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Respiratory Inflammation and Short-Term Ambient Air Pollution Exposures in Adult Beijing Residents with and without Prediabetes: A Panel Study

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Background: Accumulating evidence suggests that individuals with glucose metabolism disorders are susceptible to mortality associated with fine particles. However, the mechanisms remain largely unknown.

Objectives: We examined whether particle-associated respiratory inflammation differed between individuals with prediabetes and healthy control participants.

Methods: Based on a panel study [A prospective Study COmparing the cardiometabolic and respiratory effects of air Pollution Exposure on healthy and prediabetic individuals (SCOPE)] conducted in Beijing between August 2013 and February 2015, fractional exhaled nitric oxide (FeNO) was measured from 112 participants at two to seven visits to indicate respiratory inflammation. Particulate pollutants—including particulate matter with an aerodynamic diameter of $\leq$2.5 μm ($PM_{2.5}$), black carbon (BC), ultrafine particles (UFPs), and accumulated-mode particles—were monitored continuously at a single central monitoring site. Linear mixed-effects models were used to estimate associations between ln-FeNO with pollutant concentrations at individual 1-h lags (up to 24 h) and with average concentrations at 8 and 24 h before the clinical visit. We evaluated glucose metabolism disorders as a potential modifier by comparing associations between participants with high vs. low average fasting blood glucose (FBG) and homeostasis model assessment insulin resistance (HOMA-IR) levels.

Results: FeNO was positively associated with all pollutants, with the strongest associations for an interquartile range increase in 1-h lagged exposures (ranging from 21.3% for $PM_{2.5}$ to 74.7% for BC). Associations differed significantly according to average HOMA-IR values when lagged 6–18 h for $PM_{2.5}$, 15–19 h for BC, and 6–15 h for UFPs, with positive associations among those with HOMA-IR $\geq$1.6 while associations were closer to the null or inverse among those with HOMA-IR <1.6. Associations between $PM_{2.5}$ and FeNO were consistently higher among individuals with average FBG $\geq$6.1 mmol/L vs. low FBG, with significant differences for multiple hourly lags.

Discussion: Glucose metabolism disorders may aggravate respiratory inflammation following exposure to ambient particulate matter. https://doi.org/10.1289/EHP4906

Introduction

Short- and long-term exposures to fine particles in ambient air have been associated with adverse health outcomes ranging from subclinical changes in cardiopulmonary biomarkers to premature mortality and morbidity (Brook et al. 2010; Pope and Dockery 2006; Yang et al. 2013). However, estimated effects vary, with some populations, such as children and the elderly, showing evidence of greater susceptibility (Pope and Dockery 2006; Yang et al. 2013). Patients with glucose metabolism disorders also may have increased susceptibility to adverse effects of air pollution exposure (Dubowsky et al. 2006; Chen and Schwartz 2008; Sade et al. 2015; Zanobetti and Schwartz 2002; O'Neill et al. 2005; Zeka et al. 2006), although the underlying mechanisms remain unclear (Khafaie et al. 2016).

Respiratory inflammation is a critical step in the biological mechanism underlying the cardiorespiratory effects of fine particle exposure (Brook et al. 2010). Individuals with diabetes are at higher risk of respiratory mortality and morbidity than people without diabetes (Zineldin et al. 2015; Fuso et al. 2012; Abd El-Azeem et al. 2013; Colbay et al. 2015; Klekotka et al. 2015; Alraei and Ziegler 2014). Some studies have also suggested the occurrence of more severe respiratory inflammation following particle exposure in animal models of diabetes mellitus (DM) than in the normal animals (Mo et al. 2009; Nemmar et al. 2013). These findings suggest that respiratory inflammation in individuals with diabetes may be related to enhanced susceptibility to particle-associated health effects (Dubowsky et al. 2006; Chen and Schwartz 2008; Zeka et al. 2006; O'Neill et al. 2005; Brook et al. 2010). However, few studies have examined the potential influence of abnormal glucose metabolism on respiratory inflammation in response to air pollution (Han et al. 2016; Hao et al. 2017).

Fractional exhaled nitric oxide (FeNO) is a noninvasive biomarker produced by a variety of airway cell types, including macrophages and epithelial cells, that is commonly used to assess respiratory inflammation caused by air pollution (Lin et al. 2011; Huang et al. 2012; Cornell et al. 2012; Delfino et al. 2006). Previous studies have reported that associations between FeNO and exposure to fine particles vary depending on particle sizes and chemical constituents (Han et al. 2016; Lin et al. 2011; Chen et al. 2015; Gong et al. 2014).

The present analysis was based on a panel study [A prospective Study COmparing the cardiometabolic and respiratory effects of air Pollution Exposure on healthy and prediabetic individuals (SCOPE)] conducted in Beijing, China, that recruited both healthy and prediabetic participants (Wang et al. 2018). Prediabetes typically presents with insulin resistance (IR), β-cell dysfunction, and

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high levels of fasting blood glucose (FBG), which is associated with high risk for some inflammatory diseases (Donath and Shoelson 2011; Tabák et al. 2012; Pickering et al. 2018). A national survey of Chinese adults reported that the prevalence of prediabetes ($6.1 \leq \text{FBG} < 7.0$ mmol/L) was much higher than that of diabetes (15.5% vs. 9.7%, respectively) (Yang et al. 2010). In the present study, we used FBG and IR to evaluate glucose metabolism in each individual, and we examined whether associations between acute respiratory inflammation (as indicated by FeNO) and short-term exposures to air pollutants—including particulate matter with an aerodynamic diameter of ≤ 2.5 μm ($PM_{2.5}$), black carbon (BC), ultrafine particles (UFPs), and accumulated-mode (Acc) particles—were modified by prediabetic status.

