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Exposure to particulate matter air pollution and risk of multiple sclerosis in two large cohorts of US nurses☆

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ABSTRACT

Background: Air pollution is thought to raise the risk of neurological disease by promoting neuroinflammation, oxidative stress, glial activation and cerebrovascular damage. Multiple Sclerosis is a common auto-immune disorder, primarily affecting young women. We conducted, to a large prospective study of particulate matter (PM) exposure and multiple sclerosis (MS) risk in two prospective cohorts of women: the Nurses Health Study (NHS) and the Nurses Health Study II (NHS II).

Methods: Cumulative average exposure to different size fractions of PM up to the onset of MS was estimated using spatio-temporal models. We used multivariable Cox proportional hazards models to estimate the hazard ratios (HR) and 95% confidence intervals (CI) of MS associated with each size fraction of PM independently. Participants were followed from 1998 through 2004 in NHS and from 1988 through 2007 for NHS II. We conducted additional sensitivity analyses stratified by smoking, region of the US, and age, as well as analyses restricted to women who did not move during the study. Analyses were adjusted for age, ancestry, smoking, body mass index at age 18, region, tract level population density, latitude at age 15, and UV index.

Results: We did not observe significant associations between air pollution and MS risk in our cohorts. Among women in the NHS II, the HRs comparing the top vs. bottom quintiles of PM was 1.11 (95% Confidence Intervals (CI): 0.74, 1.66), 1.04 (95% CI: 0.73, 1.50) and 1.09 (95% CI: 0.73, 1.62) for PM_{10} ($\leq$ 10 μm in diameter), $PM_{2.5}$ ($\leq$ 2.5 μm in diameter), and $PM_{2.5–10}$ (2.5 to 10 μm in diameter) respectively, and tests for linear trends were not statistically significant. No association between exposure to PM and risk of MS was observed in the NHS.

Conclusions: In this study, exposure to PM air pollution was not related to MS risk.

1. Introduction

Chronic exposure to air pollution has detrimental effects on many aspects of human health, (Lepeule et al., 2012; Laden et al., 2006; Pope et al., 1995; Dockery et al., 1993; Andican et al., 2012) but little is known about the effects of air pollution on risk of multiple sclerosis (MS). Cigarette smoking, a common air pollutant, is associated with an increase in MS risk, (Ascherio and Munger, 2010), (Hernan et al., 2005; Hernán et al., 2001) suggesting that exposure to environmental chemicals, such as those found in air pollution could be an important factor. To date, only one study has prospectively examined the association between air pollution and MS (Chen et al., 2017). Other related studies have found a clustering of MS cases in areas of high PM_{10} in Georgia (Gregory Ii et al., 2008) an increase in MS relapse risk with acute pollution exposure in Finland (Oikonen et al., 2003) and France (Roux et al., 2017) and a higher risk of hospital admission for MS relapse related ambient PM_{10} concentrations in Italy (Angelici et al., 2016) We thus sought to examine prospectively whether exposure to particulate matter air pollution is related to risk of MS in two cohorts of US women.

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Air pollution is a complex mixture of substances that are found in indoor and outdoor air. Air pollution includes particulate matter (PM), various gasses (such as ozone, carbon monoxide, sulfur and nitrogen oxides), airborne metals (e.g. lead, copper, manganese) and organic compounds (bacterial endotoxins and polycyclic aromatic hydrocarbons). PM is thought to be one of the more harmful components of air pollution (Block and Calderon-Garciduenas, 2009). PM is especially relevant for nervous system damage because some smaller components of PM can reach the brain and are associated with neurodegeneration (Block and Calderon-Garciduenas, 2009). Air pollution has also been associated with increased risk of other neurological diseases such as Parkinson's disease, (Finkelstein and Jerrett, 2007; Allen et al., 2014; Ritz et al., 2015; Palacios et al., 2014a; Palacios et al., 2014b) autism, (Weuve et al., 2012; Suades-Gonzalez et al., 2015; Roberts et al., 2013; Weisskopf et al., 2015) Alzheimer's disease, and reduced cognitive function (Windham et al., 2011).

We used data from two large ongoing prospective cohort studies; the Nurses Health Study (NHS) and the Nurses Health Study II (NHS II) to prospectively examine the effects of exposure to PM on the risk of MS.

2. Methods

2.1. Study population

The NHS was initiated in 1976 when 121,700 female registered nurses were recruited from 11 states and were between 30 and 55 years old at baseline. The NHS II was initiated in 1989 when 116,671 nurses between the ages of 25 and 42 were enrolled from 14 states. At present, there are at least ten nurses from each cohort in each of the contiguous states. In both cohorts, participants responded to a baseline questionnaire and biennial follow-up questionnaires regarding lifestyle factors and health outcomes. Residential street address for each nurse was collected at baseline and updated with every 2 year follow-up cycle. Over 90% of the participants have responded during each follow-up cycle. Detailed description of the study cohorts is provided elsewhere (Colditz et al., 1997). This study has been approved by the Institutional Review Board at the Brigham and Women's Hospital.

