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Particulate air pollution and circulating biomarkers among type 2 diabetic mellitus patients: the roles of particle size and time windows of exposure

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ABSTRACT

Background: Short-term associations between size-fractionated particulate matter (PM) air pollution and circulating biomarkers are not well established, especially among diabetes patients.
Methods: We conducted a longitudinal panel study involving 6 repeated measurements of 12 circulating biomarkers among 35 diabetes patients from April to June, 2013 in Shanghai, China. Real-time number and mass concentrations of PM with multiple size fractions between 0.25 and 10 μm were measured. Linear mixed-effect models were used to explore the associations between size-fractionated PM concentrations and blood biomarkers at different time windows.
Results: Short-term exposure to PM was significantly associated with elevated levels of 5 biomarkers of inflammation, 3 biomarkers of coagulation and 1 vasoconstrictor. The effects varied considerably by particle size and time windows. Overall, PM with smaller size had stronger associations, and the most significant size fractions were 0.25–0.40 μm. Even 2 h exposure to PM can lead to a significant increase in biomarkers. The effects on biomarkers of inflammation and vasoconstriction were restricted to the first 12 h after exposure, but the effects on coagulation persisted for 24–72 h. For example, an interquartile range increase in 2 h average exposure to $PM_{0.25–0.40}$ was associated with 6–20% increase in biomarkers of inflammation, 19–38% in coagulation and 17% in vasoconstriction. PM had a stronger effect among male patients than female patients.
Conclusions: Our results provided important evidence on the roles of the size and time windows of exposure in the PM-mediated effects on circulating biomarkers of inflammation, coagulation and vasoconstriction in diabetes patients in China.

1. Introduction

It is estimated that there are currently 382 million people living with diabetes around the world, and this number is expected to rise to 592 million by 2035 (Guariguata et al., 2014; WHO, 2014). Type 2 diabetes mellitus (T2DM) represents approximately 90% of diabetic patients. According to the Global Burden of Disease Study 2010, high fasting plasma glucose has been ranked as the 6th leading risk factor, which accounted for 3.4 million deaths in 2010 (Lim et al., 2012). Recently, a growing body of literature suggested that T2DM might increase susceptibility to the hazardous health effects of PM, however, the mechanism is not clear (Dubowsky et al., 2006). Potential pathways linking PM with T2DM may be proposed by examining the circulating biomarkers of inflammation, coagulation and vasoconstriction that may be involved in both the development of T2DM and PM-mediated health effects (O'Neill et al., 2007). Therefore, it is of interest to explore the effects of PM on these blood biomarkers in such a susceptible subgroup.

Furthermore, PM size may be a key determining factor for the observed health effects as its deposition in the respiratory tract, reaction surface area and chemical composition may vary by different size ranges (Leitte et al., 2011). However, only PM less than 10 μm (PM_{10}) and less than 2.5 μm ($PM_{2.5}$) are extensively

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examined in previous literature. Even so, the evidence is still limited and inconsistent regarding which specific size fractions have the strongest health effects (Adar et al., 2014). In addition, the physiological response to PM exposure involving stimulation, synthesis and secretion of different blood biomarkers takes different time to reach its peak. Consequently, different time windows required for a change in levels in response to an exposure would be expected for different biomarkers.

China is facing a rapid increase in the prevalence of diabetes (Guariguata et al., 2014). Among Chinese adults, the estimated prevalence of diabetes and prediabetes were 11.6% and 50.1% in 2010, respectively. This high prevalence highlights the importance of diabetes as a very important public health concern in China (Xu et al., 2013). Besides, China is also experiencing severe air pollution problems (Kan et al., 2012). Therefore, it has been of great significance, both from a public health viewpoint and from an environmental regulatory perspective, to understand the roles of particle size and time windows of exposure in the associations between PM exposure and circulating biomarkers. Therefore, we conducted an epidemiological panel study involving real-time monitoring of size-fractionated PM concentrations and 6 repeated measurements of 12 blood biomarkers among T2DM patients in Shanghai, China.

2. Material and methods

2.1. Study design and subjects

We recruited 35 T2DM patients from Tianping Community, which is located in a central urban district of Shanghai with a total area of 2.6 km^2 and a population of 86,000. All participants had to meet the following inclusion criteria: (1) doctor-diagnosed T2DM; (2) permanent residence address in Tianping Community; and (3) a history of regular and stable medication of hypoglycemic drugs in the past year. Exclusion criteria were current active or passive smoking, and experiencing apparent infection or severe comorbidities.

