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Association of fine particulate matter air pollution and its constituents with lung function: The China Pulmonary Health study

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ABSTRACT

The associations of long-term exposure to various constituents of fine particulate matter (≤2.5 μm in aerodynamic diameter, $PM_{2.5}$) air pollution with lung function were not clearly elucidated in developing countries. The aim was to evaluate the associations of long-term exposure to main constituents of $PM_{2.5}$ with lung function in China. This is a nationwide, cross-sectional analysis among 50,991 study participants from the China Pulmonary Health study. Multivariable linear regression models were used to obtain differences of forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), FEV_1/FVC, peak expiratory flow (PEF), and forced expiratory flow at 25–75% of exhaled FVC ($FEF_{25-75\%}$) associated with an interquartile range (IQR) change of $PM_{2.5}$ or its constituents. Residential annual $PM_{2.5}$ levels varied from 26 μg/m^3 to 92 μg/m^3 (average: 53 μg/m^3). An IQR increase of $PM_{2.5}$ concentrations was associated with lower FEV_1 (19.82 mL, 95% CI: 11.30–28.33), FVC (17.45 mL, 95% CI: 7.16–27.74), PEF (86.64 mL/s, 95% CI: 59.77–113.52), and $FEF_{25-75\%}$ (31.93 mL/s, 95% CI: 16.64–47.22). Black carbon, organic matter, ammonium, sulfate, and nitrate were negatively associated with most lung function indicators, with organic matter and nitrate showing consistently larger magnitude of associations than $PM_{2.5}$ mass. This large-scale study provides first-hand epidemiological evidence that long-term exposure to ambient $PM_{2.5}$ and some constituents, especially organic matter and nitrate, were associated with lower large- and small- airway function.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic condition characterized by airflow obstruction or impaired lung function. According to the Global Burden of Disease (GBD), 3.2 million people died from COPD worldwide in 2017 with an increase of 17.5% from 2007 to 2017, and the percentage increase in numbers of disability-adjusted life-years was 25.6% from 1990 to 2019 (GBD, 2017; GBD, 2019). The prevalence of spirometry-defined COPD was 8.6% among Chinese adults aged 20 years or older and 13.7% among people aged 40 years or older, which was higher than that in developed countries (Wang et al., 2018). According to the results of GBD, COPD was estimated to be the fourth leading cause of years of life lost in China (Zhou et al., 2019).

Ambient fine particulate matter (≤2.5 μm in aerodynamic diameter, $PM_{2.5}$) air pollution is a major public concern worldwide, especially in developing countries. It has already been known that $PM_{2.5}$ can penetrate into the lung alveoli, causing a wide range of respiratory disorders (Yu et al., 2018; Xing et al., 2016; Adams et al., 2015). Although there is strong epidemiological evidence that demonstrated a detrimental effect of long-term exposure to $PM_{2.5}$ on lung function, (Doiron et al., 2019) limited large-scale investigations have addressed this issue in China where particulate air pollution levels are much higher than that in developed countries.

Furthermore, $PM_{2.5}$ is a complex mixture and its various chemical constituents may have different effects on the respiratory system (Adams et al., 2015). Epidemiological findings on the specific $PM_{2.5}$ constituents most harmful to respiratory health are critically important in formulation of environmental regulations and health impact assessment. Nevertheless, few studies to date have evaluated the long-term effects of various $PM_{2.5}$ constituents on lung function worldwide, especially in developing countries.

Our main aim was to evaluate the associations of long-term exposure to main constituents of $PM_{2.5}$ with a range of lung function indicators in the China Pulmonary Health (CPH) study, a nationwide cross-sectional survey.

2. Materials and methods

2.1. Study participants

The CPH study enrolled a nationwide sample of adults aged 20 years or older in China between June 2012 and May 2015. Ten provinces, autonomous regions, and municipalities stratified by geographical regions (only regions below an altitude of 1500 m were included), which represented diverse socioeconomic statuses and lifestyles of six major geographical regions in China, were selected to enroll participants. Details of this national survey have been published previously (Wang et al., 2018). Briefly, a 5-stage stratified cluster sampling procedure was utilized to select a nationwide sample of adults aged 20 years or older in China. The survey invited a total of 57,779 adults from six major geographical regions in China (Northwest, 5516; North 10332; Northeast, 5131; Southwest, 9589; Central south, 10354; East, 10069;) (Fig. 1). Among 57,779 invited participants, 6,788 participants who refused to participate in the survey (n = 2,822), failed to complete lung function test (n = 1,411), or had unreliable lung function test results (n = 2,555) were excluded at the end of this survey.

The study was approved by the ethics review committees of the Capital Medical University and other participating institutes relevant. Written informed consent was obtained from all participants.

2.2. Questionnaire data collection

Data were collected at local community health centers with a standardized questionnaire administered by trained reviewers. The questionnaire recorded information on demographic characteristics, smoking status, number of smokers living in the same household, biomass use, personal medical history, and parental history of respiratory diseases. Education level was classified as primary school or lower, middle and high school, and college or above. Biomass use was defined as using woody fuels or animal waste for cooking or heating during the past 6 months or longer. History of childhood pneumonia or bronchitis was defined as being admitted to hospital at least once for these conditions before age 14 years. Chronic cough during childhood before age 14 years was categorized as frequent (cumulative > 3 months per year), sometimes (1–3 months per year), and rare (<1 month per year). Anthropometric measures including body weight and height were obtained by trained staff with participants in light clothing without shoes.

[1] These authors contributed equally to this work.

