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Ozone, NO_2 and PM_{10} are associated with the occurrence of multiple sclerosis relapses. Evidence from seasonal multi-pollutant analyses

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A R T I C L E I N F O

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A B S T R A C T

Background: Triggers of multiple sclerosis (MS) relapses are essentially unknown. PM_{10} exposure has recently been associated with an increased risk of relapses.
Objectives: We further explore the short-term associations between PM_{10}, NO_2, benzene (C_6H_6), O_3, and CO exposures, and the odds of MS relapses' occurrence.
Methods: Using a case-crossover design, we studied 424 MS patients living in the Strasbourg area, France between 2000 and 2009 (1783 relapses in total). Control days were chosen to be ± 35 days relative to the case (relapse) day. Exposure was modeled through ADMS-Urban software at the census block scale. We consider single-pollutant and multi-pollutant conditional logistic regression models coupled with a distributed-lag linear structure, stratified by season ("hot" vs. "cold"), and adjusted for meteorological parameters, pollen count, influenza-like epidemics, and holidays.
Results: The single-pollutant analyses indicated: 1) significant associations between MS relapse incidence and exposures to NO_2, PM_{10}, and O_3, and 2) seasonality in these associations. For instance, an interquartile range increase in NO_2 (lags 0–3) and PM_{10} exposure were associated with MS relapse incidence (OR = 1.08; 95%CI: [1.03–1.14] and OR = 1.06; 95%CI: [1.01–1.11], respectively) during the "cold" season (i.e., October-March). We also observed an association with O_3 and MS relapse incidence during "hot" season (OR = 1.16; 95%CI: [1.07–1.25]). C_6H_6 and CO were not significantly related to MS relapse incidence. However, using multi-pollutant models, only O_3 remained significantly associated with the odds of relapse triggering during "hot" season.
Conclusion: We observed significant single-pollution associations between the occurrence of MS relapses and exposures to NO_2, O_3 and PM_{10}, only O_3 remained significantly associated with occurrence of MS relapses in the multi-pollutant model.

1. Introduction

Multiple Sclerosis (MS) is the most frequent neuro-inflammatory disease of the central nervous system (CNS), affecting almost 2.3 million people worldwide (Browne et al., 2014). The prevalence in France is about 1.5 individuals for 1000 (Foulon et al., 2017). In about 85% of cases, patients experience relapse(s) (Browne et al., 2014), that is, patients experience exacerbations of neurologic disabilities followed by partial or complete remission. Relapses characterize the relapsing-remitting MS course.

The etiology of MS remains unclear, yet clearly multifactorial (McKay et al., 2016). Genetic predispositions (*HLA-DRB1*, *IL2RA* and *IL7R* most associated genes) may represent only one quarter of estimated heritability of MS (Sawcer et al., 2014). Main environmental factors found to be influencing susceptibility to experience an MS onset are Epstein-Barr virus infection, tobacco consumption (either passive or active) and reduced levels of vitamin D increase or low sunlight exposure. In addition, women appear to be at greater risk than males (Ascherio et al., 2014; Belbasis et al., 2015; Lauer, 2010). Relapses predisposing risk factors have been investigated to a lesser extent and

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associations reported are discordant, namely young age, short MS duration, low serum vitamin D levels, smoking, psychological and other stress, vaccination, infections, post-partum, breast feeding and assisted reproduction (McKay et al., 2016; Kalincik, 2015).

Relapses' incidence varies across seasons (Damasceno et al., 2012; Fonseca et al., 2009; Handel et al., 2011; Harding et al., 2017; Jin et al., 2000; Ogawa et al., 2004; Salvi et al., 2010; Spelman et al., 2014; Tremlett et al., 2008), suggesting a possible role of season-dependent factors such as meteorological variables (Watad et al., 2016) and ambient air pollution (Angelici et al., 2016; Oikonen et al., 2003; Roux et al., 2017).

A few studies have investigated the role of air pollution in the development of MS, reporting mixed results (Chen et al., 2017; Gregory et al., 2008; Heydarpour et al., 2014). In Teheran, significant clustered patterns ($p < .001$) and difference in exposure to sulfur dioxide (SO_2), PM_{10}, NO_2 and nitrogen oxides (NOx) were observed in MS cases compared to random controls (Heydarpour et al., 2014). Gregory et al. (2008) also suggested that PM_{10} might play a role in MS onset (Gregory et al., 2008). However, these studies suffered from a number of limitations (e.g. small sample size, imprecise exposure assessment etc.). Recently, Chen et al. (2017) observed, using a Cox proportional hazards model adjusted for individual features and latitude, that proximity living to heavy traffic was not associated with a higher incidence of MS (Chen et al., 2017). Concerning relapses, some studies investigated the link between air pollution and the odds of relapses triggering (Tremlett et al., 2008; Oikonen et al., 2003; Roux et al., 2017; Mehrpour et al., 2013; Vojinović et al., 2015), MS-related hospitalization (Angelici et al., 2016) and MS inflammatory activity (Bergamaschi et al., 2017). Associations were observed in several studies between PM_{10} exposure and MS relapse risk (Angelici et al., 2016; Oikonen et al., 2003; Roux et al., 2017; Bergamaschi et al., 2017). Among studies that examined possible influence of other air pollutants such as CO, O_3, SO_2 and NOx (Tremlett et al., 2008; Oikonen et al., 2003; Mehrpour et al., 2013), one study reported exposure to acidic gas (NO_2, NO and SO_2) to be associated with risk of relapse (Oikonen et al., 2003). Overall, the authors did not take into consideration pertinent confounding factors such as meteorological parameters, infections etc.

