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The role of influenza vaccination in mitigating the adverse impact of ambient air pollution on lung function in children: new insights from the Seven Northeastern Cities Study in China

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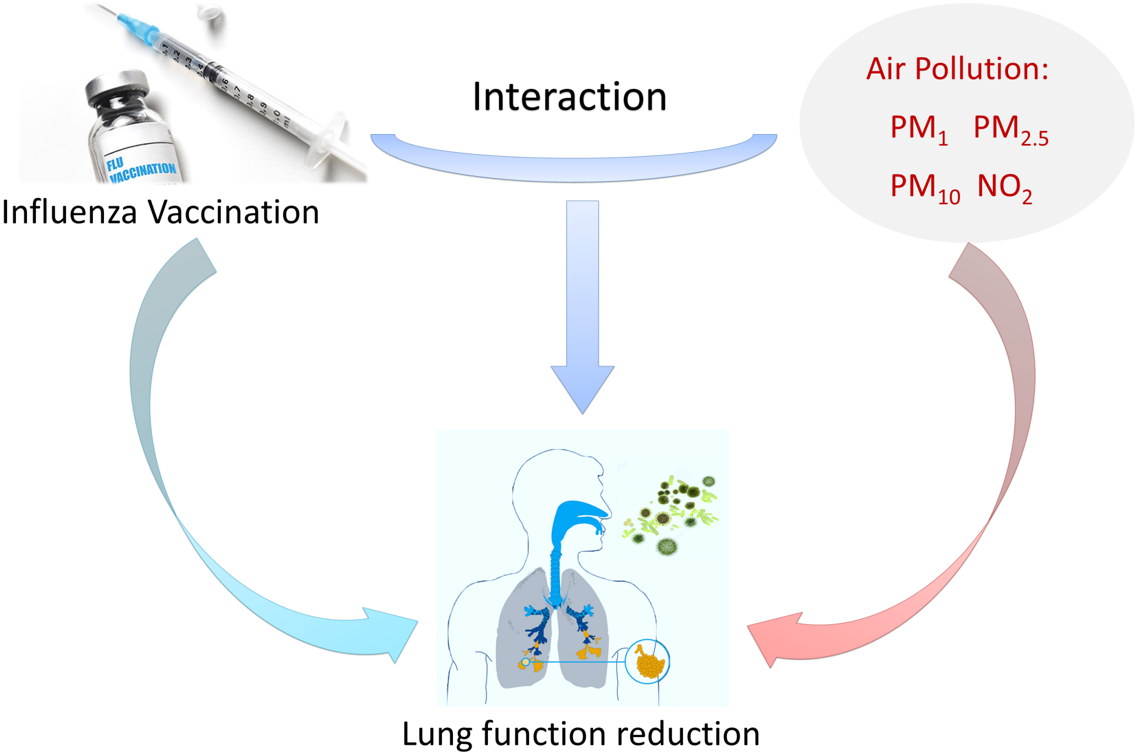
FLU VACCINATION
Influenza Vaccination
Interaction
Air Pollution:
PM_1 $PM_{2.5}$
PM_{10} NO_2
Lung function reduction

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ABSTRACT

Background

Ambient air pollution exposure and influenza virus infection have been documented to be independently associated with reduced lung function previously. Influenza vaccination plays an important role in protecting against influenza-induced severe diseases. However, no study to date has focused on whether influenza vaccination may modify the associations between ambient air pollution exposure and lung function.

Methods

We undertook a cross-sectional study of 6740 children aged 7-14 years into Seven Northeast Cities (SNEC) Study in China during 2012-2013. We collected information from parents/guardians about sociodemographic factors and influenza vaccination status in the past three years. Lung function was measured using portable electronic spirometers. Machine learning methods were used to predict 4-year average ambient air pollutant exposures to nitrogen dioxide (NO_2) and particulate matter with an aerodynamic diameter <1μm (PM_1), <2.5μm ($PM_{2.5}$) and <10μm (PM_{10}). Two-level linear and logistic regression models were used to assess interactions between influenza vaccination and long-term ambient air pollutants exposure on lung function reduction, controlling for potential confounding factors.

Results

Ambient air pollutions were observed significantly associated with reductions in lung function among children. We found significant interactions between influenza vaccination and air pollutants on lung function, suggesting greater vulnerability to air pollution among unvaccinated children. For example, an interaction ($p_{interaction}$=0.002) indicated a -283.44 mL (95% CI: -327.04, -239.83) reduction in forced vital capacity (FVC) per interquartile range (IQR) increase in PM_1 concentrations among unvaccinated children, compared with the -108.24 mL (95%CI: -174.88, -41.60) reduction in FVC observed among vaccinated children. Results from logistic regression models also showed stronger associations between per IQR increase in PM_1 and lung function reduction measured by FVC and peak expiratory flow (PEF) among unvaccinated children than the according ORs among vaccinated children [i.e., Odds Ratio (OR) for PM_1 and impaired FVC: 2.33 (95%CI: 1.79, 3.03) vs 1.65 (95%CI: 1.20, 2.28); OR for $PM_{2.5}$ and impaired PEF: 1.45 (95%CI: 1.12,1.87) vs 1.04 (95%CI: 0.76,1.43)]. The heterogeneity of the modification by influenza vaccination of the associations between air pollution exposure and lung function reduction appeared to be more substantial in girls than in boys.

Conclusion

Our results suggest that influenza vaccination may moderate the detrimental effects of ambient air pollution on lung function among children. This study provides new insights into the possible co-benefits of strengthening and promoting global influenza vaccination programs among children.

Keywords: air pollution, lung function, influenza vaccination

1. Introduction

Air pollution is the most significant global environmental risk factor for mortality and morbidity. It was estimated to be responsible for approximately 6.5 (5.7-7.3) million deaths in 2015 (Landrigan et al. 2018). The associations between air pollution and pulmonary function have been studied extensively since the mid 20th century (Landrigan et al. 2018). It is now acknowledged that children are more sensitive to the adverse effects of pollutants and virus infections than adults given their lungs continue to grow during childhood and immature immune system (Kajekar 2007; Nicholas et al. 2017). They also tend to spend more time outside, have a higher respiratory ventilation rate than adults, and expose to more air pollution relative to their body weight (Heinrich and Slama 2007; Landrigan et al. 2019). Therefore, the effects of air pollution on children respiratory health are of great concern. Lung function is an objective and measurable indicator for estimating respiratory health. Many studies have assessed lung function reduction associated with air pollution exposure and among children (Brunekreef et al. 2018; Fuentes et al. 2018; Gehring et al. 2013). Epidemiological studies have consistently indicated that air pollution exposures are associated with decreased lung function (Hu et al. 2019; Knibbs et al. 2018; Usemann et al. 2019).