2.3. Lung function test

Trained and certified technicians carried out lung function tests before and after bronchodilator inhalation using a MasterScreen Pneumo PC spirometer (CareFusion, Yorba Linda, CA, USA) according to a standard protocol (Miller et al., 2005). Daily calibration with a 3 L syringe was performed for spirometers. For each participant, we performed spirometric manoeuvres with the participant in a seated position, wearing a nose clip, and using a disposable mouthpiece. Participants were required to do up to eight forced expiratory manoeuvres until forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) were reproducible within 150 mL. Peak expiratory flow (PEF), forced expiratory flow at 25%, 50%, and 75% of exhaled FVC ($FEF_{25\%}$, $FEF_{50\%}$, and $FEF_{75\%}$), average FEF between 25% and 75% of the exhaled volume ($FEF_{25\text{-}75\%}$), inspiratory capacity (IC), vital capacity (VC), FEV_3, and FEV_6 were also tested.

Quality control of lung function test results based on the American Thoracic Society and European Respiratory Society criteria were conducted by an expert panel on all reports of pulmonary function tests in local centers and on 20% of randomly selected reports in the leading center.

2.4. Air pollutant exposure assessment

We modelled residential annual-mean exposures to $PM_{2.5}$ total mass and 5 main chemical constituents for each participant during the year they received the lung function test. These constituents included organic matter (OM, which includes the mass of elements such as oxygen attached to organic carbon), black carbon (BC), ammonium, sulfate, and nitrate. These data were obtained from the V4.CH.02 product developed by the Dalhousie University Atmospheric Composition Analysis Group (DUACAG), which extended the V4.NA.02 methodology to China, and has been described in detail elsewhere (van Donkelaar et al., 2019). Briefly, ground-level $PM_{2.5}$ was first estimated by combining Aerosol Optical Depth (AOD) retrievals from multiple sources including the NASA MODIS, MISR, and SeaWIFS instruments with the GEOS-Chem chemical transport model, and subsequently calibrated to ground-based observations of $PM_{2.5}$ using Geographically Weighted Regression (GWR). This GWR was performed on a monthly timescale from 2014 to 2016 using ground-based $PM_{2.5}$ observations from the recently expanded monitoring network over China using predictors with a spatial resolution of up to $0.01^\circ \times 0.01^\circ$ (approximately 1×1 km at the equator). $PM_{2.5}$ prior to this period are predicted based on the relative changes estimated by global DUACAG V4.GL.02 $PM_{2.5}$ dataset (van Donkelaar et al., 2019). GEOS-Chem simulation was further applied to partition this $PM_{2.5}$ mass into various constituents. The exact home address of participants in CPH study was available. We obtained exact geographical coordinates of each participant's residential address through geocoding. Concentrations of $PM_{2.5}$ and its constituents were subsequently assigned based on these geocodes. The corresponding annual means for each participant were calculated according to their address information and the monthly estimates of $PM_{2.5}$ and its constituents. The resultant annual-mean $PM_{2.5}$ concentrations were consistent with out of sample, cross-validation observations over China ($R^2 = 0.78$; slope = 1.02; root mean squared error = 9.4 μg/m^3).

2.5. Statistics analyses

Difference of lung function parameters, including the means and 95% confidence intervals (CIs), per interquartile range (IQR) change of $PM_{2.5}$ or its constituents were analyzed in multivariable linear regression models. Age (20–29, 30–39, 40–49, 50–59, 60–69, ≥70 years), sex, residence (urban/rural), geographic region (northeast/north/northwest/southwest/central/east/south), education, occupation, body mass index, smoking history (current smoker/former smoker/nonsmoker), smoking exposure (pack-years), number of smokers in the household (none, 1, ≥2), biomass use, season for lung function test (to account for the seasonality of lung function), history of pneumonia or bronchitis during childhood, chronic cough during childhood, and parental history of respiratory diseases were included as covariates.

In addition, we conducted several stratified analyses by a range of variables, including sex, age, education, body mass index, cigarette smoking, number of smokers living in the same household, biomass use, history of pneumonia or bronchitis during childhood, chronic cough during childhood, and parental history of respiratory diseases. We further evaluated the potential interaction by adding a multiplicative

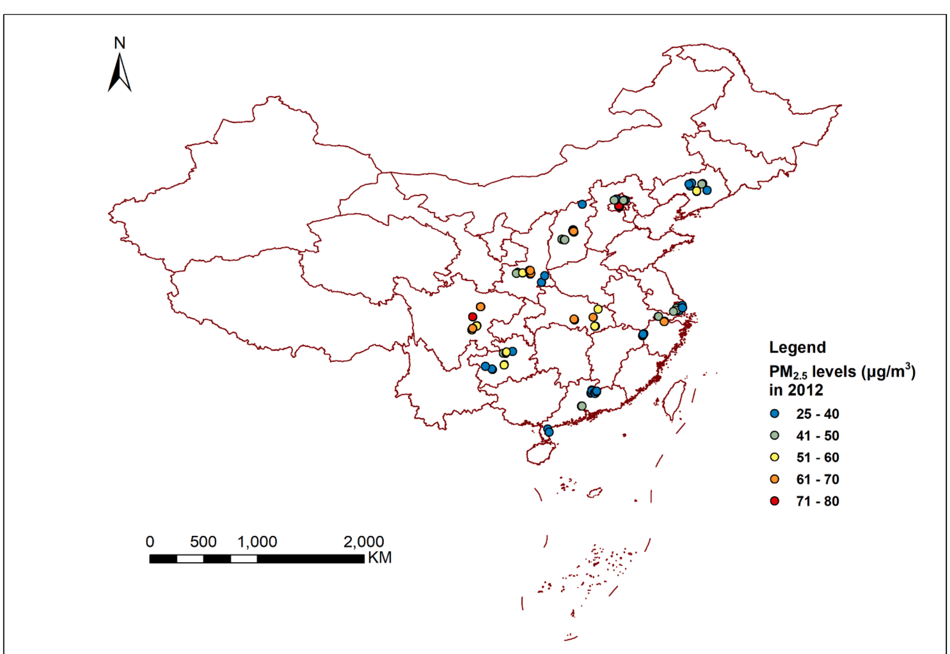

Fig. 1. Locations of study sites and their annual-mean $PM_{2.5}$ concentrations in 2012. $PM_{2.5}$, particulate matter with an aerodynamic diameter less than or equal to 2.5 μm.

interaction term between $PM_{2.5}$ and a categorization variable.

