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Air pollution exposure increases the risk of rheumatoid arthritis: A longitudinal and nationwide study☆,☆☆

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ABSTRACT

Objective: Rheumatoid arthritis (RA) has been associated with inhaled pollutants in several studies, and it is a disease of chronic inflammation. The association between air pollution and the risk of RA remains unclear. Therefore, we conducted this nationwide, retrospective, sex-stratification study to evaluate this association.
Methods: We collected data from the Longitudinal Health Insurance Database (LHID), maintained by the Taiwan Bureau of National Health Insurance, and the Taiwan Air Quality-Monitoring Database (TAQMD), released by the Taiwan Environmental Protection Agency. The TAQMD provides the daily concentrations of particulate matter with the aerodynamic diameter <2.5 μm ($PM_{2.5}$) and nitrogen dioxide (NO_2) from 74 ambient air quality-monitoring stations distributed all over Taiwan during 1998–2010. The LHID and TAQMD were linked according to the residential areas of insurants and the areas where the air quality-monitoring stations were located. A residential area was defined according to the location of the clinic and hospital that treated acute upper respiratory tract infections. The yearly average air pollutant concentrations were categorized into 4 levels based on quartiles. We evaluated the risk of RA in residents exposed to 4 levels of $PM_{2.5}$ and NO_2 concentrations.
Results: We detected an increased risk of RA in participants exposed to $PM_{2.5}$ and NO_2. Among four quartiles of NO_2 concentration, namely Q1, Q2, Q3, and Q4, the adjusted hazard ratios (aHRs) in Q2, Q3, and Q4 compared with that in Q1 were 1.07 (95% confidence interval [CI] = 0.76–1.50), 1.63 (95% CI = 1.16–2.31),and 1.49 (95% CI = 1.05–2.12), respectively. Regarding the $PM_{2.5}$ concentrations, the aHRs after exposure to the Q2, Q3, and Q4 levels were 1.22 (95% CI = 0.85–1.74), 1.15 (95% CI = 0.82–1.62), and 0.79 (95% CI = 0.53–1.16), respectively.
Conclusion: The results of this nationwide study suggest an increased risk of RA in residents exposed to NO_2.

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1. Introduction

Increased risks of cardiovascular and cerebrovascular diseases have been observed in people exposed to long-term ambient air pollution (To et al., 2015; Beckerman et al., 2012). In addition, it may trigger tissue-specific inflammation (Mostafavi et al., 2015; Brook et al., 2010). Previous studies have reported that exposure to air pollutants increases the levels of interleukin-6 and tumor necrosis factors (Ljungman et al., 2009; Panasevich et al., 2009). Rheumatoid arthritis (RA) is a chronic disorder of inflammation that targets joints and cartilages and leads to severe disability (Lawrence et al., 1998; Alamanos and Drosos, 2005). Although the pathogenic mechanisms of RA remain unclear, genetic factor is a risk factor for RA. Several studies have suggested that a specific genotype may increase the risk of RA (Shen et al., 2015; Solus et al., 2015). Furthermore, epidemiological evidence indicates a significant association between the risk of RA and exposure to environmental factors, such as cigarette smoking, dioxin, noise, and traffic-related air pollution (Kobayashi et al., 2008; Hart et al., 2009; De Roos et al., 2014; Costenbader et al., 2006). A Mexican study reported a marginally higher level of inflammatory mediators in Mexico City children who were exposed to air pollution than in those who were not (Calderon-Garciduenas et al., 2013). An animal study reported that co-exposure to several air pollutants caused abnormal myocardial mitochondria, inflammatory cell infiltration, and endothelial dysfunction (Zhang et al., 2015). Nonetheless, the association between environmental factors, such as air pollution and the risk of RA, remains debatable (Essouma and Noubiap, 2015). Therefore, we conducted this nationwide, retrospective study to evaluate the effect of air pollution exposure on the risk of RA.

