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Original Article

Acute effects of ambient temperature and particulate air pollution on fractional exhaled nitric oxide: A panel study among diabetic patients in Shanghai, China

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ABSTRACT

Background: Epidemiological studies have shown the associations of ambient temperature and particulate matter (PM) air pollution with respiratory morbidity and mortality. However, the underlying mechanisms have not been well characterized. The aim of this study is to investigate the associations of temperature and fine and coarse PM with fractional exhaled nitric oxide (FeNO), a well-established biomarker of respiratory inflammation.

Methods: We conducted a longitudinal panel study involving six repeated FeNO tests among 33 type 2 diabetes mellitus patients from April to June 2013 in Shanghai, China. Hourly temperature and PM concentrations were obtained from a nearby fixed-site monitoring station. We then explored the associations between temperature, PM, and FeNO using linear mixed-effect models incorporated with distributed lag nonlinear models for the lagged and nonlinear associations. The interactions between temperature and PM were evaluated using stratification analyses.

Results: We found that both low and high temperature, as well as increased fine and coarse PM, were significantly associated with FeNO. The cumulative relative risk of FeNO was 1.75% (95% confidence interval [CI], 1.04–2.94) comparing 15 °C to the referent temperature (24 °C) over lags 0–9 days. A 10 μg/m^3 increase in fine and coarse PM concentrations were associated with 1.18% (95% CI, 0.18–2.20) and 1.85% (95% CI, 0.62–3.09) FeNO in lag 0–1 days, respectively. PM had stronger effects on cool days than on warm days.

Conclusions: This study suggested low ambient temperature, fine PM, and coarse PM might elevate the levels of respiratory inflammation. Our findings may help understand the epidemiological evidence linking temperature, particulate air pollution, and respiratory health.

Introduction

A number of epidemiological studies have linked short-term variations in temperature and particulate matter (PM) air pollution with respiratory morbidity and mortality.[1,2] However, the underlying mechanisms responsible for these associations have not been well characterized. Inflammation constitutes a key pathway in the development and exacerbations of respiratory diseases. Fractional exhaled nitric oxide (FeNO) is recommended by the American Thoracic Society as a non-invasive biomarker of airway inflammation and has been widely used in clinical practice and epidemiological studies of respiratory diseases.[3–5]

FeNO has been associated with PM exposure in China and other parts of the world.[6–10] Previous investigators have proposed that PM's effects increase with smaller sizes.[11] However, recent toxicological studies suggested a greater inflammatory potential in the

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coarse fraction of PM ($PM_{10-2.5}$) than in the fine fraction of PM ($PM_{2.5}$),[12,13] and few population-based studies has evaluated the effects of $PM_{10-2.5}$ on FeNO. On the other hand, to the best of our knowledge, there were no studies investigating the association between ambient temperature and FeNO, leading to a lack of biological support to the observed association between temperature variations and respiratory mortality and morbidity.

Therefore, we conducted a longitudinal panel study to investigate the associations of ambient temperature, $PM_{2.5}$, and $PM_{10-2.5}$ with FeNO in a group of type 2 diabetes mellitus (T2DM) patients in Shanghai, China. Diabetes patients were selected because they have been found in previous studies to be particularly vulnerable to ambient stimulus due to their inherent high inflammatory state.[14–18]

Methods

Subjects and study design

A total of 35 T2DM patients were recruited from an urban community (Tianping) of Shanghai, which has an area of 2.6 km^2 and a population of 86,000. Only doctor-diagnosed T2DM patients who had a permanent residence in Tianping Community were recruited in this study.[19] We excluded those who were current active or passive smokers (at home), had an alcohol drinking habit, or were experiencing apparent cardiopulmonary comorbidities.[20–22]

Six follow-up visits were conducted every 2 weeks in Tianping Community Health Service Center during April to June of 2013 to capture day-to-day variations in both environmental and health indicators. For each participant, we scheduled health examinations at the same time of the day and in the same day of the week to avoid possible temporal variations. Baseline information, including age, sex, income, duration of T2DM, medication use, oral supplements, fast and postprandial blood glucose, and anti-diabetic medication, was collected using self-administered questionnaires. Height and weight were measured at the first follow-up to calculate the body mass index (BMI). We also asked all participants to recall their occupational exposure to PM, and to record any changes in medications and whether they went out of the central urban areas of Shanghai during the study period.