Methods

Study Design and Participants

Participant recruitment and study design for the SCOPE study is described in detail elsewhere (Wang et al. 2018). Briefly, SCOPE was a panel study launched between August 2013 and February 2015 that enrolled 60 prediabetic participants ($6.1 \leq \text{FBG} < 7.0$ mmol/L) and 60 healthy control participants (FBG < 6.1 mmol/L) identified based on the results of their annual health examination in the previous year. The participants were nonsmokers or had quit smoking more than 3 y previously, between 50 and 65 years of age, without a family history of diabetes, and living in communities within 10 km of the air pollution monitoring site. Male:female ratio, percentage of participants with a monthly salary of ≥8,000 Chinese Yuan Renminbi (CNY), and percentage of participants with at least a high school degree were matched between prediabetes and control groups. All participants were required to complete a baseline questionnaire at enrollment regarding their age, sex, income, education, medication use, disease history, dietary and commuting habits, residential location, and smoking history (nonsmoker vs. former smoker). In addition, all participants completed between two and seven follow-up visits to the Peking University Hospital (Beijing, China) with at least 1 month between consecutive visits. The study was approved by the institutional review board (IRB 0000105213024) of Peking University Health Sciences Centre, and written consent was obtained from all participants.

Eight participants were excluded from analyses because they resumed smoking during the follow-up period. To better represent the glucose metabolism status of each participant throughout the study period, we recategorized the remaining 112 individuals into high- and low-FBG groups based on their average FBG level analyzed across repeated visits, using a cutoff value of 6.1 mmol/L. According to the 1999 World Health Organization diagnostic criteria, $6.1 \leq \text{FBG} < 7.0$ mmol/L and ≥7.0 mmol/L of FBG were chosen to characterize prediabetes and diabetes, respectively (WHO 1999). The 112 participants were also split into high- and low-IR groups based on their average homeostasis model assessment IR (HOMA-IR), using a median measurement of 1.6 as a cutoff value.

Hourly concentrations of ambient $PM_{2.5}$, BC, UFPs, Acc particles, and meteorological parameters [temperature and relative humidity (RH)] were measured using instruments located on the roof of an 18-m–high building at Peking University (PKU site, Beijing, China) (Wang et al. 2018). The PKU site is located in an educational and residential district without major emission sources nearby, and ambient fine particles during the study period were mainly attributed to industrial and secondary pollution sources (Zhang et al. 2013). Participants were asked to fast for at least 8 h before each clinic visit. During each visit, participants rested for 10 min and completed a short questionnaire with sections on sleeping habits, alcohol and food intake, medication use, passive smoke exposure (>0.5 h), and acute respiratory disease over the previous 3 d. Clinical examinations were started at 0800 hours. Serum samples were first collected in pro-coagulation tubes by trained nurses and then placed immediately in ice-filled boxes. FeNO was measured immediately after the serum collection, before 0900 hours.

Exposure Assessment

The mass concentration of $PM_{2.5}$ was monitored at a 1-h resolution using a tapered element oscillating microbalance (TEOM; RP1400a instrument; Thermo Scientific). The particle number concentration in the size range 5.6–560 nm was monitored with a 1-min resolution using 32 size channels on a fast mobility particle sizer (FMPS; Model 3,091; TSI). In each size range, the FMPS provides a normalized concentration (NC) calculated as $NC = dN/(\log D_u - \log D_l)$, where dN, D_u, and D_l are the number concentration, and the largest and smallest diameters of particles in the corresponding channel, respectively. The number concentrations in 32 size ranges were calculated as $dN = NC \times (\log D_u - \log D_l)$ and accumulated into the number concentration of UFPs (5.6–93.1 nm) and Acc particles (93.1–560 nm).

The mass concentration of BC was monitored with a 5-min resolution, using a multi-angle absorption photometer (MAAP; Model 5012; Thermo Scientific). Temperature and RH were monitored using a weather station attached to a four-channel aerosol sampler (TH-16A; Tianhong). All instruments were self-calibrated weekly. The FMPS was maintained weekly for cleaning of the sampling inlets, the high-voltage electrode, and the electric column during calibration.

Health Measurements

To obtain FeNO samples, the participants were asked to inhale through activated carbon to remove ambient nitric oxide and to exhale into individual aluminum bags at a flow rate of 150 L/h at a positive pressure of 13 cmH_2O. The nitric oxide concentrations in the samples were analyzed using a calibrated chemiluminescence nitrogen oxide analyzer (Model 42i; Thermo Scientific). Serum levels of FBG and fasting plasma insulin (FINS) were measured with an Olympus AU2700 biochemistry analyzer at Peking University Hospital. HOMA-IR was calculated using the levels of FBG and FINS ($\text{HOMA-IR} = \text{FBG} \times \text{FINS}/22.5$) to estimate the basal insulin sensitivity (Levy et al. 1998). Weight was measured for each participant using a weighing scale (HBF-358-BW; Omron Healthcare, Inc.), and height was measured using a meter stick. Body mass index (BMI) was calculated as the weight divided by the square of the height.

Statistical Analyses

Linear mixed-effect (LME) models were used to estimate associations between FeNO and exposure to each measured pollutant, and fixed and random effects were estimated using the restricted maximum likelihood method. Random participant-specific intercepts were used to control for within-participant variation among the repeated measurements, but random slopes were not considered. The dependent variable, FeNO, was ln-transformed because of its right-skewed distribution. The independent variables were the concentrations of air pollutants, including $PM_{2.5}$ and BC, and number concentrations of UFPs and Acc particles. In LME models, we examined the differences in FeNO associated with air pollutant concentrations at hourly lags (1–24 h), and 8 and 24 h average concentrations prior to the starting time of visits (8 h and 24 h ACPV, respectively). All models were adjusted for day of the week, sex, age (continuous), and smoking history (nonsmoker vs. former smoker). We modeled daily average temperature and RH on the day before the visit and averaged up to 7 d before each clinic visit using natural cubic splines with ≤3 degrees of freedom (df). We

used the Akaike information criterion to select the final models, which included temperature on the previous day (as a simple continuous variable) and average RH during the 7 d before the visit (natural cubic spline with 3 df).