Investigators have increasingly focused on potential associations between infectious diseases and air pollution exposure, including influenza (CWS Chen et al. 2018; MacIntyre et al. 2014; Nhung et al. 2018). The results of experimental studies suggest that air pollutant exposure increases vulnerability to viral respiratory infections (Castranova et al. 2001; Pardo et al. 2019). Epidemiological studies also suggest associations between greater ambient air pollution exposure and a higher risk of upper and lower respiratory virus infections, especially influenza infection (Feng et al. 2016; Nhung et al. 2018; Xu et al. 2013). Air pollution might exacerbate the risk for influenza infection, (Ghosh et al. 2015), this process may initiate an inflammatory reaction, oxidative stress, and immune response, reducing lung function and increasing the risk of infection (Kelly and Fussell 2015; Yang et al. 2017). However, influenza vaccination could potentially protect respiratory health from air pollution, particularly in locations with a high health burden due to both risk factors. So far, no study explores it.

Influenza vaccination is an important pathway for the prevention of influenza and other diseases complication, recommended by World Health Organization (WHO 2018), a recent meta-analysis reported an influenza vaccine coverage rate of only 9.4% among the general population of mainland China (Wang et al. 2018). An experiment study showed that influenza vaccine could generates durable, strain-specific humoral immunity, especially for live-attenuated influenza vaccines which could generate lung tissue-resident memory T cells resulting in providing long-term protection against non-vaccine viral strains besides of vaccine viral strains. Epidemiologic studies have indicated influenza vaccination may protect lung function from severe respiratory diseases triggered by influenza infections in addition to reducing influenza infection risk (Grijalva et al. 2015; Kopsaftis et al. 2018; Vasileiou et al. 2017). In despite of the potentially protective effects of influenza vaccine, no study to date has examined associations of both influenza vaccination and long-term ambient air pollution exposure with lung function. Therefore, we hypothesized that influenza vaccination would modify associations between air pollution exposure and respiratory function. To test the hypothesis, we analyzed data from the Seven Northeastern Cities Study (SNEC) in China, a large population-based investigation with detailed data on influenza vaccination status, air pollution concentrations and lung function outcomes among 6740 children. We found the interactions existed between long-term air pollution and influenza vaccination on lung function.

2. Methods

2.1. Study design and recruitment

We undertook a population-based cross-sectional study of children aged 7-14 years from April 1st 2012 to October 31st 2013 in China: the Seven Northeast Cities (SNEC) Study. The study protocol was described in detail in a previous publication (Hu et al. 2017a). Briefly, we selected seven cities in Liaoning province in order to maximize heterogeneity of ambient air pollutants levels (Fig S1). As summarized in Figure 1, we identified children residing in 24 administrative districts of the seven cities, which were selected based on ambient air pollutants concentrations levels from 2009 to 2012: five districts in Shenyang, four districts in Dalian and Fushun, two districts in Liaoyang, and three districts each in Anshan, Benxi, and Dandong. Each district had only one ground-based air quality monitor station. We targeted schools within a two-kilometer radius around air monitoring stations located in each district to enroll participants. Chinese regulations mandate attendance at schools nearest to a student’s home; all participants lived within two kilometers of their school. We chose one or two elementary schools and one middle school randomly according to the size of the schools around each monitoring station. For schools with fewer than 500 students, we selected two schools in the district. For each school, we randomly chose one or two classes per grade. All students within selected classrooms were eligible to be enrolled if they had lived in the current study district for at least two years when we conducted the study.

We enrolled 7109 participants from 7326 eligible students (97%), and excluded 4.0% of participants who had lived for less than two years in the study district and 1.2% who did not complete the study questionnaire, leaving a total of 6740 in the current analysis (Figure 1). The Ethical Review Committee of Human Experimentation at Sun Yat-Sen University approved the study protocol (Ethics Approval Number: 2016016). The parents/legal guardians of each participating child completed written informed consent before study enrollment.

2.2. Study questionnaire

Informed consent forms, study background information and study questionnaires were distributed to the participants' parents/legal guardians ahead of the study. Participants' parent/legal guardian completed a comprehensive study questionnaire. The questionnaire included demographic, socioeconomic and lifestyle information about the participants and their families. Trained nurses measured participants' height and weight according to the World Health Organization standardized protocol for physical examination.

2.3. Pulmonary function measurement (spirometry)

We performed spirometry according to American Thoracic Society (ATS)/European Respiratory Society (ETS) recommendations (Miller et al. 2005), as described in detail in a previous publication (Hu et al. 2017b). In brief, measurements included forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), peak expiratory flow (PEF) and maximal mid-expiratory flow (MMEF) from two portable electronic type spirometers

(Spirolab, MIR, Italy). All study personnel completed a training program to ensure compliance with standardized data collection protocols, including spirometry. We explained the procedure to each participant and asked them to complete the spirometry tests three times. Each participantneeded to be tested in the standing position, wearing a nose clip and in a quiet and comfortable room. The time interval between each measurement was at least two minutes, and the differences between in the three times measured results of FVC and FEV_1 should be less than 5%, respectively. FVC and FEV_1 values should be the largest measurement from the three measurements. The captured results of measured lung function values (FVC, FEV_1, PEF, and MMEF) were continuous variables. Meanwhile, we used our previously developed equations to predict reference values for impaired lung function among Chinese children, according to gender, age, height and weight (Ma et al. 2013). We defined binary variables of reduced lung function as FVC less than 85%, FEV_1 less than 85%, PEF less than 75%, or MMEF less than 75% of predicted values for Chinese children as described in a previous publication (Ma et al. 2013).

2.4. Assessment of ambient air pollutants

Daily concentrations of particular matter (PM) with an aerodynamic diameter of 1 μm or less (PM_1), 2.5 μm or less ($PM_{2.5}$), 10 μm or less (PM_{10}) and nitrogen dioxide (NO_2), were predicted with a machine learning modeling at a 0.1° x 0.1° scale, based on air pollutants concentrations recorded by ground-based air quality monitoring stations (G Chen et al. 2018a; G Chen et al. 2018b). A full description of our exposure assessment strategy can be found in our previous publication and the Supplementary Material eMethods 1 (Yang et al. 2018; Zhang et al. 2019). All air pollutant measures were carried out according to the State

Environmental Protection Administration of China standards (SEPA 1992). We used machine learning methods (i.e., random forests) to predict PM concentrations linking the ground-monitored air pollution data to satellite remote sensing Moderate Resolution Imaging Spectroradiometer (MODIS) products and aerosol optical depth data (AOD), meteorology data and land use information as previously described in detail (G Chen et al. 2018a; G Chen et al. 2018b) and by eMethods 1 in the Supplementary Material. The assessment for NO_2 concentrations was based on the satellite-derived Ozone Monitoring Instrument (OMI) Nitrogen Dioxide (NO_2) Data Product (i.e., Daily Level-3 NO_2 Product) and other predictors. Ten-fold cross-validation was performed to validate the prediction models. The R^2 values of daily and annual air pollution predictions ranged from 55% to 83% and 72% to 86%, respectively. The root mean squared errors (RMSE) of daily and annual predictions for air pollutants ranged from 12.4 $\mu g/m^3$ to 31.5 $\mu g/m^3$ and 6.5 $\mu g/m^3$ to 14.4 $\mu g/m^3$, respectively. Detailed information related to the prediction of air pollutants is provided in Supplementary Table S1. Then the annual average values of air pollutants concentrations were calculated by predicted air pollutants concentrations from 2009 to 2012, which considered as long-term ambient air pollution exposure in this study.