Between April 13th and June 30th 2013, 6 repeated follow-ups were scheduled every 2 weeks. The subjects were randomly divided into 4 subgroups and were invited to take part in the body examinations on weekends in each of 2-week interval (6 times in total) to capture day-to-day variations in levels of PM and biomarkers. For each follow-up, the body examinations were arranged at the same day time (8:30 a.m. to 10:00 a.m.) to control for possible circadian rhythm of biomarkers. Body examinations were performed at the Tianping Community Health Center (TCHC). Specifically, data on height, weight, fasting blood glucose levels, as well as individual information (age, sex, income, education, duration of T2DM, medication use, oral supplements) were collected during the first visit. Blood draws were made by certified nurses at the TCHC. Study subjects were also asked to record any change in medications and whether they went out of the central urban areas of Shanghai during the study period. The study protocol was approved by the Institutional Review Board in the School of Public Health, Fudan University. We obtained written consent forms from all participants.

2.2. Blood analyzes

For each follow-up, peripheral blood samples (5 ml) were drawn and kept in water bath (37 °C) for 10 min. Then, these blood samples were centrifuged at 4000 rpm for 10 min. The serum was extracted and transferred into 1 ml microtube (Nunc, Naperville, IL, USA). All procedures were completed within 30 min after blood withdrawal to minimize in-vitro changes in biomarkers. Lastly, these samples were immediately transferred to our laboratory and stored at −80 °C.

The following 3 categories of circulating biomarkers were analyzed: (1) inflammation: C-reactive protein (CRP), P-selectin, vascular cell adhesion modecule-1 (VCAM-1), interleukin-1b (IL-1b), interleukin-10 (IL-10), tumor necrosis factor-α (TNF-α), intercellular adhesion molecule-1 (ICAM-1); (2) coagulation: fibrinogen, plasminogen activator inhibitor-1 (PAI-1), von Willebrand factor (vWF), soluble CD40 ligand (sCD40L); and (3) vasoconstriction: endothelin-1 (ET-1). All the aforementioned markers have been linked with PM in previous population-based studies.

All biomarkers were analyzed by commercial Millpore MILLIPLEX™ MAP human cytokine/chemokine kit (Millipore Corp., Billerica, MA), which is based on the Luminex® xMAP® technology. The level for each biomarker was simultaneously quantified using the MagPix system and xPONENT software (Luminex). All cytokines tests were performed according to the manufacturer's instructions, and all results were found to fall within the quality control ranges.

2.3. Exposure measurements

Real-time data of ambient PM were obtained from an automatic continuous monitoring system (the Environmental Dust Monitor 365, GRIMM, Grimm Aerosol Technik GmbH & Co. KG, Ainring, Germany) installed on the rooftop of a six-floor building (18 m high) of TCHC. We measured hourly particle number concentrations (PNCs) with size distributions between 0.25 μm and 10 μm (23 different size channels). Considering the very small number concentrations for particles >1 μm, we alternatively analyzed particle mass concentration (PMC) for those >1 μm in our analysis. Therefore, we obtained hourly mean PNCs of the following size fractions (Meng et al., 2013): $PNC_{0.25-0.28}$, $PNC_{0.28-0.30}$, $PNC_{0.30-0.35}$, $PNC_{0.35-0.40}$, $PNC_{0.40-0.45}$, $PNC_{0.45-0.50}$, $PNC_{0.50-0.65}$ and $PNC_{0.65-1.0}$. For PMCs, we derived real-time concentrations of PM_{10} and $PM_{2.5}$ from the nearest state-owned air quality monitoring station that was about 2.5 km away from the TCHC. We calculated $PM_{2.5-10}$ by subtracting $PM_{2.5}$ from PM_{10}. To allow for the adjustment for gaseous pollutants, we also derived hourly data for sulfur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO) and ozone (O_3) from the same station.

We also obtained daily mean temperature and relative humidity from a meteorological station 2 km away from the TCHC.

2.4. Statistical analysis

Environmental and individual data were merged by the time of blood draw. We used linear mixed-effect models to evaluate the associations between PM concentrations and circulating biomarkers (Verbeke and Molenberghs, 2009). This model allows each subject to serve as his/her control over time and has the advantage of accounting for correlations among multiple repeated measurements collected per person by including a random intercept for each subject (Dubowsky et al., 2006). Before statistical analysis, the levels of biomarkers were log-transformed because they were highly skewed. Then, size-fractionated PNC or PMC was incorporated as the fixed-effect term.

In the basic model, we included several covariates as fixed-effect terms: (1) an indicator variable of “month” of blood sampling to exclude monthly trends in these biomarkers; (2) an indicator variable for “day of the week”; (3) the moving average of mean temperature and relative humidity on the concurrent day and previous 3 days to control for the confounding effects of weather conditions (Schauble et al., 2012); (4) individual characteristics including age, sex, body mass index, income, duration of T2DM and baseline levels of fasting blood glucose; (5) binary variables