Finally, we performed three sensitivity analyses. Firstly, we reanalyzed the data after excluding participants who were current or former smokers. Secondly, we reanalyzed the data after excluding study participants with pre-existing respiratory diseases. These diseases included self-reported clinically-diagnosed COPD, asthma, bronchiectasis, pulmonary interstitial fibrosis, lung cancer, and spirometry-defined COPD (post-bronchodilator $FEV_1/FVC < 0.70$ according to 2019 Global Initiative for Chronic Obstructive Lung Disease guidelines) (Singh et al., 2019). Thirdly, $PM_{2.5}$ was added into the models as a constituent-$PM_{2.5}$ joint model.

Statistical analyses were performed with SAS 9.4 (SAS Institute Inc., Cary, NC). All tests were 2 sided, and false discovery rate (FDR) adjusted P value < 0.05 was considered statistically significant. FDR-adjusted P values (q values) were employed to determine the statistical significance for the association of $PM_{2.5}$ and 6 constituents with 13 indicators of lung function.

3. Results

3.1. Descriptive statistics

The demographic characteristics of 50,991 participants (21,446 men and 29,545 women) from CPH study are presented in Table 1. Women were less educated, less likely to be smokers, and lived with more smokers in the same household. Most lung function measurements in men were higher than those in women.

Taking the year of 2012 for an example, Fig. 1 illustrates the annual-average $PM_{2.5}$ mass concentrations. As shown in Table S1, $PM_{2.5}$ levels varied considerably from 26 $\mu g/m^3$ to 92 $\mu g/m^3$ with an average of 53 $\mu g/m^3$; sulfate, nitrate and OM accounted for the largest mass fractions of $PM_{2.5}$, followed by ammonium and BC. The IQRs of $PM_{2.5}$, BC, OM, ammonium, sulfate, nitrate, and soil dust were 22.42, 1.30, 6.12, 3.09, 5.51, 5.89, and 3.93 $\mu g/m^3$, respectively. The Pearson correlation coefficients of $PM_{2.5}$ with BC, OM, ammonium, sulfate, nitrate, and soil dust were 0.85, 0.91, 0.92, 0.78, 0.90, and 0.56, respectively (Table S2).

3.2. Associations of $PM_{2.5}$ and its constituents with lung function

There were statistically significant and inverse associations of $PM_{2.5}$ and its constituents with most indicators of lung function, but the magnitude varied by specific indicators.

Table 2 provides the estimates on forced expiratory volume indicators of lung function associated with an IQR increase of $PM_{2.5}$ and its constituents. $PM_{2.5}$ and all 6 constituents were statistically significantly associated with lower measurements of FEV_1 and FVC, except for the association of sulfate and soil dust with FVC. An IQR increase of $PM_{2.5}$ concentrations was associated with lower FEV_1 (19.82 mL, 95% CI: 11.30–28.33) and FVC (17.45 mL, 95% CI: 7.16–27.74). These magnitude of associations were consistently slightly larger for OM and nitrate than for $PM_{2.5}$ mass. The associations of $PM_{2.5}$ and its constituents with FEV_1/FVC were insignificant or weak.

Table 3 shows the estimates on forced expiratory flow indicators of lung function per IQR increase of $PM_{2.5}$ and its constituents. $PM_{2.5}$ and all 6 constituents were statistically significantly associated with declines in PEF and $FEF_{25\%}$. An IQR increase of $PM_{2.5}$ concentrations was associated with lower PEF (86.64 mL/s, 95% CI: 59.77–113.52) and $FEF_{25\%}$ (62.94 mL/s, 95% CI: 36.27–89.61). OM, BC, and nitrate had consistently larger associations in magnitude with these indicators than $PM_{2.5}$ mass. $PM_{2.5}$ and some constituents including OM, ammonium, and nitrate were statistically significantly associated with lower $FEF_{50\%}$, $FEF_{75\%}$, $FEF_{25\text{-}75\%}$. Nitrate showed the strongest associations with these three indicators.

Table 4 presents the estimates on other ventilatory indicators of lung function associated with an IQR increase of $PM_{2.5}$ and its constituents. $PM_{2.5}$ and all of the constituents except for soil dust had inverse and

Table 1
Demographic characteristic of study participants from China Pulmonary Health study.