2.5. Meteorological factors

We estimated average daily temperature and relative humidity using a spatial statistical model based on data collected by meteorological stations in each of the seven study cities. We assigned individual-level annual average temperatures and annual average relative humidity based on daily averages from 2009 to 2012.

2.6. Influenza vaccination exposure

The influenza vaccine exposure status of participants was based on the parents'/guardians' response to the question "Have you ever received the influenza vaccine in the past three years?" The licensed seasonal influenza vaccines are used widely for influenza prevention, especially for children, old people, pregnant women and others with chronic disease. During the study period, the available vaccines are inactivated influenza vaccines approved by the Health Ministry in China.

2.7. Potential confounders

We examined potential confounding variables as common predictors of lung function and air pollutant exposure based on the literature (Gauderman et al. 2004; Hu et al. 2017a). A directed acyclic graph (DAG) was used to select a minimally sufficient set of covariates to adjust for confounding (Greenland et al. 1999) (Fig S2), with DAGitty v3.0 software (www.dagitty.net). Potential confounders included: age (years), gender (boy or girl), parental education (completed 12-year normal education; Yes/No), annual family income (<10,000 Yuan, 10,000 – 30,000 Yuan, 30,001 – 100,000 Yuan, >100,000 Yuan), environmental tobacco smoke exposure (passive smoke exposure in the home; Yes/No), body mass index (BMI) calculated as weight divided by height squared (kg/m^2) and categorized as normal, overweight (>85th percentile), or obese (>95th percentile) according to BMI-for age smoothed percentile curve charts from the US Centers for Disease Control and Prevention (Kuczmarski et al. 2000), annual average temperature and annual average relative humidity. Additional details about study covariates are provided in Supplementary Material eMethods 2.

2.8. Statistical analysis

We examined the distributions of all continuous variables using the mean (± standard deviation, SD) and categorical variables with n (%). We used Student's t-tests and Chi-square tests for continuous and categorical variables, respectively, to compare differences between vaccinated and unvaccinated children. Spearman's rank correlation coefficients were used to examine correlations between air pollutants.

We identified a linear trend for associations between ambient air pollutant concentrations and lung function and so we used two-level linear and logistic regression models to estimate associations between lung function and air pollution. Children were the first-level units and study districts were the second-level units. Details are provided in the Supplementary Material eMethods3. We used single-pollutant models were to avoid multi-collinearity, given strong correlations among air pollutants (Table S2). We operationalized air pollutant concentrations as continuous variables to maximize statistical power and as quartiles to investigate non-linear associations. For continuous air pollutants, we expressed effect estimates per change in the interquartile range (IQR) (i.e., differences between the 75th percentile and the 25th percentile). We adjusted for age, gender, parental education, household income, environmental tobacco smoke exposure, BMI category, annual average temperature and annual average relative humidity based on our DAG. We included the cross-product term "air pollutant × influenza vaccination status" in each model to assess the interaction.

In addition, we used a series of sensitivity analyses to assess the robustness of our models. To assess the impact of gender differences, we stratified the analysis by gender. To reduce the impact of indoor air pollution exposure, asthma and other respiratory diseases on lung function, we analyzed excluding children with household indoor fuel use, asthma and home renovation in the past two years, children with asthma and children with a history of pneumonia, bronchitis and pertussis, respectively. To control the impacts of other related factors, we also further adjusted regression models for home with mildew and family history of atopy.

All statistical analyses were carried out with SAS 9.4 (SAS Institute, Cary, NC USA) and R version 3.5.3. Statistical significance was defined as a two-tailed *p*-value less than 0.05 for main effects and *p*-value less than 0.10 for interactions.

3. Results

Characteristics of the children are presented in Table 1. The total of 6740 children aged 7-14 years, including 3358 (49.82%) girls. In this study, approximately 32.31% of the children had received at least one influenza vaccination in the past three years. Participants were 11.56 years of age on average and 50.18% were boys. The characteristics were different in age, sex, parental education more than higher school, household income, BMI, environmental tobacco smoke exposure, household fuel use, home mildew, home renovation in the past three years between vaccinated participants and unvaccinated participants in Table 1. The prevalence rates of lung function reduction were 8.58% for FEV_1 (defined as <75% predicted value) and 11.26% for FVC (defined as <85% predicted value).

The distributions of 2009-2012 average air pollutant concentrations are shown in Table 2. Average concentrations levels of $PM_{2.5}$ and PM_{10} were much higher than WHO air quality guideline standards (for $PM_{2.5}$: 54.0 μg/m^3 vs 10.0 μg/m^3; for PM_{10}: 95.6 μg/m^3 vs 20.0 μg/m^3). The interquartile range (IQR) of air pollutants are also displayed in Table 2: 13.1 μg/m^3 for PM_1, 10.0 μg/m^3 for $PM_{2.5}$, 13.8 μg/m^3 for PM_{10} and 7.3 μg/m^3 for NO_2. The annual average daily mean temperature was 8.4 β (± 1.1β). The annual average daily relative humidity was 62.0 (± 3.4).

The linear trend analysis results for associations between quartiles of ambient air pollutant concentrations and lung function among children are shown in Figure 2. All *p*-values for linear trends were statistically significant. Table 3 displays the results of two-level linear regression models to describe associations of air pollutants with continuous lung function measurements, adjusted for confounding variables. The results of unadjusted associations are provided in Table S4. We detected statistically significant interactions between influenza vaccination and air pollutants, suggesting greater vulnerability among unvaccinated children. For example, an interaction ($p_{interaction}$= 0.002) indicated a -283.44 mL (95%CI: -327.04, -239.83) reduction in FVC per IQR increase in PM_1 concentrations among unvaccinated children, compared with the -108.24 mL (95%CI: -174.88, -41.60) reduction in among vaccinated children. We detected a similar interaction for $PM_{2.5}$ ($p_{interaction}$= 0.037). Likewise, an interaction ($p_{interaction}$=0.002) indicated a -195.86 mL reduction (95%CI: -235.23, -156.50) in FEV_1 per IQR increase PM_1 concentration among unvaccinated children, yet 67.90 mL lower (95%CI: -126.55, -9.24) among vaccinated children. Again, we detected a similar interaction for $PM_{2.5}$ ($p_{interaction}$= 0.022). There was no modification of influenza vaccination on the associations between PM_{10} and the lung function values.