Analyses to assess modification by glucose status were performed by modeling product interaction terms between individual exposures and dichotomous terms for high or low FBG or HOMA-IR, respectively, in addition to lower-order terms. *p*-Values for the product terms were used to test differences in associations between each group.

In sensitivity analyses, single-pollutant LME models were used to evaluate whether the exposure–response associations changed after further adjustment for variables collected from baseline (fixed) or follow-up (time-varying) questionnaire, including self-reported hypoglycemic drug use, BMI, income (<2,000 vs. 2,000–5,000 vs. 5,000–8,000 vs. >8,000 CNY), education (≥senior vs. ≤junior high school degree), sleeping hours at night, commuting habits (walking or bicycle vs. car or public transit), alcohol and irritating food (barbecue, pickled food, seafood, hotpot, and preservative-containing food) intake, passive smoke exposure (>0.5 h vs. ≤0.5 h), chronic (asthma and chronic obstructive pulmonary disease) and acute (flue, cold, acute laryngopharyngitis, and acute bronchitis) respiratory disease, and living distance from home to monitor (continuous). Two other sensitivity analyses were also conducted: The first limited the analyses to study visits with complete data for all four pollutants, and the second was limited to subgroups of participants with at least three visits. In addition, we used distributed lag models (DLMs) to simultaneously estimate effects over multiple hourly lags, with the lag–response function modeled as a third-degree polynomial and a linear association between each pollutant and ln-transformed FeNO. For each pollutant, we used the lowest concentration measured during the study period as the reference (threshold) value. In addition, we ran two-pollutant LME models for each pairwise combination of the four pollutants at lag 1 h, and derived variance inflation factors to assess collinearity between the paired pollutants.

Results from the LME models are reported as the estimated percentage difference in FeNO with an interquartile range (IQR) increase in each pollutant, with lag-specific IQRs derived according to the distribution at each hourly lag. Statistical significance was considered at $p < 0.05$. All data analyses were performed using R statistical software (version 3.1; R Development Core Team).

Results

In total, 112 participants completed 547 clinical visits (Table 1). The majority of participants were female (62%), had a high school education or above (88%), and a monthly salary of <8,000 CNY (64%). Only 3% reported chronic respiratory disease and 12% were former smokers. About half reported that they preferred to commute on foot or bicycle. Acute respiratory disease during the previous 3 d was reported before 14% of visits (77 visits, 53 participants). There were relatively few reports of exposure to secondhand smoke >0.5 h (80 visits, 17 participants) or alcohol use (76 visits, 41 participants) before study visits, whereas consumption of irritating food was reported before half of all of visits (104 participants). Nine participants who were diagnosed with diabetes during the follow-up reported using hypoglycemic drugs before some study visit (22 visits total).

Although SCOPE participants ($n = 120$) were initially selected to include equal numbers of prediabetic ($6.1 \le$ FBG < 7.0 mmol/L) and normal FBG (<6.1 mmol/L) participants at baseline (Wang et al. 2018), only 33% of participants in the present analysis were classified as high FBG based on values averaged over all study visits while 53% ($n = 59$) were classified as high HOMA-IR based on average values (see Table S1). When jointly classified by FBG and HOMA-IR, 38% were low for both, 24% were high for both, 29% were high HOMA-IR and low FBG, and 8.9% were low HOMA-IR and high FBG. The numbers of visits followed a similar joint distribution. Of the 37 participants classified as high FBG based on average values, 17 had FBG ≥6.1 mmol/L at all of their study visits (69 visits), and 20 had elevated FBG in only a subset of their 106 study visits (see Table S2). Sixteen participants in the high-FBG group were diagnosed with diabetes during the follow-up. Of the 59 classified as high IR based on average values, 33 had HOMA-IR ≥1.6 at all of their study visits (136 visits), and 26 had elevated HOMA-IR in only a subset of their 145 study visits.

Table 1. Characteristics of the study participants at baseline and averaged over multiple study visits.

Data source	Characteristics	*N* (%)	Mean ± SD	Range
Baseline questionnaire at enrollment ($N = 112$)	Age (y)	112 (100)	57 ± 4	50–65
	Home distance to monitor (km)	109 (97)	2.2 ± 3.2	0–8.4
	Sex			
	Male	43 (38)		
	Female	69 (62)		
	Chronic respiratory disease[a]			
	Yes	3 (3)		
	No	109 (97)		
	Smoking history[b]			
	Yes	13 (12)		
	No	99 (88)		
	Monthly salary ≥8,000 CNY			
	Yes	40 (36)		
	No	72 (64)		
	High school or above			
	Yes	99 (88)		
	No	13 (12)		
	Walking or bicycle[c]			
	Yes	53 (47)		
	No	59 (53)		
Short questionnaire at each visit ($N = 547$)[d]	Night sleeping hours	545 (99.6)	6.6 ± 0.9	4.5–10.0
	Body mass index (kg/m^2)	547 (100)	24.5 ± 3.4	16.9–40.4
	Hypoglycemic drug use			
	Yes	22 (4)		
	No	524 (96)		
	Passive smoke exposure ≥0.5 h			
	Yes	80 (15)		
	No	466 (85)		
	Acute respiratory disease[e]			
	Yes	77 (14)		
	No	469 (86)		
	Alcohol intake			
	Yes	76 (14)		
	No	470 (86)		
	Irritating food[f]			
	Yes	273 (50)		
	No	274 (50)		

Note: CNY, Chinese Yuan Renminbi; SD, standard deviation.
[a]Chronic respiratory disease included asthma and chronic obstructive pulmonary disease.
[b]Smoking history denoted former smokers who had quit smoking for more than 3 y (Yes), and nonsmoker (No).
[c]Walking or bicycle was the main commuting mode choice (Yes), instead of car or public transit (No).
[d]Short questionnaire recorded information during the 3 d before visits.
[e]Acute respiratory disease included flu, cold, acute laryngopharyngitis, and acute bronchitis.
[f]Irritating food mainly included barbecue, pickled food, seafood, hotpot, and preservative-containing food.