	All participants (N = 50991)	Men (N = 21446)	Women (N = 29545)
Age, years	49.38 ± 13.86	48.97 ± 14.63	49.69 ± 13.26
Residence (%)			
Urban	32,879 (64.48)	13,572 (63.28)	19,307 (65.35)
Rural	18,112 (35.52)	7874 (36.72)	10,238 (34.65)
Geographic region (%)			
Northeast	5131 (10.06)	1535 (7.16)	3596 (12.17)
Southwest	9589 (18.81)	4130 (19.26)	5459 (18.48)
North	10,332 (20.26)	4449 (20.75)	5883 (19.91)
East	10,069 (19.75)	4004 (18.67)	6065 (20.53)
South	4934 (9.68)	2220 (10.35)	2714 (9.19)
Central	5420 (10.63)	2604 (12.14)	2816 (9.53)
Northwest	5516 (10.82)	2504 (11.68)	3012 (10.19)
Education level (%)			
Primary school or lower	12,755 (25.01)	3930 (18.33)	8825 (29.87)
Middle or high school	29,170 (57.21)	12,732 (59.37)	16,438 (55.64)
College or above	9066 (17.78)	4784 (22.31)	4282 (14.49)
Body mass index, kg/m^2	23.99 ± 3.52	24.21 ± 3.50	23.83 ± 3.53
Height, cm	161.51 ± 8.31	167.84 ± 6.69	156.91 ± 6.03
Weight, kg	62.75 ± 11.30	68.33 ± 11.32	58.70 ± 9.39
Cigarette smoking			
Never-smoker	36,429 (71.44)	7842 (36.57)	28,587 (96.76)
Former smoker	2838 (5.57)	2626 (12.24)	212 (0.72)
Current smoker	11,724 (22.99)	10,978 (51.19)	746 (2.52)
Smokers in the household (%)			
0	26,759 (53.54)	14,181 (67.33)	12,578 (43.49)
1	19,284 (38.58)	5641 (26.78)	13,643 (47.17)
≥2	3939 (7.88)	1240 (5.89)	2699 (9.33)
Biomass use (%)	13,628 (27.13)	5866 (27.76)	7762 (26.67)
History of pneumonia or bronchitis during childhood (%)	2444 (4.83)	1037 (4.88)	1407 (4.79)
Chronic cough during childhood (%)			
Rare	45,096 (89.52)	18,970 (89.64)	26,126 (89.43)
Sometimes	3753 (7.45)	1657 (7.83)	2096 (7.17)
Frequent	1528 (3.03)	535 (2.53)	993 (3.40)
Parental history of respiratory diseases (%)	5196 (10.28)	2093 (9.86)	3103 (10.58)
Lung function			
FEV_1, L	3.40 ± 0.89	4.06 ± 0.81	2.92 ± 0.58
FVC, L	2.67 ± 0.74	3.13 ± 0.76	2.34 ± 0.52
FEV_1/FVC (%)	78.53 ± 9.11	76.68 ± 10.05	79.88 ± 8.11
FEV_1 %predicted (%)	97.40 ± 18.38	94.29 ± 19.76	99.65 ± 16.96
FVC %predicted (%)	104.07 ± 69.76	101.11 ± 105.50	106.23 ± 17.55
PEF (L/s)	6.22 ± 1.99	7.42 ± 2.06	5.35 ± 1.39
$FEF_{25\%}$ (L/s)	5.44 ± 1.81	6.29 ± 2.02	4.83 ± 1.35

(continued on next page)

Table 1 (*continued*)

	All participants (N = 50991)	Men (N = 21446)	Women (N = 29545)
$FEF_{50\%}$ (L/s)	3.18 ± 1.26	3.52 ± 1.45	2.93 ± 1.04
$FEF_{75\%}$ (L/s)	1.06 ± 0.62	1.17 ± 0.71	0.97 ± 0.53
$FEF_{25\text{-}75\%}$ (L/s)	2.29 ± 1.10	2.56 ± 1.26	2.09 ± 0.92
IC (L)	2.57 ± 0.74	2.98 ± 0.74	2.27 ± 0.57
VC (L)	3.55 ± 0.91	4.23 ± 0.81	3.06 ± 0.60
FEV_3 (L)	3.17 ± 0.84	3.74 ± 0.83	2.75 ± 0.57
FEV_6 (L)	3.30 ± 0.86	3.92 ± 0.81	2.86 ± 0.57
FEV_3/ FEV_6 (%)	94.54 ± 3.66	93.92 ± 4.12	94.99 ± 3.22

Abbreviations: $FEF_{25\%}$, forced expiratory flow at 25% of exhaled forced vital capacity; $FEF_{25\text{-}75\%}$, forced expiratory flow at 25–75% of exhaled forced vital capacity; $FEF_{50\%}$, forced expiratory flow at 50% of exhaled forced vital capacity; $FEF_{75\%}$, forced expiratory flow at 75% of exhaled forced vital capacity; FEV_1, forced expiratory volume in one second; FEV_3, forced expiratory volume in three seconds; FEV_6, forced expiratory volume in six seconds; FVC, forced vital capacity; IC, inspiratory capacity; PEF, peak expiratory flow; VC, vital capacity.

Table 2
Mean differences of FEV_1, FVC, and FEV_1/FVC per interquartile increase of concentrations of $PM_{2.5}$ and constituents.

	FEV_1 (mL)		FVC (mL)		FEV_1/FVC (%)	
	β (95% CI)	*q* value	β (95% CI)	*q* value	β (95% CI)	*q* value
$PM_{2.5}$ (22.42 μg/m^3)	−19.82 (-28.33, −11.30)	<0.0001	−17.45 (-27.74, −7.16)	0.0013	−0.17 (-0.32, −0.03)	0.028
BC (1.30 μg/m^3)	−15.67 (−22.10, −9.24)	<0.0001	−20.88 (-28.65, −13.11)	<0.0001	0.03 (-0.08, 0.14)	0.63
OM (6.12 μg/m^3)	−21.40 (-31.73, −11.08)	0.0001	−19.94 (−32.41, −7.47)	0.0026	−0.17 (-0.34, 0.01)	0.08
NH_4^+ (3.09 μg/m^3)	−19.29 (-27.17, −11.40)	<0.0001	−17.82 (-27.34, −8.30)	0.0004	−0.13 (-0.27, 0.00)	0.07
SO_4^{2-} (5.51 μg/m^3)	−12.14 (-21.87, −2.41)	0.019	−10.41 (−22.17, 1.34)	0.10	−0.09 (-0.26, 0.07)	0.29
NO_3^- (5.89 μg/m^3)	−23.53 (-31.82, −15.24)	<0.0001	−20.07 (-30.08, −10.05)	0.0002	−0.20 (-0.35, −0.06)	0.0065
Soil dust (3.93 μg/m^3)	−16.46 (-25.57, −7.35)	0.0006	−10.24 (-21.24, 0.77)	0.08	−0.29 (-0.45, −0.14)	0.0004

Abbreviations: BC, black carbon; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; NH_4^+, ammonium; NO_3^-, nitrate; OM, organic matter; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than or equal to 2.5 μm; SD, standard deviation; SO_4^{2-}, sulfate.
The models were adjusted for sex, age, residence (urban/rural), geographic region (northeast/north/ northwest/southwest/central/east/ south), education level, occupation, body mass index, smoking history (current smoker/former smoker/nonsmoker), smoking exposure (pack-years), smokers living in the home, biomass use, type of biomass use (woody fuels, animal waste, or both), duration of biomass use (years), the season for pulmonary function test, history of pneumonia or bronchitis during childhood, chronic cough during childhood, and parental history of respiratory diseases.
q values were false discovery rate adjusted *P* values.

