and non-categorized exposure data (p value for trend across quartiles < 0.001). Longer temporal lags were also considered (0–21 and 0–28 day lag) but the effect was much less consistent.

All the analysis were also conducted without adjusting for temperature and the result trends were confirmed (*data not shown*).

4. Discussion

Particulate air pollution is a global public health threat. Numerous epidemiologic studies have associated acute (Katsouyanni et al., 2001, 1997; Kinney and Ozkaynak, 1991; Schwartz and Dockery, 1992; Schwartz and Marcus, 1990) and chronic (Dockery et al., 1993; Pope et al., 2004; Pope et al., 1995) exposures to particulate air pollution with early death from multiple causes (Pope et al., 2004; Schwartz and Dockery, 1992). In addition to the well-known respiratory and cardiovascular effects of air pollution, preliminary evidence is emerging for neurological effects of airborne PM (Calderon-Garciduenas et al., 2002, 2004; Campbell et al., 2005; Donaldson et al., 2005; Elder et al., 2006).

There is increasing evidence that a number of environmental factors are important in the development and course of MS (O’Gorman et al., 2012). In particular, many different infections have been proposed to play a role in MS pathogenesis, with the most consistent findings implicating past infection with EBV (Lunemann et al., 2007; Tai et al., 2008). In the present study, we considered MS-related hospital admissions occurring in Lombardy Region and then evaluated the levels of PM₁₀ exposure, in the days that preceded them. By dividing PM₁₀ into quartiles, we found a dose-response increase in the number of hospital admissions. In particular, if the average of PM₁₀ exposure in the 7 days before the admission was in the highest quartile, there were 42% more hospital admissions for MS, compared to the lowest quartile.

Poor air quality has been associated with exacerbation of existing autoimmune disease, (Ritz, 2010) including type 1 diabetes, rheumatic disease, and systemic lupus erythematosus. Oikonen et al. (Oikonen et al., 2003) demonstrated a fourfold higher risk of MS relapse on days when the concentration of particulate air pollution was in the highest quartile. One explanation is that increased exposure to particulate air pollution may enhance susceptibility to transmissible infections, thereby triggering MS relapse (Oikonen et al., 2003). However, other mechanisms might explain this relationship. For example, exposure to air pollution could contribute to the development of autoimmunity by enhancing antigen presentation, thus augmenting the autoimmune response (Ritz, 2010).

A recent work conducted in Tehran, Iran, has evaluated the possible association between the distribution of MS prevalent cases and long-term air pollution levels. Prevalent cases showed a clustered pattern and a significant difference in PM₁₀ exposure was observed in MS cases compared with controls (Heydarpour et al., 2014).

By using hospital admission records, we were able to examine an extended period of time (2001–2009) and a large number of hospital admissions for MS relapse ($n = 8287$). This approach, however, has several inherent limitations, including the lack of data on the duration and effectiveness of immunomodulatory therapy. Since it has been estimated that many MS patients were treated with immunomodulatory therapy, and such treatment has a strong impact on limiting relapse frequency, the observed effect of PM exposure might be underestimated.

A second limitation is that, given the design of the study, ambient air pollution was used as a surrogate for personal exposure to air pollution, which may have resulted in measurement error. However, the consequence of using ambient measures to estimate exposure is likely to be only a moderate underestimation of the effects of pollution, (Zeger et al., 2000) which would not explain the significant associations found in our study. Our study was based on readings of hourly air pollution data from 53 different monitoring sites throughout the Lombardy region, which were selected on the basis of their ability to represent local background air pollution, as determined by correlation with random in situ measurements in the adjacent territory. The analysis was based on nine different areas that showed spatially homogeneous pollution patterns, as determined by the high longitudinal correlation of the measures from the monitoring stations in the same area and of random measurements at different within-area locations (Baccarelli et al., 2007a). We considered several potential confounders that could have influenced the relation between exposure and MS-related hospitalizations (e.g., day of week, season, day-off, population in each area and with spline smoothers of temperature and time trend). Therefore, the chance that the observed associations reflected bias resulting from confounders is minimized.

One additional limitation is our use of PM₁₀ as the principal exposure. Air pollution involves exposure to a complex mixture of gaseous and particulate environmental pollutants, such as, for example, fine and ultrafine particles, nitrogen dioxide, ozone, and sulfur dioxide. Therefore, we cannot exclude effects from other pollutants as well as interactions between different pollutants. Because MS-related hospitalizations is not a sudden process, we averaged PM₁₀ measurements for different time intervals before the hospital admission, instead of considering a single day of exposure. In addition to biological variability of the immune response in MS, another factor determining the timing of relapse is time between the onset of clinical symptoms and patient's decision to contact the hospital to seek medical attention.