Table 2. Levels of FBG, HOMA-IR, and FeNO in different subgroups.

Category	N^a	n	Mean ± SD		Median (25th, 75th)
			FBG (mmol/L)	HOMA-IR	FeNO (ppb)
All participant	112	519	6.0 ± 0.9	1.9 ± 1.3	18.4 (10.8, 28.4)
Low-FBG group[b]	75	357	5.6 ± 0.3	1.7 ± 0.8	18.7 (11.2, 28.9)
High-FBG group	37	162	6.8 ± 1.1	2.5 ± 1.8	18.2 (10.5, 28.2)
p1[c]	—	—	<0.01	<0.01	0.57
Low HOMA-IR group	53	255	5.7 ± 0.5	1.1 ± 0.3	18.1 (10.5, 27.7)
High HOMA-IR group	59	264	6.2 ± 1.0	2.7 ± 1.4	18.7 (11.4, 28.9)
p2	—	—	<0.01	<0.01	0.19

Note: —, not applicable; FBG, fasting blood glucose; FeNO, fractional exhaled nitric oxide; HOMA-IR, homeostasis model assessment insulin resistance; SD, standard deviation.
[a]Number of the participants (N) and visits completed by participants (n).
[b]Low-FBG, high-FBG, low HOMA-IR, and high HOMA-IR groups referred to participants with average level of FBG <6.1 mmol/L, FBG ≥6.1 mmol/L, HOMA-IR <1.6, and HOMA-IR ≥1.6, respectively.
[c]p1 was p-value of unpaired t-test between low- and high-FBG groups, and p2 for low and high HOMA-IR groups. Test variables were FBG, HOMA-IR, and ln-transformed FeNO.

As expected, average values were higher in the high- vs. low-FBG and high vs. low HOMA-IR groups (6.8 ± 1.1 vs. 5.6 ± 0.3 mmol/L for FBG, and 2.7 ± 1.4 vs. 1.1 ± 0.3 for HOMA-IR, respectively, $p < 0.01$ for both comparisons) (Table 2). Median values of FeNO were slightly higher in the high vs. low HOMA-IR groups {18.7 [95% confidence interval (CI): 11.4, 28.9] vs. 18.1 (95% CI: 10.5, 27.7) ppb}, and slightly lower in the high- vs. low-FBG groups [18.2 (95% CI: 10.5, 28.2) vs. 18.7 (95% CI: 11.2, 28.9) ppb], but the differences were not significant ($p = 0.19$ and 0.57, respectively). Twenty-eight FeNO measurements of 27 participants were missing due to physical discomfort of participants or power outage of the analyzer. Average concentrations of $PM_{2.5}$, BC, UFPs, and Acc particles 1 h before clinic visits (lag 1 h) were 72.8 ± 77.1 $\mu g/m^3$, 6.1 ± 3.6 $\mu g/m^3$, (1.6 ± 0.7) × 10^4 counts/cm^3, and (4.4 ± 3.2) × 10^3 counts/cm^3, respectively, and were similar with 24 h ACPV (Table 3). The daily variation and hourly average of $PM_{2.5}$ concentrations at the PKU site during the study time period were consistent with those queried from the Wan Liu state-controlled monitoring station nearby (see Figure S1). $PM_{2.5}$ and BC measurements were missing due to power outages or extreme weather events for 34 d during the study period, and UFP and Acc particle measurements were missing for 117 d. $PM_{2.5}$, BC, and Acc concentrations were strongly correlated with each other (Spearman correlation coefficients of 0.56–0.87), but not with UFP concentrations (correlations of −0.02 to 0.13) (see Table S3).

FeNO was significantly higher in association with IQR increases in lag 1–15 h BC, 1–17 h UFPs, and 1–16 h Acc particles (Figure 1, Table S4). Associations were strongest at a lag of 1 h, and attenuated with increasing lag time. IQR increases in lag 1 h BC, UFPs, and Acc particles were associated with 74.7% (95% CI: 63.7%, 85.8%), 74.4% (95% CI: 66.0%, 82.8%), and 67.3% (95% CI: 57.7%, 76.9%), respectively. Associations with $PM_{2.5}$ peaked at lag 1 h [21.3% (95% CI: 13.8%, 28.8%)] and 9 h [15.5% (95% CI: 8.7%, 22.2%)]. Average concentrations of all four pollutants during the 8- and 24-h periods before each study visit were also associated with higher FeNO (see Table S5).

Associations between FeNO and IQR increases in 1- to 24-h lagged $PM_{2.5}$ were consistently positive for the high-FBG group, whereas corresponding estimates were weaker or null for the low-FBG group, with significant differences between the two groups at several time points (Figure 2, Table S6). In general, associations with BC, UFPs, and Acc concentrations were also stronger in the high-FBG group, although the difference was significant for lag 1 h UFPs only [62.3% (95% CI: 51.9%, 72.6%) vs. 98.6% (95% CI: 85.0%, 112.2%), respectively, $p = 0.013$]. Associations with IQR increases in 8- and 24-h average $PM_{2.5}$ were positive in the high-FBG group but null in the low-FBG group ($p_{interaction} = 0.022$ and 0.017, respectively) (see Figure S2, Table S7).