The results of two-level logistic regression models describing associations between dichotomized lung function measures and air pollution exposure are described in Table 4, adjusted for confounding variables. The unadjusted associations are provided in Table S5. We found that exposure to greater concentrations of all air pollutants was significantly associated with a higher odds ratio (OR) of lung function reduction, measured as dichotomized FVC, FEV_1, PEF and MMEF, adjusted for confounding variables. We also detected several statistically significant interactions between influenza vaccination and air pollutants, suggesting greater vulnerability among unvaccinated children. For instance, an interaction ($p_{interaction}$=0.058) indicated that the adjusted OR for reduced FVC (defined as <85% of the predicted value) per IQR increase in PM_1 was 2.33 (95%CI: 1.79, 3.03) in unvaccinated children but 1.65 (95%CI: 1.20, 2.28) in vaccinated children. Similarly, a significant interaction ($p_{interaction}$=0.033) indicated that the adjusted OR of impaired PEF (defined as <75% of the predicted value) per IQR increase in PM_1 was 1.56 (95%CI: 1.13, 2.14) in unvaccinated children, but 0.98 (95%CI: 0.67, 1.44) in vaccinated children. Furthermore, we detected statistically significant interactions for associations between ambient $PM_{2.5}$ ($p_{interaction}$=0.061) and NO_2 ($p_{interaction}$=0.085) concentrations with influenza vaccination for reduced PEF.

Sensitivity analyses

The heterogeneity of the modification by influenza vaccination of the associations between air pollution exposure and lung function reduction appeared to be more substantial in girls than in boys (Table 5). For girls, per IQR increase in PM_1 and $PM_{2.5}$ was associated with higher estimated β value for lung function reduction by FVC in unvaccinated girls than the according β value in vaccinated girls [for FVC, PM_1: -225.85mL (95%CI: -276.03, -175.68) vs -103.19 (95%CI: -173.35, -33.04), $p_{\text{interaction}}$ = 0.025; $PM_{2.5}$: -171.27 (95%CI: -212.35, -130.19) vs

-79.80 (95%CI: -138.12, -21.48), $p_{\text{interaction}}$ = 0.052]. A similar pattern was observed for the associations between FEV_1 and PM_1 or $PM_{2.5}$ (Table 5). For boys, per IQR increase in PM_1 was associated with higher estimated β value for lung function reduction by FVC and FEV_1 in unvaccinated girls than the according β value in vaccinated girls [for FVC, -325.77 (95%CI: -392.37, -259.17) vs -107.01 (95%CI: -213.18, -0.84), $p_{\text{interaction}}$ =0.052; for FEV_1: -218.90 (95%CI: -277.87, -159.92) vs -70.16 (95%CI: -160.47, 20.15), $p_{\text{interaction}}$ =0.056]. The interactions between influenza vaccination and air pollutants measured by ground air monitoring stations on lung function were showed in Table S6-S7. When we excluded children with asthma, children with indoor air pollution exposure, children with pneumonia/bronchitis/pertussis and children living in a house in close to a roadway, the pattern of the results were consistent with the corresponding results among all study participants (Tables S8-S11). We also found similar results when we additionally adjusted the regression models for, home mildew and family history of atopy (Tables S12-S13).

4. Discussion

4.1. Key findings

In this large population-based cross-sectional study, we found that influenza vaccination modified associations between long-term ambient air pollution exposure and lung function reduction. To our knowledge, the current study is the first attempt to explore the impact of influenza vaccination on the adverse effects of ambient air pollution exposure on lung function in children.

4.2. Comparisons with other studies and interpretations

The detrimental effects of long-term exposure to ambient air pollution on lung function have been documented previously, which were consistent with our results (Gauderman et al. 2004; Milanzi et al. 2018; Wilker et al. 2019). However, there are no studies focus on the modification of influenza vaccination on the associations between air pollution and lung function which to compare our results. We found only one previous epidemiological study that assessed potential effect modification by vaccination on the associations between short-term air pollution and acute coronary syndrome (ACS) (Huang et al. 2016). A case-crossover study of 1835 aging Taiwan National Health Insurance Research Dataset members, reported significantly stronger associations between greater short-term (i.e., 3 day) ambient $PM_{2.5}$, PM_{10}, NO_2 and CO exposures and an elevated risk of ACS among subjects without three-year continual influenza vaccine coverage than among subjects with three year continual influenza vaccine coverage (Huang et al. 2016). Compared with our study, although the previous study had different study designs, participants' characteristics and health outcomes, it indirectly supported our results indicating benefits of influenza vaccination on mitigating the lung function reduction resulting from air pollution exposure. Besides the long-term reducing air pollution and related intervention strategies, it could provide new insight into a possible individual intervention to be against the impact of air pollution on health.

An interesting finding of the present study is that we found significant interactions between air pollutants PM_1 and $PM_{2.5}$ and influenza vaccination on lung function reduction, but we did not find any significant interactions between PM_{10} and influenza vaccination. Different PM sizes and compositions may have different influences on the respiratory system(Kelly and Fussell 2012). In this study, we found the associations among PM_1, $PM_{2.5}$ and PM_{10} with lung function reduction were decreasing in descending order. Compared to PM_{10}, the smaller sized PM_1 and $PM_{2.5}$, which penetrate more deeply into the lung, are believed to have greater potential for adverse effects on lung function (Pope and Dockery 2006). In our study, the mean $PM_1/PM_{2.5}$ ratio was 0.87 for seven highly industrialized Chinese cities, which indicated that PM_1 was the major constituent of $PM_{2.5}$. We also found the smaller sized PM_1 may play a great role than $PM_{2.5}$ in lung function reduction, which is consistent with our previous studies (Yang et al. 2019; Yang et al. 2018). The possible reason was that fine and even smaller ultrafine PM may translocate from the respiratory system through pulmonary alveoli into the bloodstream and be transported to other parts of the body (DeMeo et al. 2004; Elder et al. 2006). PM_{10} and $PM_{2.5}$ are commonly measured for assessment of air quality throughout the world, yet our results provide new insight into the importance of PM_1 exposure as a potential new air quality indicator for health assessment. This is of particular significance, since modern cars, with a very efficient combustion process, emit very little in terms of larger particles (> 1 µm), but often a significant number of smaller particles (< 1 µm).

In this study, we explored influenza vaccination as a modifier of air pollution-lung function associations in children. The potential possibly mechanisms by which influenza vaccination might modify associations in children are unknown. Influenza virus may potentiate the adverse effects of air pollutants on lung function, leading to more serious respiratory disease (Desforges et al. 2018; Wong et al. 2009). Thus, the influenza vaccine may reduce the risk of coexposure to influenza and air pollution, thereby offering protection. Unfortunately, we did not capture a history of influenza infection in this study and so we were unable to explore this hypothesis. Additionally, airborne PM exposure may induce oxidative stress, airway inflammation and unbalance of Th1/Th2 immune responses, which have been explored in experimental studies (Huang et al. 2009; Kelly and Fussell 2015). Viruses are unable to survive independently without attaching to other particles (Yang et al. 2011). Particles carrying bioaerosols, such as the influenza virus bioaerosolsmay penetrate the respiratory tract deeply, triggering airway inflammation and an alveolar immune response, with adverse impacts on lung function (Ghosh et al. 2015). Therefore, the influenza vaccine might help to moderate dysfunction associated with local airway immune responses, in particular as the influenza virus immune response follows a similar Th1/Th2 immune pathway as the immune response to air pollutant exposure (Mann et al. 2009; Yamaguchi et al. 2009). Further experimental studies and field trial epidemiological studies are necessary to explore and prove this hypothesis.