Another limitation is that we used information on residence taken from hospital admission records, but that does not tell us where the subject really spent the majority of his/her time on the days before relapse. Although the above mentioned limitations, our findings are highly suggestive that air pollution might be a mighty increase MS-related hospitalizations. Further studies specifically designed to investigate contextually the effects of particulate air pollution on MS patients are required to help elucidate in detail this possible environmental trigger for MS development and relapses.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by Lombardy Region Research Contracts UniMi 9167/2007 and UniMi 31557/2010. Prof. Bollati received support from the EU Programme “Ideas” (ERC-2011-StG 282413). Prof. Baccarelli received support from the NIEHS-HSPH Center for Environmental Health (ES000002).

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Fig. 1. Map of the Lombardy region (Italy) showing the location of the 53 air pollution monitors in the 9 areas identified for the study (Fig. 1A) and the mean population of each city area, between 2001 and 2009 (Fig. 1B).

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 (<i>n</i> = 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%)

Variables	Lombardy Hospital Admissions 2001–2009 (<i>n</i> = 8287(100%))
Hospital (with generic Neurology Department)	370(4.46%)
Others	549(6.62%)

Table 2

Lombardy Hospital admission, mean population and %proportion in each area of residence, in period 2001–2009.

Area of residence 2001–2009	Lombardy Hospital Admissions 2001–2009 <i>n</i> = 8287(100%)	Mean population 2001–2009 <i>N</i> = 9,419,553(100%)	%Proportion of hospital admission on mean population 2001–2009
Area 1, Milan, urban area	1232(14.87%)	1,289,414(13.69%)	0.096
Area 2, Milan, suburban area	2128(25.68%)	2,018,327 (21.43%)	0.105
Area 3, Bergamo and Brescia 18	766(9.24%)	697,491(7.40%)	0.110
Area 4, Po river valley (towns > 15,000 population)	796 (9.61%)	812,334(8.62%)	0.098
Area 5, Po river valley (remaining territory)	2295(27.69%)	2,545,144(27.02%)	0.090
Area 6, major northern cities(Varese, Como, Lecco)	411(4.96%)	210,855(2.24%)	0.195
Area 7, lower Valtellina valley	42(0.51%)	139,539 (1.48%)	0.030
Area 8, Alps	170(2.05%)	285,445(3.03%)	0.060
Area 9, Pre-Alpine territory	1542(18.61%)	1,421,000(15.09%)	0.109

Table 3

PM₁₀ and temperature levels, measured in the period between 2001 and 2006, according to seasonality.

	PM10 (µg/m ³)						Temperature (°C)					
	Min	p25	Mean	Std	p75	Max	Min	p25	Mean	Std	p75	Max
Days of data available	Days of data available						Days of data available					
Season	27,702	1.67	22.6	42.48	28.6	54.6	301.19	29,366	-19.05	6.15	13.06	33.32
Sep–Nov	6902	2.09	22.94	40.6	23.94	53.39	210.72	7319	-7.16	8.74	12.93	27.41
Dec–Feb	6878	3.67	39.48	65.26	35.43	85.01	301.19	7306	-19.05	1.23	3.78	28.46
Mar–May	6916	1.88	21.93	37.28	22.41	46.55	214.49	7394	-9.69	9.33	12.91	27.86
Jun–Aug	7006	1.67	18.01	27.11	12.9	34.41	100.53	7347	-3.44	20.28	22.55	33.32

Table 4

Hospital admission rate ratio for MS hospitalization in association with exposure to PM₁₀ in the days before hospital admission.

Time period before hospitalization	2nd Quartile			3rd Quartile			4th Quartile			<i>p</i> -trend			
	RR	95% CI	<i>p</i> -value	RR	95% CI	<i>p</i> -value	RR	95% CI	<i>p</i> -value				
Average days 0–1	1.16	1.08	1.25	< 0.0001	1.23	1.14	1.33	< 0.0001	1.33	1.23	1.43	< 0.0001	0.003
Average days 0–3	1.22	1.14	1.30	< 0.0001	1.25	1.16	1.36	< 0.0001	1.40	1.34	1.46	< 0.0001	< 0.0001
Average days 0–7	1.21	1.16	1.26	< 0.0001	1.36	1.3	1.42	< 0.0001	1.42	1.39	1.45	< 0.0001	< 0.0001
Average days 0–14	1.24	1.2	1.28	< 0.0001	1.28	1.14	1.33	< 0.0001	1.34	1.27	1.41	< 0.0001	0.020
Average days 7–14	1.18	1.10	1.27	< 0.0001	1.18	1.11	1.25	< 0.0001	1.19	1.14	1.24	< 0.0001	0.045
Average days 0–21	1.08	0.99	1.09	0.428	1.20	1.17	1.25	0.039	1.15	1.14	1.16	0.046	0.080
Average days 0–28	1.05	0.97	1.11	0.254	1.03	0.94	1.12	0.225	1.01	0.94	1.08	0.045	0.092

RR: Hospital Admission Rate Ratio, adjusted for day of week, season, day-off, resident population in each area and with spline smoothers of temperature and time trend.