IQR increases in the 6- to 24-h lagged $PM_{2.5}$ concentrations were associated with higher increases in FeNO in the high-IR group than in the low-IR group, with significant differences at lag 6–18 and 23 h (Figure 2, Table S8). In general, associations with BC, UFPs, and Acc concentrations were also stronger in the high- vs. low-IR group after a 6-h lag, with significant differences for BC and UFPs at several lags. The association between FeNO and an IQR increase in average UFPs in the previous 24 h was significantly stronger in the high- vs. low-IR group (see Figure S2, Table S7).

Positive associations between 1-h lagged $PM_{2.5}$ and FeNO became null or inverse after adjusting for BC and Acc particles in the population as a whole, and in all FBG and HOMA-IR subgroups (Figure 3, Table S9). Associations with 1-h lagged BC, UFPs, and Acc particles remained positive in two-pollutant models, although most were closer to the null and the association between Acc particles and FeNO was no longer significant after adjustment for BC. Patterns were similar in the FBG and HOMA-IR subgroups. Variance inflation factors in two-pollutant models of 1-h lagged exposures ranged from 1.0 to 6.4, indicating only

Table 3. Average levels of the 1-h and 24-h ambient pollutants and meteorological parameters prior to the starting time of the clinical visits.

Time window	Variable	Unit	n^a	Mean (SD)	Range	IQR
1 h	$PM_{2.5}$	$\mu g/m^3$	503	72.8 (77.1)	0.7–350.6	87.1
	BC	$\mu g/m^3$	503	6.1 (3.6)	0.5–15.7	6.3
	UFPs	$10^3/cm^3$	430	15.9 (6.7)	2.2–37.8	9.4
	Acc	$10^3/cm^3$	430	4.4 (3.2)	0.1–14.5	4.9
24 h	$PM_{2.5}$	$\mu g/m^3$	503	74.7 (67.3)	1.0–325.4	63.4
	BC	$\mu g/m^3$	503	5.3 (3.1)	0.5–12.7	4.8
	UFPs	$10^3/cm^3$	430	15.5 (4.5)	2.9–27.5	6.0
	Acc	$10^3/cm^3$	430	4.5 (3.0)	0.1–13.1	4.5
	Temperature	°C	547	13.6 (10.0)	−3.9–33.7	17.8
	Relative humidity	%	547	47.8 (19.4)	11.9–99.6	33.7

Note: Acc, accumulated-mode particles; BC, black carbon; IQR, interquartile range; $PM_{2.5}$, particulate matter with an aerodynamic diameter of ≤2.5 μm; SD, standard deviation; UFPs, ultrafine particles.
[a]n denotes the number of visits with valid matched pollution concentration out of a total number of 547 person-visits.