The differences of associations between air pollution and lung function reduction by influenza vaccination appeared to be more substantial in girls than those in boys, although a larger sample study will be necessary to formally test the hypothesis. The possible reasons are considered as follows: Growth spurt of lung function for girls at 12.3 years old, which is 2 years earlier than that of boys (Wang et al. 1993). Developmental differences in lung function among boys and girls might account for the disparity. Alternately, smaller lungs, with comparatively larger parenchymal volume and airway diameter may enhance girls’ resiliency to air pollutants relative to boys (Becklake and Kauffmann 1999; Lee et al. 2019). Additionally, influenza vaccination may increase individual immunity against virus infection and influence the testosterone levels which may modulate genes related to lipid metabolism leading to the differences between girls and boys (Furman et al. 2014). At the same time, air pollution could impact differentially as progesterone and estrogen concentrations and modify the pulmonary immune response between boys and girls (Frump et al. 2015; Fuentes et al. 2018).

4.3. Opportunities for intervention

It is critical to identify interventions to mitigate the adverse impacts of air pollution on respiratory health, especially for children (Landrigan et al. 2018). Beyond the long-term goal of cut emissions policies and implementing renewable energy policies at State level in China, influenza vaccination might offer the co-benefits of mitigating the adverse effects of air pollution on respiratory health at the individual level. The findings in this study could also provide with evidence for the benefit of influenza vaccine and the improvement of influenza vaccination status among children in China. The influenza vaccination coverage in China has not reached the targeted coverage rate 75% recommended by WHO. This study may motivate children to inoculate influenza vaccine and improve the immune defense for against the detrimental impact of air pollution on lung function and other respiratory diseases complication in China and other countries, resulting in decrease the burden of diseases from influenza related diseases or air pollution.

4.4. Strength and limitations

There are several strengths to this study, which lend confidence to the validity of our results. We enrolled a large, randomly selected sample of children in seven Chinese cities, with a high participation rate, and located in a heavily industrialized area with high air pollutant levels. This approach of a large sample size allowed adequate power to detect modest interactions between air pollution exposure and influenza vaccination and minimized the chance for a selection bias. Additionally, in this study, children lived within two kilometers of their school, indicating that the assessment of air pollutants may capture both home and school exposures. However, the potential limitations of the present study should be recognized. First, the cross-sectional study design precludes the assessment of temporality. However, given the novel nature of the study hypothesis, we believe it unlikely for respiratory sensitivity to air pollutants to have influenced influenza vaccination. Second, the predicted air pollutant concentrations at an individual level using machine learning modeling may have misclassified exposure for some participants. However, we believe that any misclassification is unlikely to have been related to lung function or influenza vaccination and so any bias was likely towards the null hypothesis. Third, residual confounding may have resulted if parents/guardians of children with respiratory problems were more likely to recall potential risk factors when self-completing the study questionnaires than parents of children without respiratory problems. However, we found similar results in a sensitivity analyzes excluding children with respiratory disorders (i.e., asthma, bronchitis, pneumonia, and pertussis) and so the impact was likely minimal. Likewise, we relied on parent/guardian self-report of influenza vaccination and we did not capture the exact time of influenza vaccination. The influence of this limitation is difficult to predict and so a future study employing medical records for vaccine administration will be required to assess the impact.

5. Conclusions

This study suggests that influenza vaccination may minimize the detrimental impact of ambient air pollution exposure on lung function in children. Our results offer new insights into the possible co-benefits of strengthening and promoting global influenza vaccination programs to mitigate the detrimental effects of air pollution on respiratory health, especially among children. Further comprehensive prospective intervention studies will help confirm these impacts.

Declaration of interests

We declare no competing interests.

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Table 1 Characteristics of children participating in the China Seven Northeastern Cities (SNEC) Study, by influenza vaccination.

Variables	Total (n=6740)	Non-Influenza vaccination (n=4562)	Influenza vaccination (n=2178)
Continuous variables	Mean ± SD	Mean ± SD	Mean ± SD
BMI (kg/m^2)	20.01 ± 4.67	20.06±4.34	19.90±5.29
Age (year) [a]	11.56 ± 2.07	11.46 ± 2.04	11.79±2.10
Exercise time per week (hour)	7.58 ± 7.77	7.55 ± 7.34	7.64 ± 8.61
Categorical variables	n (%)	n (%)	n (%)
Girls [a]	3358 (49.82)	2236 (49.01)	1122 (51.52)
Parental education ≥ high school [a]	4211 (62.48)	2592 (64.69)	1260 (57.85)
Household income per year (RMB) [a]			
<10000	1634 (24.24)	1069 (23.43)	565 (25.94)
10,000 – 30,000	2394 (35.52)	1645 (36.06)	749 (34.39)
30,001 – 100,000	2437 (36.16)	1685 (36.94)	752 (34.53)
>100,000	275 (4.08)	163 (3.57)	112 (5.14)
BMI [a]			
Normal weight	4518 (67.03)	3013 (66.05)	1505 (69.1)
Overweight	1068 (15.85)	761 (16.68)	307 (14.1)
Obese	1154 (17.12)	788 (17.27)	366 (16.8)
Environmental Tobacco smoke exposure [a]	3281 (48.68)	2157 (47.28)	1124 (51.61)
Household fuel use [a]	676 (10.03)	435 (9.54)	241 (11.07)
Home mildew [a]	898 (13.32)	639 (14.01)	259 (11.89)
Home renovation in the past 3 years [a]	2416 (35.85)	1573 (34.48)	843 (38.71)
Family history of atopy	1390 (20.62)	926 (20.30)	464 (21.30)
Doctor-diagnosed asthma	460 (6.82)	308 (6.75)	152 (6.97)
Doctor-diagnosed pneumonia	1057 (15.68)	768 (16.83)	289 (13.27)
Doctor-diagnosed bronchitis	196 (2.91)	130 (2.85)	66 (3.03)
Doctor-diagnosed pertussis	44 (0.65)	25 (0.55)	19 (0.87)
Spirometric parameters mean (SD)			
FVC(L)	2.63 ± 0.76	2.63 ± 0.75	2.61 ± 0.76
FEV$_1$ (L)	2.46 ± 0.70	2.46 ± 0.70	2.46 ± 0.70
PEF (L/s)	4.78 ± 1.41	4.78 ± 1.42	4.77 ± 1.40
MMEF (L/s)	3.35 ± 1.05	3.33 ± 1.06	3.39 ± 1.03
Lung function reduction n (%)			
FVC <85% predicted	759 (11.26)	497 (10.89)	262 (12.03)
FEV$_1$ <85% predicted	578 (8.58)	390 (8.55)	188 (8.63)
PEF <75% predicted	458 (6.80)	297 (6.51)	161 (7.39)
MMEF <75% predicted [a]	634 (9.41)	452 (9.91)	182 (8.36)

Abbreviations: BMI: Body Mass Index; FVC, forced vital capacity; FEV$_1$, forced expiratory volume in 1s; MMEF, maximal mid-expiratory flow; PEF, peak expiratory flow; SD: standard deviation;

[a] For difference between vaccinated and unvaccinated, $p<0.05$.