statistically significant associations with FEV_3/FEV_6, IC, and VC. An IQR increase of $PM_{2.5}$ concentrations was associated with lower FEV_3/FEV_6 (0.21%, 95% CI: 0.14–0.27), IC (32.09 mL, 95% CI: 21.49–42.70), and VC (18.76 mL, 95% CI: 8.12–29.40). Sulfate was more closely associated with FEV_3/FEV_6 and IC than other constituents, and BC was more closely associated with VC. For FEV_3 and FEV_6, the associations were more prominent with nitrate and OM, and no statistically significant association was found with sulfate.

Generally, in the two sensitivity analyses, the exclusion of participants who were smokers or had pre-existing chronic respiratory diseases did not substantially change the associations between $PM_{2.5}$ and its constituents and lung function parameters (Tables S3-S5). Specifically, according to the results of the sensitivity analyses, the association magnitude tended to be slightly larger. In the sensitivity analysis including $PM_{2.5}$ into the model, the negative associations of BC, OM, and NH_4^+ with FVC, association of BC, NH_4^+, and SO_4^{2-} with PEF, and association of NH_4^+ and SO_4^{2-} with IC were still statistically significant.

3.3. The results of subgroup analyses

The interaction of $PM_{2.5}$ with sex, age, biomass use, history of pneumonia or bronchitis during childhood, and chronic cough during childhood was statistically significant for the associations of $PM_{2.5}$ with FEV_1 and FVC (Fig. 2). The corresponding inverse associations were statistically significant only among women, never smokers, participants without biomass use, participants without a history of pneumonia or bronchitis during childhood, and participants who had rare chronic cough during childhood.

4. Discussion

In this cross-sectional, nationwide study among Chinese populations, we found long-term exposure to ambient $PM_{2.5}$ air pollution was inversely associated with lower levels of lung function parameters. The association of 6 predominant chemical constituents in $PM_{2.5}$ mass with lung function parameters varied. Up to our knowledge, the present study is the largest investigation to explore the associations between long-term exposure to $PM_{2.5}$ constituents and a wide range of lung function indicators. Therefore, our findings lend credence to an association between long-term $PM_{2.5}$ exposure and large- and small- airway function and also shed light on the targeted control of particulate air pollution sources.

Forced expiratory volume parameters are main indicators of mechanical ventilatory function and are influenced by genetic and environmental factors. Our study findings about association of $PM_{2.5}$ with FEV_1 and FVC was consistent with most of previous epidemiological studies (Doiron et al., 2019; Liu et al., 2017; Rice et al., 2015). The magnitude of associations was somewhat lower than that estimated in developed countries. The relatively weaker associations of $PM_{2.5}$ on lung function in the present study may be due to the levelling-off phenomenon at the higher end (e.g., in China) of exposure–response relationship curves that have been reported in multiple studies (Guo et al., 2018; Chen et al., 2017; Liu et al., 2019). Furthermore, in consistent with the UK Biobank study, (Doiron et al., 2019) the present study also found a larger effect in magnitude of $PM_{2.5}$ on FEV_1 than FVC, denoting a obstructive effect of $PM_{2.5}$.

Previous findings about the effects of $PM_{2.5}$ on FEV_1/FVC were quite inconsistent (Doiron et al., 2019; Rice et al., 2015; Guo et al., 2018; Schikowski et al., 2014; Forbes et al., 2009). The current study observe a statistically significant association, which is consistent with the UK Biobank study and the Taiwan MJ Health Management Institution cohort study even though the effect of $PM_{2.5}$ in our study was much smaller. In their study, every IQR (1.27 μg/m^3 and 8.54 μg/m^3, respectively) increment in $PM_{2.5}$ was associated with a decrease of 2.46% (95% CI: 2.17–2.75) and 0.36% (95% CI: 0.32–0.38) in FEV_1/FVC, respectively (Doiron et al., 2019; Guo et al., 2018). However, no

Table 3
Mean differences of PEF, $FEF_{25\%}$, $FEF_{50\%}$, $FEF_{75\%}$, $FEF_{25-75\%}$ per interquartile increase of concentrations of $PM_{2.5}$ and constituents.

	PEF (mL/s)		$FEF_{25\%}$ (mL/s)		$FEF_{50\%}$ (mL/s)		$FEF_{75\%}$ (mL/s)		$FEF_{25-75\%}$ (mL/s)	
	β (95% CI)	*q* value	β (95% CI)	*q* value	β (95% CI)	*q* value	β (95% CI)	*q* value	β (95% CI)	*q* value
$PM_{2.5}$ (22.42 μg/m^3)	−86.64 (-113.52, −59.77)	<0.0001	−62.94 (-89.61, −36.27)	<0.0001	−43.05 (-62.23, −23.87)	<0.0001	−16.63 (-25.17, −8.10)	0.0003	−31.93 (-47.22, −16.64)	<0.0001
BC (1.30 μg/m^3)	−150.84 (-171.10, −130.58)	<0.0001	−91.20 (-111.33, −71.07)	<0.0001	−16.18 (-30.67, −1.70)	0.036	4.05 (-2.40, 10.49)	0.24	3.63 (-7.93, 15.19)	0.56
OM (6.12 μg/m^3)	−146.72 (-179.28, −114.16)	<0.0001	−93.67 (-125.99, −61.35)	<0.0001	−43.16 (-66.41, −19.91)	0.0005	−14.51 (-24.85, −4.17)	0.0082	−27.05 (-45.59, −8.52)	0.0060
NH_4^+ (3.09 μg/m^3)	−104.93 (-129.80, −80.06)	<0.0001	−71.14 (-95.83, −46.46)	<0.0001	−36.86 (-54.62, −19.11)	<0.0001	−14.54 (-22.44, −6.64)	0.0005	−26.50 (-40.65, −12.35)	0.0004
SO_4^{2-} (5.51 μg/m^3)	−87.93 (-118.63, −57.23)	<0.0001	−58.55 (-89.02, −28.09)	0.0003	−23.96 (-45.88, −2.05)	0.040	−8.14 (-17.89, 1.61)	0.12	−4.34 (-21.80, 13.12)	0.63
NO_3^- (5.89 μg/m^3)	−118.59 (-144.74, −92.43)	<0.0001	−81.00 (-106.96, −55.04)	<0.0001	−47.89 (-66.56, −29.22)	<0.0001	−20.74 (-29.05, −12.44)	<0.0001	−42.24 (-57.13, −27.35)	<0.0001
Soil dust (3.93 μg/m^3)	142.42 (113.70, 171.14)	<0.0001	55.51 (26.99, 84.03)	0.0003	−63.65 (-84.16, −43.14)	<0.0001	−31.64 (-40.76, −22.52)	<0.0001	−69.67 (-85.98, −53.35)	<0.0001