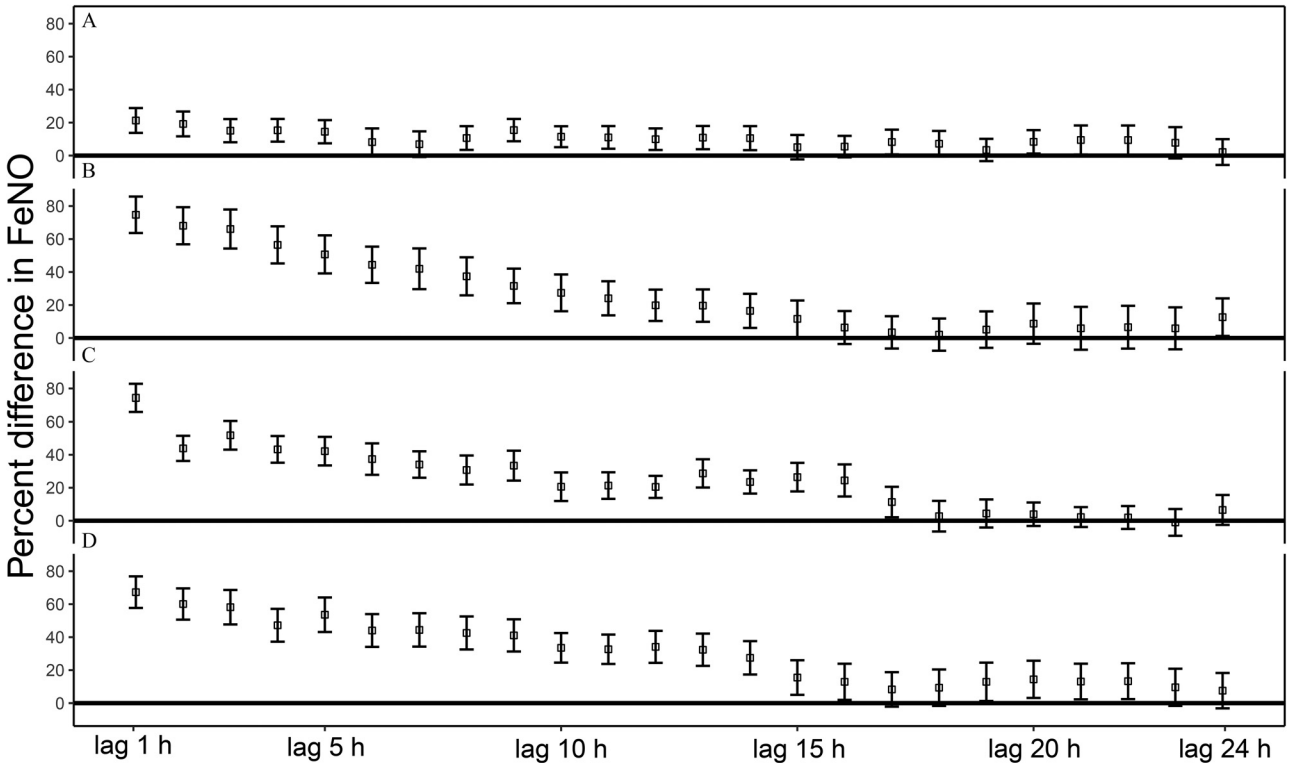

Figure 1. Estimated percent difference in FeNO (95% CI) per IQR increase in 1- to 24-h lagged (A) $PM_{2.5}$, (B) BC, (C) UFPs, and (D) Acc concentrations. All models were single-pollutant linear mixed-effects models of ln-FeNO with random participant-specific intercepts, adjusted for ambient temperature on the previous day, average relative humidity during the 7 d before the visit, day of the week, age (continuous), sex, and smoking history (nonsmoker vs. former smoker). See Table S4 for corresponding numeric data. Note: Acc, accumulated-mode particles; BC, black carbon; CI, confidence interval; FeNO, fractional exhaled nitric oxide; IQR, interquartile range; $PM_{2.5}$, particulate matter with an aerodynamic diameter of $\leq$2.5 μm; UFPs, ultrafine particles.

mild multicollinearity. Associations showed little change after additionally adjusting for BMI, hypoglycemic drug use, income, education, sleeping and commuting habits, alcohol use, irritating food intake, passive smoke exposure, chronic and acute respiratory disease, and distance from home to the monitor (see Table S10). In general, associations were slightly stronger after excluding 162 visits with missing pollutant data and were similar to the primary estimates when restricted to 99 participants with at least three visits.

Lag patterns based on DLM models were similar to patterns based on the LME models (see Figure S3, Table S11). FeNO was positively associated with 1-h lagged BC, UFPs, and Acc concentrations, and associations attenuated with longer lag times. $PM_{2.5}$ was positively associated with FeNO at lag 1 h and had a second peak at lag 16 h.

Discussion

FeNO was increased in association with short-term exposure to ambient particles, namely, $PM_{2.5}$, BC, UFPs, and Acc particles, in SCOPE study participants classified as healthy and prediabetic at baseline. Associations with $PM_{2.5}$, BC, and UFPs were stronger in individuals with higher average HOMA-IR during the study period, and associations with $PM_{2.5}$ were stronger among those with higher average FBG during the study.

Our results are consistent with previous studies of FeNO and short-term exposures to $PM_{2.5}$, BC, UFPs, and Acc particles (see Table S12). For example, Han et al. (2016) reported that IQR increases of 8-h ACPV of $PM_{2.5}$ (24.0 $\mu g/m^3$), BC (2.1 $\mu g/m^3$), UFPs (8.5×10^3 counts/cm^3), and Acc particles (2.2×10^3 counts/cm^3) were associated with 5–9.25% increases in FeNO in elderly participants with diabetes. Hao et al. (2017) reported a 4.7-ppb increase in FeNO associated with a 60-$\mu g/m^3$ increase in 24-h ACPV of $PM_{2.5}$ exposure in elderly participants with diabetes. Jansen et al. (2005) reported that increases of 10- and 1-$\mu g/m^3$ 24-h ACPV of $PM_{2.5}$ and BC exposure were associated with increases of 4.2 and 3.2 ppb, respectively, in FeNO in elderly participants with chronic respiratory disease. The concentrations of the four pollutants measured in our study were higher, and the ranges were wider, than those in several studies that combined the effects of exposure to ambient particles and glucose metabolism disorders (Zeka et al. 2006; Sade et al. 2015; Chen and Schwartz 2008; Dubowsky et al. 2006; O'Neill et al. 2005).

Several toxicological experiments have also suggested that impaired glucose metabolism enhances susceptibility to particle-associated respiratory inflammation (Mo et al. 2009; Nemmar et al. 2013). In an *in vitro* study of alveolar macrophages, levels of reactive oxygen species and pro-inflammatory cytokine mRNA expression following exposure to urban particles were greater in macrophages from diabetic rabbits than those from healthy rabbits (Mo et al. 2009). A study of the respiratory effects of exposure to diesel exhaust particles (DEPs) reported increased oxidative stress and elevated pro-inflammatory cytokine levels in bronchoalveolar lavage fluid from diabetic mice compared to nondiabetic control participants after intratracheal DEPs instillation (Nemmar et al. 2013).

As a crucial upstream pathway in the mechanism underlying the cardiorespiratory effects of fine particle exposure, respiratory inflammation closely interacts with the development of systemic inflammation, which is important in cardiorespiratory disease (Brook et al. 2010; Sinden and Stockley 2010). Our findings suggest that associations between air pollution exposures and FeNO, a marker of respiratory inflammation, were stronger in participants