2. Methods and materials

2.1. Data source

We collected data from the Longitudinal Health Insurance Database (LHID), maintained by the Taiwan Bureau of National Health Insurance, and the Taiwan Air Quality-Monitoring Database (TAQMD), released by the Taiwan Environmental Protection Agency (EPA), Executive Yuan. The LHID contains data of one million insurants randomly selected from the registry of beneficiaries covered by the Taiwan National Health Insurance (NHI) program before the year 2000. The NHI covers over 99% of the residents in Taiwan (Database NHIR, 2015). The LHID includes data of all inpatient claims, outpatient claims, and medical treatment records of each insurant from 1996 to 2010. The identification numbers of all insurants are coded to protect their privacy. The diseases are coded in the LHID according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

The TAQMD contains the daily concentrations of particulate matter with the aerodynamic diameter <2.5 μm ($PM_{2.5}$) and nitrogen dioxide (NO_2). Those data were collected from 74 ambient air quality-monitoring stations distributed all over Taiwan during 1998–2010. The LHID and TAQMD were linked according to the residential areas of insurants and the areas where the air quality-monitoring stations were located. A residential area was defined according to the location of the clinic and hospital that treated acute upper respiratory tract infections (ICD-9-CM code 460).

2.2. Study population, endpoints, and confounding factors

People residing in the area where an air quality-monitoring station was located and those covered by the NHI before 1998 were selected as the study population. People with a history of RA (ICD-9-CM code 714) before 2000 were excluded. All participants were followed from January 1, 2000 until the diagnosis of RA withdrawal from the NHI, or December 31, 2010. The confounding factors were age, sex, urbanization level of residence, monthly income, and chronic obstructive pulmonary disease (COPD; ICD-9-CM codes 490–496). Residential areas were classified into 7 levels based on Liu's report; level 1 represented the area with the highest urbanization level and level 7 represented the area with the lowest one. Monthly income was classified into 4 groups; <NT$14,400, NT$14,400–18,300, NT$18,301–21,000, and >NT$21,000.

2.3. Exposure measurement

A yearly average air pollutant concentration was calculated by dividing the cumulative daily air pollutant concentration by the duration from 1998 to the endpoint for each study participant. In this study, the mean and median follow years in RA patients were 5.78 and 5.76, respectively (data not shown). The yearly average air pollutant concentrations were categorized into 4 groups based on quartiles. $PM_{2.5}$ concentration was categorized as Q1 (<10,760 μm/m^3), Q2 (10,760–12,161 μm/m^3), Q3 (12,162–15,056 μm/m^3), and Q4 (>15,056 μm/m^3). NO_2 concentration was categorized as Q1 (<66,213 ppm), Q2 (66,213–86,098 ppm), Q3 (86,099–99,882 ppm), and Q4 (>99,882 ppm).

2.4. Ethics statement

Personal information of patients are encrypted by the NHIRD to protect privacy and provide anonymous identification numbers associated with relevant patients' information, such as date of birth, sex, medical services received and prescriptions. This study was approved to fulfill the condition for exemption by the Institutional Review Board (IRB) of China Medical University (CMUH-104-REC2-115). The IRB has also specifically waived the consent requirement.

2.5. Statistical analysis

All analyses were conducted using SAS software Version 9.4 (SAS Institute Inc., Cary, NC, USA), and the significance level was set at a 2-tailed $P < 0.05$. The chi-squared test was used to analyze the differences in sex, urbanization level, monthly income, history of COPD, and incidence of RA. ANOVA was used to analyze average age differences. The incidence of RA (per 10,000 person-years) was calculated for 4 levels of air pollutant concentrations. Cox proportional hazard regression analysis was used to assess the risk of RA in participants living in residential areas corresponding to the Q2–Q4 levels of air pollutant concentrations compared with those living in residential areas corresponding to the Q1 level of air pollutant concentrations. A multivariate Cox proportional hazard regression model was used to adjust for sex, age, monthly income, urbanization level and COPD.

3. Results

A total of 244,413 participants with $PM_{2.5}$ concentration data and 247,419 participants with NO_2 concentration data were analyzed. The mean and median follow years in RA patients were 5.78 and 5.76, respectively (data not shown). Table 1 shows the baseline characteristics of participants exposed to 4 levels of $PM_{2.5}$ concentration. Compared with the participants exposed to the Q1, Q2, and Q3 levels of $PM_{2.5}$ concentration, those exposed to the Q4 level were marginally the oldest, comprised majorly men, involved the least prevalence of RA, and exhibited the highest prevalence of COPD. The most highly urbanized towns exhibited a Q1 level of $PM_{2.5}$ concentration. The distributions of urbanization levels and insurance fees were similar. Compared with the participants exposed to the Q2, Q3, and Q4 levels of NO_2 concentration, those exposed to the Q1 level were youngest and exhibited the least prevalence of RA and highest prevalence of COPD (Table 2). Participants exposed to the Q4 level of NO_2 concentration reported the highest insurance fees and resided in the most highly urbanized towns. Table 3 presents the associations between pollutants levels and the risk of RA.

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