FeNO measurements

The FeNO measurements were obtained using a portable NIOX MINO machine (Aerocrine AB, Solna, Sweden) according to the standardized procedures by the American Thoracic Society.[3] Briefly, subjects were required to sit quietly, rinse the mouth twice with purified drinking water, and then empty theirs lungs by complete expiration. After that, they inhaled nitric oxide-free air to the lung capacity through a disposable filter attached in the machine. Finally, they exhaled the air through the machine at an exhalation rate of 50 ± 5 mL/s. The standard mode of 10-second exhalation time was used in all tests. To maintain a stable flow during exhalation, the participants were guided by an exhalation flow-driven animation. Quality control was automatically performed, and the device would not display a reading if the subject exhaled at a flow rate below or above the required speed. All our participants were asked to avoid eating and drinking for at least 1 h before the test.

Exposure measurements

We obtained hourly concentrations of $PM_{2.5}$ and PM_{10} from a fixed-site air quality monitoring station, which was approximately 2.5 km away from the Tianping community. We calculated the real-time concentrations of $PM_{10-2.5}$ by subtracting $PM_{2.5}$ from PM_{10} concentrations measured in the same hours. Both $PM_{2.5}$ and PM_{10} were measured using the tapered element oscillating microbalance method. According to the rules of Chinese government, the location of this monitor is mandated not to be in the direct vicinity of traffic or industrial sources; not to be influenced by local pollution sources; and to avoid buildings, housing, and large emitters such as coal-, waste-, or oil-burning boilers, furnaces, and incinerators. Likewise, there were no apparent emission sources, such as industry and trunk roads, within and around this urban community. Therefore, the monitoring data may well represent the background air pollution level in urban Shanghai, as well as the general exposure levels of the study participants.

Hourly temperature and relative humidity data were derived from a monitoring station of Shanghai Meteorology Bureau, which was approximately 2 km from this community.

Statistical analysis

Environmental exposure data were linked with FeNO values for each participant by the time of each test. We used mixed-effects models combined with the distributed lag nonlinear model (DLNM) to estimate the short–term associations of temperature and PM with FeNO levels. The mixed-effects model allows each participant to serve as his or her own control and allows adjustment of variations in repeated measurements for the same subject. The DLNM has the advantage of accounting for the possibly nonlinear effects of an exposure and the colinearity of different lags.[23,24] FeNO levels were naturally log-transformed because they were right skewed, and they were then introduced into the model as a dependent variable.

Briefly, we first built the cross-basis functions in each DLNM for temperature and PM. We used a natural cubic spline function with three equally spaced internal knots for temperature and a linear function for PM in the exposure-response functions. We introduced a natural cubic spline function with two internal knots at equally spaced log-values of lags in the cross-basis functions. The referent for temperature was set as the point with minimum effects on FeNO, and the referent for PM was set as the lowest concentrations during the study period. Thereafter, we incorporated the cross-basis functions in the mixed-effect models, with adjustment for individual characteristics (i.e., age, sex, BMI, income, and duration of diabetes), relative humidity, temperature (for PM models), and day of the week. Finally, a random intercept for each subject was added to account for correlations among multiple repeated measurements. In order to explore the lag structures, we used a maximum lag up to 10 days for temperature and up to 7 days for PM. We also performed a sensitivity test for all 198 FeNO measurements collected during the study period from 33 participants by adjusting the calendar days for seasonality in basic models of temperature and PM, separately.

In order to evaluate the potential modifying effect of temperature in the association between PM and FeNO, we conducted a stratified analysis by dichotomizing the study period into warm and cool days and then examining the associations between $PM_{2.5}$ or $PM_{10-2.5}$ and FeNO using the above models.

All statistical tests were two-sided, and p-values <0.05 were considered statistically significant. The models were constructed in R software (Version 3.2.0, R Foundation for Statistical Computing, Vienna, Austria) with the packages '*lme4*' and '*dlnm*'. The results for temperatures were presented as the relative risks (RRs) comparing a given temperature to the referent temperature because a nonlinear relationship was hypothesized. The results for temperatures were presented as RRs of FeNO comparing a given value to the referent temperature. The results for PM were presented as