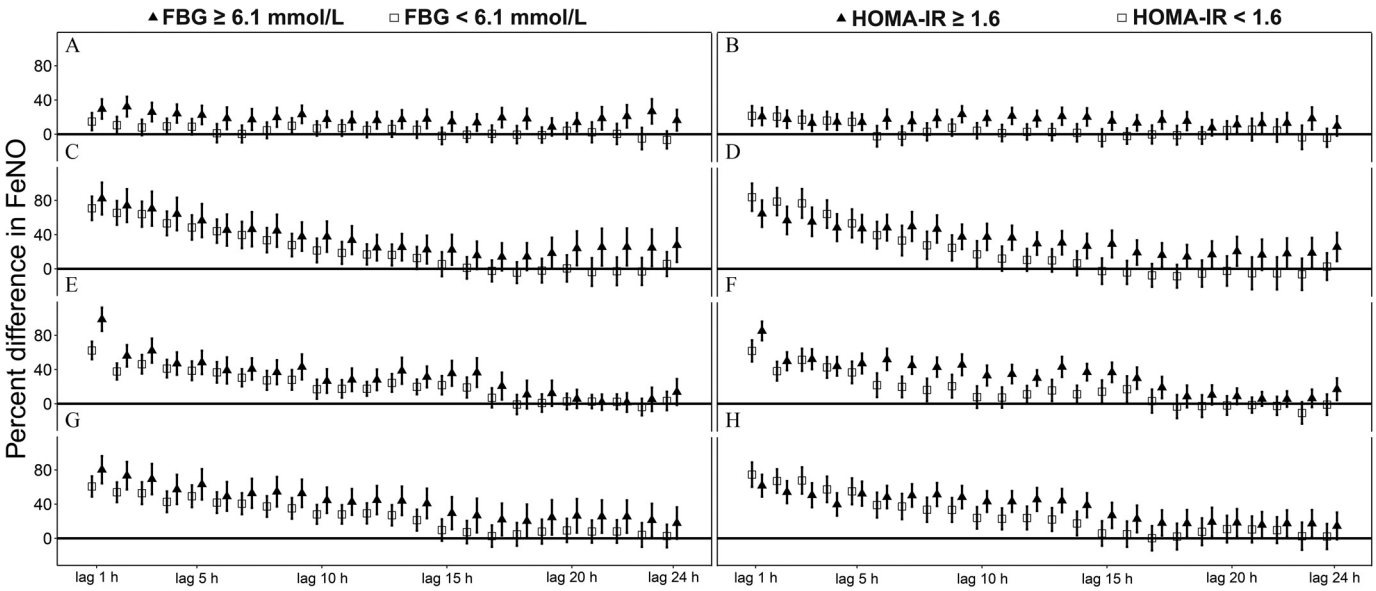

Figure 2. Estimated percent difference in FeNO (95% CI) per IQR increases in 1–24 h lagged particle concentrations according to high and low FBG (A) $PM_{2.5}$, (C) BC, (E) UFPs, and (G) Acc and HOMA-IR (B) $PM_{2.5}$, (D) BC, (F) UFPs, and (H) Acc based on average values over all study visits. All models were single-pollutant linear mixed-effects models of ln-FeNO with random participant-specific intercepts, adjusted for ambient temperature on the previous day, average relative humidity during the 7 d before the visit, day of the week, age (continuous), sex, and smoking history (nonsmoker vs. former smoker). Low-FBG, high-FBG, low-IR, and high-IR groups referred to participants with average level of FBG <6.1 mmol/L, FBG ≥6.1 mmol/L, HOMA-IR <1.6 and HOMA-IR ≥1.6, respectively. See Tables S6 and S8 for corresponding numeric data and interaction *p*-values for all pairs of estimates according to FBG and HOMA-IR. The IQRs for each pollutant and lag period are provided in Table S4. Note: Acc, accumulated-mode particles; BC, black carbon; CI, confidence interval; FBG, fasting blood glucose; FeNO, fractional exhaled nitric oxide; HOMA-IR, homeostasis model assessment insulin resistance; IQR, interquartile range; IR, insulin resistance; UFPs, ultrafine particles.

with glucose metabolism disorders than in participants with normal FBG and HOMA-IR values. A study of short-term $PM_{2.5}$ and BC exposures (in the previous 1–7 d) and markers of systemic inflammation in nonsmoking elderly participants reported stronger and more consistent associations in individuals with diabetes than in other participants (Dubowsky et al. 2006). An analysis of population-based data from the National Health and Nutrition Examination Survey study reported an association between annual