Table 2 Distributions of predicted air pollutant exposures among children participating in the China Seven Northeastern Cities (SNEC) Study.

Air pollutant(μg/m^3)	Mean ± SD	Median (Min/Max)	IQR	NAAQS[a]	WHO guideline[b]
PM_1	46.8 ± 6.5	45.2 (41.0/54.1)	13.1	NA	NA
$PM_{2.5}$	54.0 ± 6.1	52.1 (48.8/58.8)	10.0	35.0	10.0
PM_{10}	95.6 ± 9.8	94.6 (89.3/103.1)	13.8	100.0	20.0
NO_2	33.6 ± 4.7	32.3 (20.6/42.5)	7.3	40.0	40.0
Temperature (°C) [c]	8.4 ± 1.1	7.82 (6.7/10.7)	1.3	NA	NA
Relative humidity [d]	62.0 ± 3.4	62.0 (52.0/68.0)	1.0	NA	NA

Abbreviations: IQR: interquartile range (range from 25th to 75th percentile of district-specific concentrations); NO_2, nitrogen dioxide; PM_1, particles with aerodynamic diameter of no greater than 1.0 μm; $PM_{2.5}$, particles with aerodynamic diameter of no greater than 2.5 μm; PM_{10}, particles with aerodynamic diameter of no greater than 10.0 μm; SD: standard deviation.

[a] NAAQS: Annual National Ambient Air Quality Standards of China in 2012; NA: no guidelines for PM_1.

[b] World Health Organization’s 2005 air quality guidelines; no guidelines for PM_1.

[c] Temperature: annual average temperature during 2009-2012; no guidelines for temperature.

[d] Relative humidity: annual average relative humidity; no guidelines for relative humidity.

Table 3 Differences (95% CI) in lung function measures associated with a one IQR greater ambient air pollutant concentration (μg/m^3) among children in the northeast of China, by influenza vaccination.

Variables	**Total** **β (95% CI)** [a]	**Non-influenza vaccination** **β (95% CI)** [ab]	**Influenza vaccination** **β (95% CI)** [ab]	***p*-value for interaction**[c]
FVC (mL)				
PM_{1}	-222.97 (-259.17, -186.77)	-283.44 (-327.04, -239.83)	-108.24 (-174.88, -41.60)	0.002
$\mathrm{PM}_{2.5}$	-173.29 (-203.26, -143.33)	-204.87 (-240.25, -169.50)	-97.40 (-152.25, -42.57)	0.037
PM_{10}	-130.03 (-155.26, -104.79)	-136.17 (-165.09, -107.25)	-111.73 (-161.25, -62.19)	0.775
NO_{2}	-123.27 (-149.01, -97.54)	-122.20 (-152.00.99, -92.39)	-152.05 (-205.39, -98.71)	0.448
FEV_{1} (mL)				
PM_{1}	-154.52 (-186.89, -122.16)	-195.86 (-235.23, -156.50)	-67.90 (-126.55, -9.24)	0.002
$\mathrm{PM}_{2.5}$	-123.22 (-150.00, -96.45)	-145.26 (-177.17, -113.35)	-64.54 (-112.82, -16.25)	0.022
PM_{10}	-95.61 (-118.12, -73.10)	-101.00 (-127.02, -74.98)	-74.60 (-118.19, -31.01)	0.350
NO_{2}	-93.18 (-116.12, -70.24)	-94.07 (-120.84, -67.31)	-101.43 (-148.32, -54.55)	0.778
PEF (mL/s)				
PM_{1}	-209.42 (-281.62, -137.22)	-253.84 (-342.28, -165.40)	-133.00 (-261.84, 4.16)	0.351
$\mathrm{PM}_{2.5}$	-168.77 (-228.48, -109.06)	-178.70 (-250.40, -107.02)	-139.18 (-244.99, -33.37)	0.726
PM_{10}	-137.58 (-187.77, 88.39)	-133.54 (-192.00, -75.08)	-138.43 (-233.36, -43.51)	0.910
NO_{2}	-118.63 (-169.82, -67.44)	-121.86 (-181.98, -61.73)	-115.53 (-217.09, -13.96)	0.942
MMEF (mL/s)				
PM_{1}	-41.25 (-95.98, 13.49)	-46.12 (-114.07, 21.84)	-33.82 (-126.46, 58.82)	0.421
$\mathrm{PM}_{2.5}$	-38.89 (-84.18, 6.42)	-34.80 (-89.96, 20.34)	-36.36 (-112.60, 39.89)	0.618
PM_{10}	-39.80 (-77.86, -1.74)	-34.93 (-79.89, 10.03)	-33.65 (-102.18, 34.88)	0.840
NO_{2}	-35.43 (-74.17, 3.32)	-32.54 (-78.71, 13.62)	-16.64 (-89.75, 56.48)	0.671

Abbreviations: CI, confidence interval; FVC, forced vital capacity; FEV_{1}, forced expiratory volume in 1s; MMEF, maximal mid-expiratory flow; NO_{2}, nitrogen dioxide; PEF, peak expiratory flow; PM_{1}, particles with aerodynamic diameter of no greater than 1.0 μm; $\mathrm{PM}_{2.5}$, particles with aerodynamic diameter of no greater than 2.5 μm; PM_{10}, particles with aerodynamic diameter of no greater than 10.0 μm.

[a] Models were adjusted for age, gender, parental education, household income, environmental tobacco smoke exposure, BMI category, annual average temperature and annual average relative humidity.

[b] β were scaled to the interquartile range (75th %tile – 25th %tile) for the concentration of each air pollutant (13.1 μg/m^3 for PM_{1}; 10.0 μg/m^3 for $\mathrm{PM}_{2.5}$; 13.8 μg/m^3 for PM_{10} and 7.3 μg/m^3 for NO_{2}).

[c] *p*-value for cross-product term air pollutant × vaccination, $p<0.10$.

Table 4 Adjusted ORs (95%CI) for lung function reduction associated with a one IQR greater ambient air pollutant concentration (μg/m^3) among children in the northeast of China, by influenza vaccination.