2.2. MS ascertainment

The ascertainment of MS in the NHS and NHS II cohorts has been previously described (Hernan et al., 1999; Ascherio et al., 2001). All cohort participants are asked on the biennial cohort follow-up questionnaire whether they were diagnosed with MS since the previous follow-up. Participants who report a new diagnosis are contacted for permission to request diagnostic confirmation from their treating neurologist. For cases reported prior to 2002, the certainty of diagnosis ("definite," "probable," "possible" or "other diagnosis") was based on that provided by the treating neurologist. This approach had high validity relative to the Poser criteria for MS. (Hernan et al., 1999) Starting in 2002, we further improved the ascertainment criteria and asked treating neurologists to provide copies of the participant's medical record and relevant MRI reports, in addition to completing the diagnostic questionnaire. Our study MS specialist reviews all medical records sent in by the treating neurologists and determines whether each case meets the definition of MS based on the McDonald criteria for MS. (McDonald et al., 2001)

2.3. Air pollution assessment

A detailed discussion of the assessment of exposure to PM_{10}, $PM_{2.5}$ and $PM_{10-2.5}$ air pollution has been previously published (Yanosky et al., 2008; Yanosky et al., 2014). Briefly, for PM_{10}, generalized additive models were developed to estimate exposure for all residential addresses from 1988 through 2007 (Yanosky et al., 2008) using monthly average PM_{10} data from USEPA's Air Quality System (AQS), a nationwide network of continuous and filter-based monitors, combined with data from the Interagency Monitoring of Protected Visual Environments (IMPROVE) network, and several Harvard-based research studies. Model covariates, including population density, distance to nearest road, elevation, and urban land use, were derived using a geographic information system (GIS). For $PM_{2.5}$, the approach was similar; although, because EPA AQS monitoring data for $PM_{2.5}$ was not available prior to 1999, separate models were created for pre- and post-1999 $PM_{2.5}$. The model for $PM_{2.5}$ after 1999 was obtained in a way analogous to PM_{10}, as described above. For the period prior to 1999, the model for $PM_{2.5}$ was derived from a combination of the pre-1999 PM_{10} model with the spatio-temporal post-1999 $PM_{2.5}/PM_{10}$ ratio, and further refined using estimated extinction coefficients from airport visibility data. $PM_{2.5-10}$ was estimated for the whole study period by subtracting model values for $PM_{2.5}$ from those for PM_{10}. In a cross-validation study that held out a sub-section of the monitors and compared predicted and observed values, the PM_{10}, $PM_{2.5}$ and $PM_{2.5-10}$ models had little bias and a high degree of precision: the normalized mean bias factor (NMBF), a measure of bias was -1.6%, -5.1%, -3.2% for models of PM_{10}, $PM_{2.5}$ and $PM_{2.5-10}$, respectively and the normalized mean error factor (NMEF), a measure of precision was 14.3%, 24.4% and 38.9% for models of PM_{10}, $PM_{2.5}$ and $PM_{2.5-10}$, respectively (Yanosky et al., 2008; Yanosky et al., 2014).

2.4. Statistical analysis

Participants contributed person time to the follow up period from 1988 (the date air pollution was first modeled in our cohorts) to the date of onset of the first symptoms of MS, death from any cause, or end of follow-up (31 May 2004 for NHS and 31 May 2007 for NHS II). Follow-up for MS was stopped in 2004 in NHS, due to the ageing of the cohort and MS occurring primarily earlier in life, and follow-up was stopped in 2007 because air pollution models were only available until then. We used the Cox proportional hazards model with time on a monthly scale to study the association between air pollution and risk of MS. We calculated hazard ratios (HRs) and 95% CIs for each quintile of PM exposure, as well as in a linear model for each 10 $\mu g/m^3$ increase in PM. Quintiles of PM were determined on the initial dataset, and were the same for all analyses and sensitivity analyses; quintile ranges are listed in Table 1. For tests of trend, we used the median value of each quintile as a continuous variable to minimize the influence of outliers. We performed tests for trend by using the median value in each quintile as a continuous variable to allow for non-linear associations. Effect modification was assessed via the Wald test from multiplicative interaction terms. All models were adjusted for age in years and calendar period. Final analyses were additionally adjusted for smoking status (never/former/current smoker), pack years smoking, body mass index (BMI) at age 18 (in categories: < 18.5, 18.5–21, 21–23, 23–25, 25–27, 27–30, 30 +), population density, region (northeast, midwest, west, south), tract-level household income, latitude tier at age 15: north/south/middle) (Hernan et al., 1999) and state-level measures of UV index. Model covariates were chosen based on their role as known risk factors for MS (smoking, BMI at age 18, latitude at age 15) or on their association with quintile of air pollution in our datasets (median household income, population density, UV index, region of residence). Adjustment for dietary Vitamin D was not possible because of a large amount of missing data on dietary Vitamin D. We also conducted additional sensitivity analyses adjusted for season, median housing value, and Scandinavian ancestry, the addition of these covariates did not significantly impact the models. Because the relevant exposure period for MS is not well known, but is thought to extend many years, possibly into childhood or even gestation, in our primary analyses, we modeled air pollution as a time-varying cumulative average from 1988/1989 through date of MS diagnosis. We conducted additional sensitivity analyses restricted to women who did not move residences during the study, with the assumption that these women more likely to retain the