Abbreviations: BC, black carbon; $FEF_{25\%}$, forced expiratory flow at 25% of exhaled forced vital capacity; $FEF_{25-75\%}$, forced expiratory flow at 25–75% of exhaled forced vital capacity; $FEF_{50\%}$, forced expiratory flow at 50% of exhaled forced vital capacity; $FEF_{75\%}$, forced expiratory flow at 75% of exhaled forced vital capacity; NH_4^+, ammonium; NO_3^-, nitrate; OM, organic matter; PEF, peak expiratory flow; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than or equal to 2.5 μm; SD, standard deviation; SO_4^{2-}, sulfate.
The models were adjusted for sex, age, residence (urban/rural), geographic region (northeast/north/ northwest/southwest/central/east/ south), education level, occupation, body mass index, smoking history (current smoker/former smoker/nonsmoker), smoking exposure (pack-years), smokers living in the home, biomass use, type of biomass use (woody fuels, animal waste, or both), duration of biomass use (years), the season for pulmonary function test, history of pneumonia or bronchitis during childhood, chronic cough during childhood, and parental history of respiratory diseases.
q values were false discovery rate adjusted *P* values.

Table 4
Mean differences of FEV_3, FEV_6, FEV_3/FEV_6, IC, and VC per interquartile increase of concentrations of $PM_{2.5}$ and constituents.

	FEV_3 (mL)		FEV_6 (mL)		FEV_3/FEV_6 (%)		IC (mL)		VC (mL)	
	β (95% CI)	*q* value	β (95% CI)	*q* value	β (95% CI)	*q* value	β (95% CI)	*q* value	β (95% CI)	*q* value
$PM_{2.5}$ (22.42 μg/m^3)	−19.42 (-29.11, −9.73)	0.0002	−16.13 (-26.78, −5.49)	0.0043	−0.21 (-0.27, −0.14)	<0.0001	−32.09 (-42.70, −21.49)	<0.0001	−18.76 (-29.40, −8.12)	0.0009
BC (1.30 μg/m^3)	−17.69 (-25.06, −10.33)	<0.0001	−14.90 (−23.17, −6.63)	0.0007	−0.11 (-0.16, −0.06)	<0.0001	−29.66 (-37.69, −21.62)	<0.0001	−25.38 (−33.42, −17.35)	<0.0001
OM (6.12 μg/m^3)	−22.27 (-34.03, −10.51)	0.0004	−17.77 (-30.75, −4.78)	0.0100	−0.24 (-0.32, −0.17)	<0.0001	−35.91 (-48.78, −23.04)	<0.0001	−21.98 (-34.88, −9.09)	0.0013
NH_4^+ (3.09 μg/m^3)	−19.47 (-28.43, −10.50)	<0.0001	−16.85 (-26.72, −6.98)	0.0013	−0.16 (-0.21, −0.10)	<0.0001	−36.17 (-45.99, −26.35)	<0.0001	−19.96 (-29.81, −10.11)	0.0001
SO_4^{2-} (5.51 μg/m^3)	−9.90 (-20.96, 1.16)	0.09	−3.56 (-15.74, 8.61)	0.58	−0.26 (-0.33, −0.18)	<0.0001	−43.21 (-55.33, −31.08)	<0.0001	−18.61 (-30.77, −6.46)	0.0039
NO_3^- (5.89 μg/m^3)	−24.40 (−33.84, −14.96)	<0.0001	−22.79 (−33.21, −12.37)	<0.0001	−0.14 (-0.20, −0.08)	<0.0001	−34.10 (-44.44, −23.76)	<0.0001	−18.75 (-29.11, −8.40)	0.0006
Soil dust (3.93 μg/m^3)	−13.44 (−23.70, −3.17)	0.014	−13.66 (-24.73, −2.59)	0.021	−0.23 (-0.30, −0.17)	<0.0001	5.83 (-5.47, 17.13)	0.33	−3.18 (-14.55, 8.20)	0.60

Abbreviations: BC, black carbon; FEV_3, forced expiratory volume in three seconds; FEV_6, forced expiratory volume in six seconds; IC, inspiratory capacity; NH_4^+, ammonium; NO_3^-, nitrate; OM, organic matter; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than or equal to 2.5 μm; SD, standard deviation; SO_4^{2-}, sulfate; VC, vital capacity.
The models were adjusted for sex, age, residence (urban/rural), geographic region (northeast/north/ northwest/southwest/central/east/ south), education level, occupation, body mass index, smoking history (current smoker/former smoker/nonsmoker), smoking exposure (pack-years), smokers living in the home, biomass use, type of biomass use (woody fuels, animal waste, or both), duration of biomass use (years), the season for pulmonary function test, history of pneumonia or bronchitis during childhood, chronic cough during childhood, and parental history of respiratory diseases.
q values were false discovery rate adjusted *P* values.