There is a need to consider multi-pollutant models in environmental epidemiology, especially in studies relating MS occurrence to air pollutants' concentrations. The environmental health-related associations are complex to investigate in observational studies due to the high correlations and possible interactions between pollutants, as well as the seasonality of the pollutants' concentrations. To our knowledge, no study has yet considered multi-pollutant analyses to estimate the associations between air pollution and MS.

In the present study, we estimate the associations of PM_{10} and other ambient air pollutants (NO_2, benzene (C_6H_6), CO and O_3) using a multi-pollutant models to address the confounding issue due to the high correlations between pollutants originating from the same source.

2. Materials and methods

2.1. Study design

We conducted a time-stratified case-crossover design to explore the associations between short-term air pollutants variations (i.e., PM_{10}, NO_2, C_6H_6, O_3, and CO) and multiple sclerosis relapses occurrences (Maclure, 1991). This study design consists in within-subject comparisons by selecting for each patient his/her own control, i.e., the air pollutant exposure levels of the same patient will be compared between days of relapse onset (case) and days without any relapse (control). A time-stratified approach was chosen to define control days (Janes et al., 2005). That is, control days were chosen to be ± 35 days relative to the case (relapse) day. This 35-days interval choice was motivated by the relapse clinical definition which confined a minimum of 30 days between two relapses. Every control day between the 30th and 35th day was excluded, justifying the reason why 158 case days only have a single control instead of two.

Time-invariant or long-term varying confounders, such as individual characteristics and behaviors, are controlled through within-subject comparisons. This approach also permits to tackle time trends such as seasonality, between days of the week variation, and the temporal autocorrelation (Janes et al., 2005).

2.2. Study setting

The Strasbourg Metropolitan Area (SMA), located in North-Eastern France, aggregates 28 municipalities, 21 of which are rural and seven urban. The SMA sprawls over 316 km^2 with 450,000 inhabitants. It is subdivided into 186 French census blocks, defined as a sub-municipal division and designed by French National Institute for Statistics and Economic Studies (INSEE). Census blocks are devised according to land use, homogeneity of population size and socio-economic features. They are the smallest spatial unit in France for which socio-economic data are made available due to French confidentiality regulations. In average, a census block is 2000 inhabitants (ranging from 2 to 4885), with a surface from 0.05 km^2 up to 19.6 km^2.

2.3. Study population and environmental data

2.3.1. Patients' and relapses' inclusion criteria

Patients' data were provided by the multiple sclerosis network alSacEP based in Alsace North-Eastern region, since 2006. All patients were managed through the European Database for Multiple Sclerosis (EDMUS) using a standardized definition and management of patients' data (Confavreux et al., 1992).

Study period was January 1, 2000 to December 31, 2009. Inclusion criteria for patients were: i) clinical definition fitting McDonalds' MS criteria; *ii*) first symptoms of MS occurred before December 31th, 2009; *iii*) patients were affected with relapsing-remitting and secondary progressive forms; *iv*) residence address within Strasbourg Metropolitan Area.

When the day of relapse occurrence was doubtful (uncertain or unknown), the relapse (*i.e.*, case day) was excluded, leading to additional patients exclusions.

The French Authority for Data Confidentiality (CNIL) approved the present protocol (DR-2015-504).

2.3.2. Air pollution data

Air pollution concentrations of PM_{10}, NO_2, C_6H_6, O_3, and CO were estimated throughout the study period on an hourly basis at the census block scale. The deterministic ADMS-Urban air dispersion model was used considering different parameters, namely background pollution measurements, emissions inventories, meteorological data but also land use or surface roughness (Atmospheric Dispersion Modeling System) (Carruthers et al., 2000). Details of parameters and model performance have been previously discussed (Havard et al., 2009; Bard et al., 2014). Previous works have shown that air pollution assessment performance proved excellent results (Laurent et al., 2008): coefficients for the modeled and effectively measured ambient concentrations were highly correlated 0.87 for NO_2, 0.73 for PM_{10} and 0.84 for O_3.

We did not assess the plausible role of sulfur dioxide (SO_2) which was suggested in the recent literature (Heydarpour et al., 2014) because i) Strasbourg Metropolitan Area concentrations are low (≤ 11 $\mu g/m^3$) in the Alsace region, and ii) it originates from a single location, which altogether decrease the preciseness of the modeling. Concentrations of $PM_{2.5}$, which represents a substantial proportion of PM_{10} (Marcazzan et al., 2001), were not measured routinely during the study period. PM_{10} is a proxy measure of $PM_{2.5}$. The potential interventions to reduce PM_{10} and $PM_{2.5}$ involve similar sources. However, benzene, rarely measured by air pollution monitoring systems, was properly measured and modeled in our study setting.