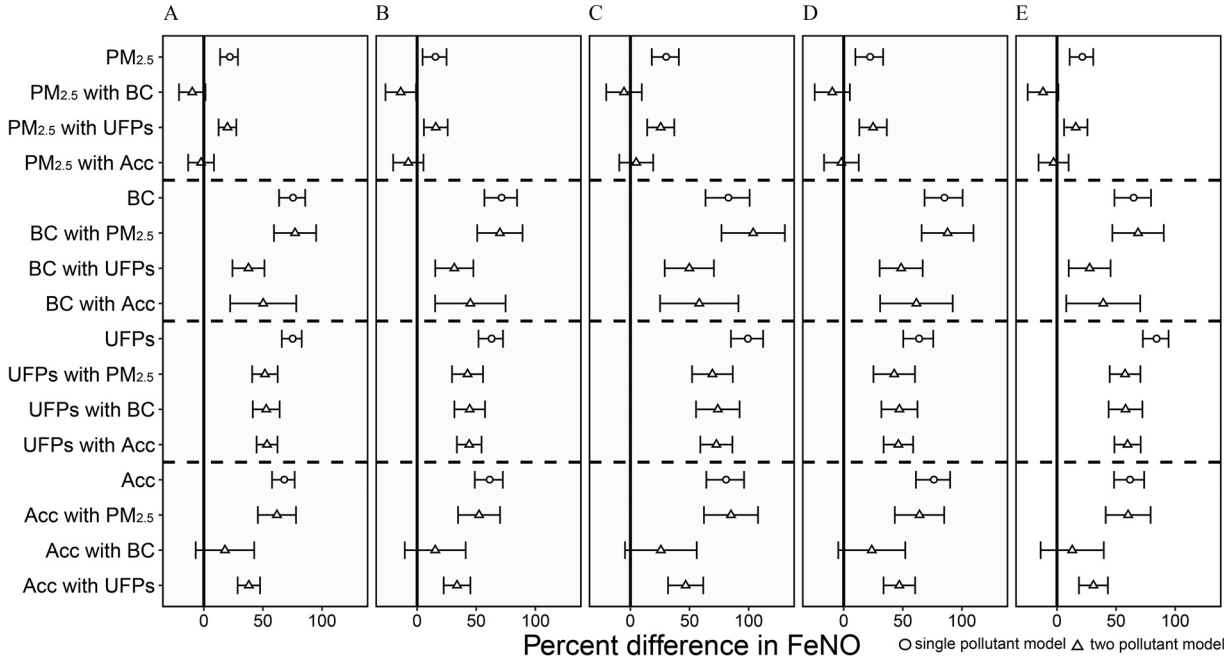

Figure 3. Estimated percent difference in FeNO per IQR increase in 1 h lagged particle concentrations based on two-pollutant models for (A) all participants, (B) low-FBG group, (C) high-FBG group, (D) low HOMA-IR group, and (E) high HOMA-IR group. All models were linear mixed-effects models of ln-FeNO with random participant-specific intercepts. The models were adjusted for other pollutants as indicated, plus ambient temperature on the previous day, average relative humidity during the 7 d before the visit, day of the week, age (continuous), sex, and smoking history (nonsmoker vs. former smoker). Low-FBG, high-FBG, low-IR, high-IR groups referred to participants with average level of FBG <6.1 mmol/L, FBG ≥6.1 mmol/L, HOMA-IR <1.6 and HOMA-IR ≥1.6, respectively. See Table S9 for corresponding numeric data and interaction *p*-values for all pairs of estimates according to FBG and HOMA-IR. The IQRs for each pollutant and lag period are provided in Table S4. Note: Acc, accumulated-mode particles; BC, black carbon; FBG, fasting blood glucose; FeNO, fractional exhaled nitric oxide; HOMA-IR, homeostasis model assessment insulin resistance; IQR, interquartile range; IR, insulin resistance; UFPs, ultrafine particles.

concentrations of average particulate matter with an aerodynamic diameter of $\leq$10 μm (PM_{10}) and white blood cell counts that increased in participants affected by increasing numbers of metabolic syndrome components (Chen and Schwartz 2008).

Stronger associations between particulate matter air pollution and inflammation among people with prediabetes, as suggested by stronger associations between air pollution and FeNO among people with elevated FBG and HOMA-IR in our study, may help explain why individuals with metabolism disorders have been reported to have more severe pulmonary dysfunction and higher respiratory morbidity and mortality following exposure to ambient particles (Zeka et al. 2006; Klein et al. 2010). Klein et al. (2010) reviewed potential mechanisms contributing to lung dysfunction in individuals with diabetes, including the formation and deposition of glycosylated proteins in chronic hyperglycemia, which have pro-inflammatory effects, and chronic tissue inflammation in the alveolar–capillary network of the lung. A case-crossover study of 20 American cities that examined individual-level modifiers of associations between $PM_{2.5}$ and daily mortality reported that a secondary diagnosis of diabetes strengthened associations between PM_{10} and respiratory and stroke mortality (Zeka et al. 2006). In contrast, a cross-sectional study of type 2 diabetes patients and hospital staff without diabetes at a hospital in Pune, India, reported that while associations between air pollution and reduced lung function were stronger in overweight vs. normal weight individuals, findings did not indicate a difference by diabetes status (Khafaie et al. 2017).

There are several possible explanations for differences in associations with ambient particles of different sizes or with chemical components: UFPs have the greatest deposition efficiency in the respiratory tract and are the slowest to be cleared (Han et al. 2016; Gong et al. 2014); Acc particles (93.1–560 nm) have the largest active surface area distribution of ambient particles and may absorb more chemicals that could activate pro-inflammatory pathways (Rich et al. 2012); carbonaceous components may carry various combustion-derived toxic species to sensitive targets in the body, such as the lung or systemic circulation (Cassee et al. 2013). Consistent with these characteristics and with previous studies (Han et al. 2016; Lin et al. 2011), associations with IQR increases in BC, UFPs, and Acc concentrations were stronger and more consistent than associations with IQR increases in $PM_{2.5}$ in our study population. UFPs have greater spatial and temporal variability than the other measured pollutants (Gong et al. 2014), and consistent with this, UFP concentrations were not highly correlated with BC or Acc concentrations in our study. However, the magnitude and pattern of associations between FeNO and UFPs were not markedly different from corresponding associations with BC and Acc concentrations.

To our knowledge, this was the first study to estimate associations between short-term air pollution exposures and FeNO, an indicator of respiratory inflammation, in prediabetic participants. Our results add support to evidence suggesting that individuals with metabolic disorders are more susceptible to particle-associated health effects. A group of participants made repeated clinical visits under different air pollution conditions, which reduced the error variance associated with intra-individual differences. However, this study also had several limitations. First, the participants were of relatively high socioeconomic status with advantageous health care services, so our findings may not be generalizable to those of lower socioeconomic status (Wang et al. 2018). Second, there was a potential for error in the estimation of exposure to UFPs based on the PKU monitoring site because UFPs are more likely to be affected by local sources and have marked spatial variation. Third, number concentrations of UFPs and Acc particles were based on particles between 5.6–560 nm in size only, thus, larger particles were not included.

Our findings suggest that study participants with glucose metabolism disorders, as indicated by elevated FBG and HOMA-IR values, were more sensitive to respiratory inflammation associated with short-term ambient air pollution exposures than healthy individuals. Associations with IQR increases in BC mass concentration and UFPs and Acc number concentrations were stronger and more consistent than associations with IQR increases in $PM_{2.5}$. These findings require confirmation, but they may be of considerable public health importance given the high prevalence of prediabetes and severe air pollution in China.

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