Variables	**Total OR (95% CI)**[ab]	**Non-influenza vaccination OR (95% CI)**[ab]	**Influenza vaccination OR (95% CI)**[ab]	***p*-value for interaction**[c]
FVC <85% predicted value				
PM_1	1.98 (1.57,2.51)	2.33 (1.79,3.03)	1.65 (1.20,2.28)	0.058
$PM_{2.5}$	1.75 (1.43,2.15)	1.91 (1.53,2.39)	1.57 (1.20,2.06)	0.183
PM_{10}	1.58 (1.30,1.92)	1.60 (1.29,1.98)	1.55 (1.20,2.01)	0.814
NO_2	1.54 (1.24,1.92)	1.49 (1.18,1.89)	1.64 (1.22,2.20)	0.525
FEV_1 <85% predicted value				
PM_1	2.04 (1.60,2.59)	2.23 (1.69,2.94)	1.76 (1.23,2.51)	0.246
$PM_{2.5}$	1.88 (1.55,2.27)	2.00 (1.61,2.49)	1.66 (1.25,2.21)	0.260
PM_{10}	1.70 (1.42,2.03)	1.75 (1.43,2.14)	1.60 (1.23,2.09)	0.556
NO_2	1.69 (1.36,2.10)	1.72 (1.35,2.18)	1.64 (1.20,2.22)	0.766
PEF <75% predicted value				
PM_1	1.31 (0.99,1.73)	1.56 (1.13,2.14)	0.98 (0.67,1.44)	0.033
$PM_{2.5}$	1.28 (1.02,1.61)	1.45 (1.12,1.87)	1.04 (0.76,1.43)	0.061
PM_{10}	1.25 (1.03,1.53)	1.37 (1.09,1.71)	1.06 (0.80,1.42)	0.107
NO_2	1.21 (0.98,1.50)	1.34 (1.05,1.71)	0.99 (0.72,1.36)	0.085
MMEF <75% predicted value				
PM_1	1.02 (0.78,1.33)	1.06 (0.79,1.42)	0.94 (0.64,1.36)	0.515
$PM_{2.5}$	1.07 (0.86,1.33)	1.12 (0.88,1.42)	0.97 (0.71,1.32)	0.386
PM_{10}	1.11 (0.91,1.34)	1.14 (0.93,1.41)	1.02 (0.77,1.35)	0.429
NO_2	1.14 (0.93,1.40)	1.18 (0.94,1.47)	1.04 (0.77,1.42)	0.461

Abbreviations: CI, confidence interval; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1s; MMEF, maximal mid-expiratory flow; NO_2, nitrogen dioxide; OR, odds ratio; PEF, peak expiratory flow; PM_1, particles with aerodynamic diameter of no greater than 1.0 μm; $PM_{2.5}$, particles with aerodynamic diameter of no greater than 2.5 μm; PM_{10}, particles with aerodynamic diameter of no greater than 10.0 μm.

[a] ORs scaled to IQR (75th%tile–25th%tile) for each air pollutant (13.1 μg/m^3 for PM_1; 10.0 μg/m^3 for $PM_{2.5}$; 13.8 μg/m^3 for PM_{10} and 7.3 μg/m^3 for NO_2).

[b] Models were adjusted for age, gender, parental education, household income, environmental tobacco smoke exposure, BMI category, annual average temperature and annual average relative humidity.

[c] *p*-value for cross-product term air pollutant × vaccination, $p<0.10$.

Table 5 Differences (95% CI) in lung function measures associated with a one IQR greater ambient air pollutant concentration (μg/m^3) among children in the northeast of China, by influenza vaccination status and gender.

Variables	Total β (95% CI) ^{ab}	Non-influenza vaccination β (95% CI) ^{ab}	Influenza vaccination β (95% CI) ^{ab}	*p*-value for interaction ^{c}
Boys (n=3382)				
FVC (mL)				
PM$_1$	-255.61 (-312.00,-199.22)	-325.77 (-392.37, -259.17)	-107.01 (-213.18, -0.84)	0.052
PM$_{2.5}$	-193.86 (-240.06,-147.65)	-229.02 (-282.57, -175.47)	-111.96 (-198.57, -25.35)	0.396
PM$_{10}$	-137.40 (-176.03,-98.78)	-145.09 (-188.65, -101.52)	-136.60 (-214.09, -59.12)	0.490
NO$_2$	-122.97 (-162.48,-83.46)	-127.11 (-172.22, -82.01)	-172.81 (-255.75, -89.87)	0.237
FEV$_1$ (mL)				
PM$_1$	-170.89 (-220.13,-121.65)	-218.90 (-277.87, -159.92)	-70.16 (-160.47, 20.15)	0.056
PM$_{2.5}$	-134.05 (-174.39,-93.70)	-158.83 (-206.21, -111.45)	-78.01 (-151.78, -4.23)	0.312
PM$_{10}$	-97.66 (-131.35,-63.98)	-104.79 (-143.25, -66.33)	-91.87 (-157.93, -25.81)	0.831
NO$_2$	-88.48 (-122.91,-54.05)	-92.96 (-132.72, -53.20)	-112.50 (-183.20, -41.81)	0.643
PEF (mL/s)				
PM$_1$	-166.35 (-272.44,-60.26)	-211.48 (-338.47, -84.50)	-65.57 (-257.94, 126.78)	0.676
PM$_{2.5}$	-139.38 (-226.31,-52.45)	-137.32 (-239.45, -35.19)	-132.83 (-289.62, 23.96)	0.630
PM$_{10}$	-109.43 (-182.06,-36.80)	-94.98 (-177.98, -11.97)	-152.88 (-292.52, -13.23)	0.279
NO$_2$	-79.96 (-154.32,-5.61)	-79.83 (-165.68, 6.00)	-103.46 (-252.68, 45.75)	0.504
MMEF (mL/s)				
PM$_1$	-30.09 (-111.35,51.15)	-23.11 (-122.46, 76.23)	-29.52 (-168.04, 109.00)	0.410
PM$_{2.5}$	-25.37 (-91.98,41.22)	-5.65 (-85.57, 74.26)	-51.77 (-165.27, 61.71)	0.864
PM$_{10}$	-17.54 (-73.16,38.07)	-2.92 (-67.81, 61.95)	-44.11 (-145.39, 57.17)	0.769
NO$_2$	-4.40 (-61.20,52.38)	3.54 (-63.41, 70.50)	-3.90 (-111.33, 103.52)	0.929
Girls (n=3358)				
FVC (mL)				
PM$_1$	-184.82 (-225.99,-143.65)	-225.85 (-276.03, -175.68)	-103.19 (-173.35, -33.04)	0.025
PM$_{2.5}$	-148.71 (-183.16,-114.27)	-171.27 (-212.35, -130.19)	-79.80 (-138.12, -21.48)	0.052
PM$_{10}$	-118.58 (-147.93,-89.23)	-121.20 (-155.10, -87.30)	-80.73 (-133.59, -27.87)	0.353
NO$_2$	-118.45 (-148.53,-88.37)	-110.76 (-145.66, -75.85)	-113.03 (-171.08, -54.97)	0.866
FEV$_1$ (mL)				
PM$_1$	-129.04 (-167.25,-90.82)	-156.69 (-203.25, -110.14)	-55.60 (-121.64, 10.43)	0.022
PM$_{2.5}$	-105.26 (-137.21,-73.32)	-120.63 (-158.74, -82.52)	-44.85 (-99.57, 9.86)	0.033
PM$_{10}$	-87.20 (-114.35,-60.04)	-89.38 (-120.82, -57.95)	-50.39 (-99.82, -0.97)	0.158