statistical significant association between $PM_{2.5}$ and FEV_1/FVC was found in the Framingham Offspring or Third Generation studies (Rice et al., 2015). The estimates on FEV_1/FVC seem to be in line with the pattern of associations with FEV_1 and FVC. Previous studies showing larger effect in magnitude of $PM_{2.5}$ on FVC than FEV_1 did not find statistically significant association of $PM_{2.5}$ with FEV_1/FVC, whereas those showing larger effect in magnitude on FEV_1 than FVC found statistically significant association of $PM_{2.5}$ with FEV_1/FVC. The inconsistency in

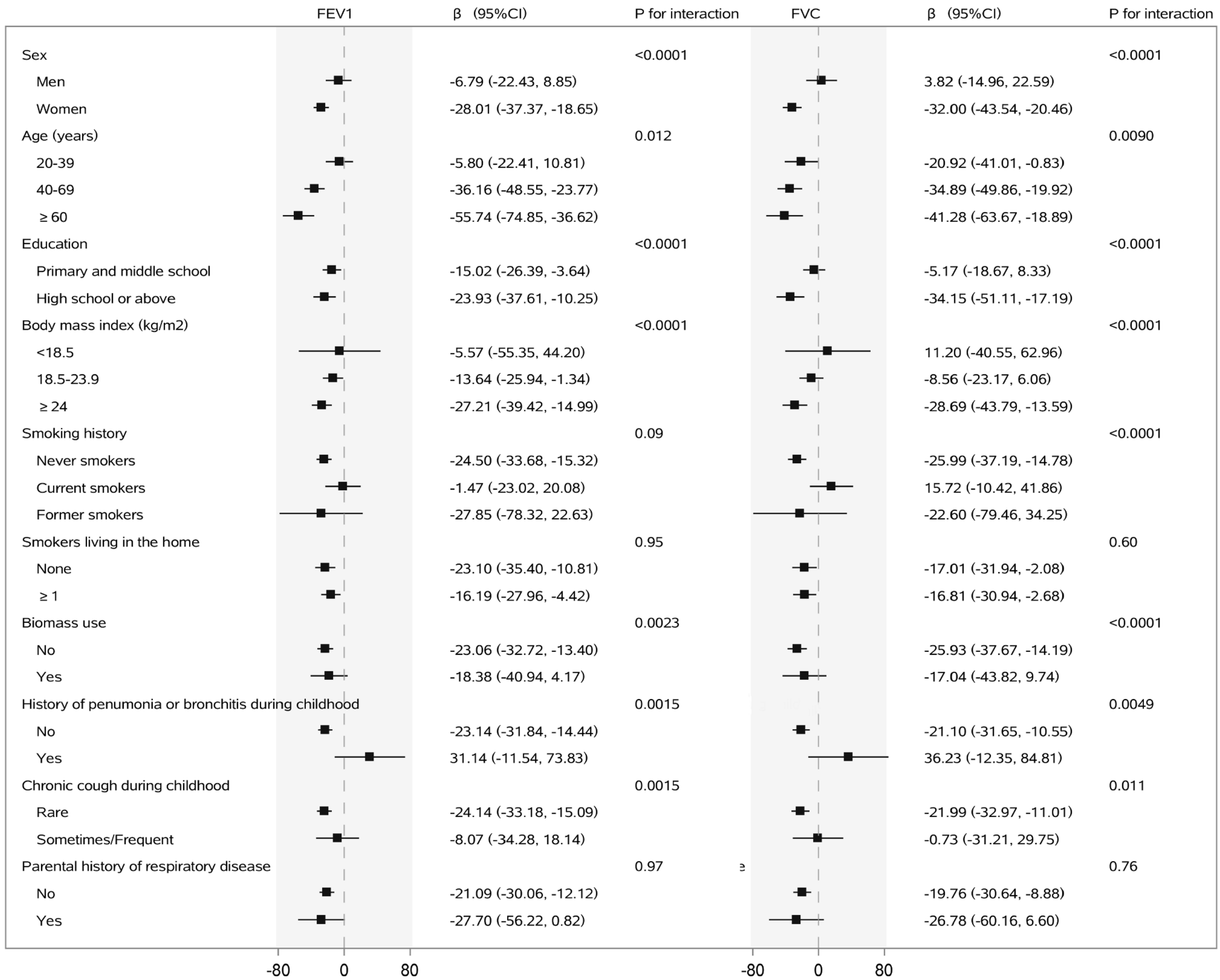

Fig. 2. Changes of FEV_1 and FVC per interquartile increase of concentrations of $PM_{2.5}$, classified by different subgroups. FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than or equal to 2.5 μm. $P_{interaction}$ values were false discovery rate adjusted.

findings of different studies may be attributable to the differences in $PM_{2.5}$ levels, $PM_{2.5}$ chemical compositions and population susceptibility.

FEF reflects the most effort-independent portion of the flow-volume curve and the most sensitive airflow to small airways, where disease of chronic airflow obstruction are thought to originate (McNulty and Usmani, 2014). Small airway was considered “quiet zone” where disease may accumulate over years before obstructive disease being noticed (Tanabe et al., 2018). PEF is effort dependent and largely a function of the caliber of large airways when a maximal effort is made (McNulty and Usmani, 2014). We found that long-term $PM_{2.5}$ exposure was significantly associated with lower FEF, which was consistent with the WHO Study on global AGEing and adult health (SAGE), among participants aged ≥ 50 years old from six low- and middle- income countries (Lin et al., 2018). Our study also found $PM_{2.5}$ to be statistically significantly associated with decreased PEF, but was not consistent with WHO SAGE study (Lin et al., 2018). In the Genetic Epidemiology of COPD (COPDGene) cohort, FEV_3/FEV_6 was found to be an indicator of small airway obstruction in current and ex-smokers with normal FEV_1/FVC (Dilektasli et al., 2016). To our knowledge, our study was the first one reporting negative associations of $PM_{2.5}$ and its constituents with FEV_3/FEV_6.

It is of great significance to identify the key toxic constituents of $PM_{2.5}$ to optimize the formulation of air pollution control measures, as well as to aid in the understanding of biological mechanism for the adverse health effects. However, very few studies have explored the long-term effects of one or two constituents on lung function (Wang et al., 2019; Franco Suglia et al., 2008; Lepeule et al., 2014; Laeremans et al., 2018). For example, the Maternal-Infant Smoking Study of East Boston, which included 272 women 18–42 years of age, found decreased (but insignificant) levels of FEV_1, FVC, and $FEF_{25-75\%}$ in association with BC (Franco Suglia et al., 2008). The present study found all the 6 constituents were statistically significantly and inversely associated with most indicators of lung function, with OM and nitrate showing consistently larger associations in magnitude than other constituents. To our knowledge, our study was the first large-scale study to compare the potentially differentiated associations of long-term exposure to various constituents of $PM_{2.5}$ with a series of lung function indicators.

Besides, we observed interactions of sex, smoking, biomass use, history of pneumonia or bronchitis or chronic cough during childhood with annual $PM_{2.5}$ exposure on FEV_1 and FVC. In our study, women were more vulnerable, which may be due to their greater airway reactivity to air pollutants and lower socioeconomic status than men (Clougherty, 2010). The effect modification of sex was in line with one study conducted among Atherosclerosis Risk in Communities (ARIC) study, which found statistically significant effects of traffic-related air pollution on lung function among women but not among men (Kan et al., 2007). The effect modification of history of pneumonia or bronchitis during childhood and chronic cough during childhood may be attributable to the much smaller sample size that attenuating the statistical power. The insignificant association among smokers and participants with biomass use may be related to the attenuated effects of $PM_{2.5}$ on lung function by smoking and biomass use through the common biological pathways.

Several limitations of this study should be addressed. First, given the cross-sectional nature, it is difficult to provide causal inferences about the relationship between $PM_{2.5}$ or its constituents and lung function impairment. Therefore, prospective cohort studies are needed to validate our study findings. Second, exposure misclassification errors were evitable as we did not directly measure the personal exposure to $PM_{2.5}$ and $PM_{2.5}$ constituents. Nevertheless, we estimated the residential concentrations at a spatial resolution of about 1×1 km, a reasonably fine precision of exposure modelling as done in previous large cohort studies (Di et al., 2017). The lack of available ground monitors for direct calibration $PM_{2.5}$ constituents, although it has been validated in North America, may increase the uncertainty of our exposure estimates of constituents. Third, limited by the data availability, we failed to evaluate the associations of long-term exposure to elemental (e.g., metallic) constituents of $PM_{2.5}$ with lung function. Lastly, attention should be paid when the results from constituent-$PM_{2.5}$ joint models due to the high collinearity between $PM_{2.5}$ and its constituents.

5. Conclusion

In conclusion, this nationwide study demonstrated long-term exposure to ambient $PM_{2.5}$ air pollution was statistically significantly associated with lower levels of both large- and small- airway function in China. Our investigation also provides first-hand epidemiological evidence that long-term exposure to some constituents, especially OM and nitrate, might be more important in impairing lung function. More prospective cohort studies are warranted to further differentiate and confirm the long-term effects of various $PM_{2.5}$ constituents on lung function.

CRediT authorship contribution statement

Ting Yang: Funding acquisition, Investigation, Methodology, Writing - review & editing. **Renjie Chen:** Conceptualization, Formal analysis, Funding acquisition, Methodology, Writing - review & editing. **Xiaoying Gu:** Conceptualization, Data curation, Formal analysis, Methodology, Writing - original draft. **Jianying Xu:** Investigation. **Lan Yang:** Investigation. **Jianping Zhao:** Investigation. **Xiangyan Zhang:** Investigation. **Chunxue Bai:** Investigation. **Jian Kang:** Investigation. **Pixin Ran:** Investigation. **Huahao Shen:** Investigation. **Fuqiang Wen:** Investigation. **Kewu Huang:** Investigation. **Yahong Chen:** Investigation, Data curation. **Tieying Sun:** Investigation. **Guangliang Shan:** Investigation. **Yingxiang Lin:** Investigation. **Sinan Wu:** Investigation. **Jianguo Zhu:** Investigation. **Ruiying Wang:** Investigation. **Zhihong Shi:** Investigation. **Yongjian Xu:** Investigation. **Xianwei Ye:** Investigation. **Yuanlin Song:** Investigation. **Qiuyue Wang:** Investigation. **Yumin Zhou:** Investigation. **Liren Ding:** Investigation. **Ting Yang:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology. **Wanzhen Yao:** Investigation. **Yanfei Guo:** Investigation. **Fei Xiao:** Investigation. **Yong Lu:** Investigation. **Xiaoxia Peng:** Investigation. **Biao Zhang:** Investigation. **Dan Xiao:** Investigation. **Zuomin Wang:** Investigation. **Hong Zhang:** Investigation. **Xiaoning Bu:** Investigation. **Xiaolei Zhang:** Investigation. **Li An:** Investigation. **Shu Zhang:** Investigation. **Zhixin Cao:** Investigation. **Qingyuan Zhan:** Investigation. **Yuanhua Yang:** Investigation. **Lirong Liang:** Investigation. **Bin Cao:** Investigation. **Huaping Dai:** Investigation. **Aaron van Donkelaar:** Investigation. **Randall V. Martin:** Investigation. **Tangchun Wu:** Investigation, Funding acquisition. **Jiang He:** Investigation. **Haidong Kan:** Conceptualization, Data curation, Funding acquisition, Methodology, Supervision, Writing - review & editing. **Chen Wang:** Conceptualization, Data curation, Investigation, Funding acquisition, Methodology, Supervision, Writing - review & editing.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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