NO_2	-90.97 (-118.78,-63.16)	-87.04 (-119.39, -54.70)	-74.01 (-127.86, -20.17)	0.493
PEF (mL/s)				
PM_1	-226.20 (-315.93,-136.46)	-259.01 (-369.81, -148.21)	-142.71 (-292.45, 7.02)	0.379
$PM_{2.5}$	-180.34 (-255.19,-105.49)	-197.32 (-288.02, -106.62)	-113.92 (-236.99, 9.15)	0.374
PM_{10}	-153.06 (-216.61,-89.52)	-157.16 (-231.83, -82.48)	-105.27 (-215.39, 4.85)	0.440
NO_2	-143.64 (-208.63,-78.64)	-145.89 (-222.52, -69.26)	-102.74 (-222.00, 16.52)	0.572
MMEF (mL/s)				
PM_1	-30.65 (-98.02,36.70)	-46.36 (-130.85, 38.13)	-17.42 (-121.90, 87.05)	0.740
$PM_{2.5}$	-34.63 (-90.97,21.70)	-47.22 (-116.68, 22.23)	-11.17 (-97.02, 74.67)	0.627
PM_{10}	-47.77 (-95.75,0.20)	-54.57 (-111.95, 2.79)	-15.52 (-92.23, 61.19)	0.590
NO_2	-52.23 (-101.33,-3.13)	-55.83 (-114.67, 2.99)	-11.48 (-94.76, 71.78)	0.645

Abbreviations: CI, confidence interval; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1s; MMEF, maximal mid-expiratory flow; NO_2, nitrogen dioxide; PEF, peak expiratory flow; PM_1, particles with aerodynamic diameter of no greater than 1.0 μm; $PM_{2.5}$, particles with aerodynamic diameter of no greater than 2.5 μm; PM_{10}, particles with aerodynamic diameter of no greater than 10.0 μm.

[a] Adjusted for age, gender, parental education, household income, environmental tobacco smoke exposure, BMI category, annual average temperature and annual average relative humidity.

[b] β were scaled to the interquartile range (75th %tile – 25th %tile) for the concentration of each air pollutant (13.1 μg/m^3 for PM_1; 10.0 μg/m^3 for $PM_{2.5}$; 13.8 μg/m^3 for PM_{10} and 7.3 μg/m^3 for NO_2).

[c] *p*-value for cross-product term air pollutant × vaccination, $p<0.10$.

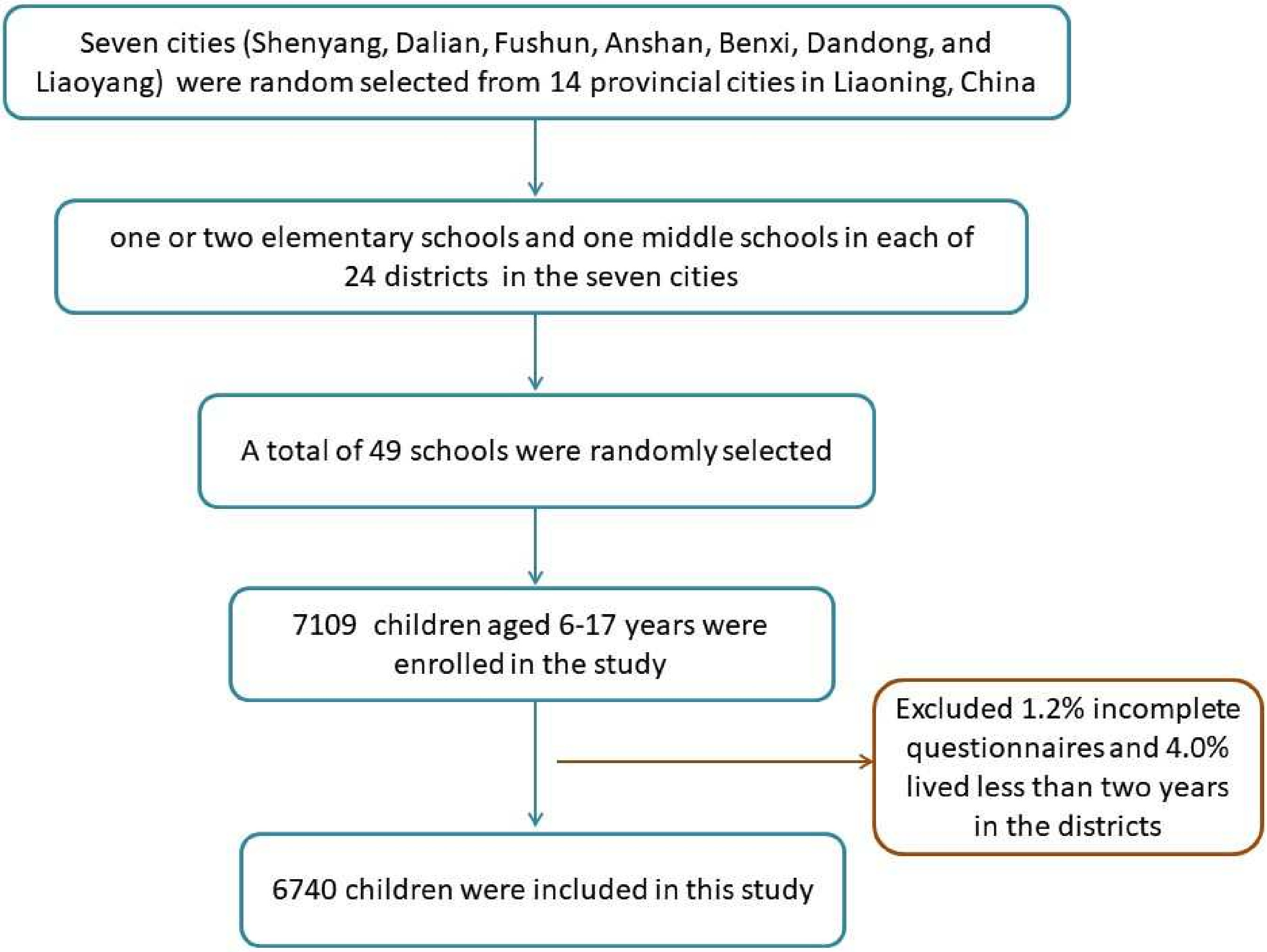


Fig 1 Study participant enrollment in the China Seven Northeastern Cities (SNEC) Study.

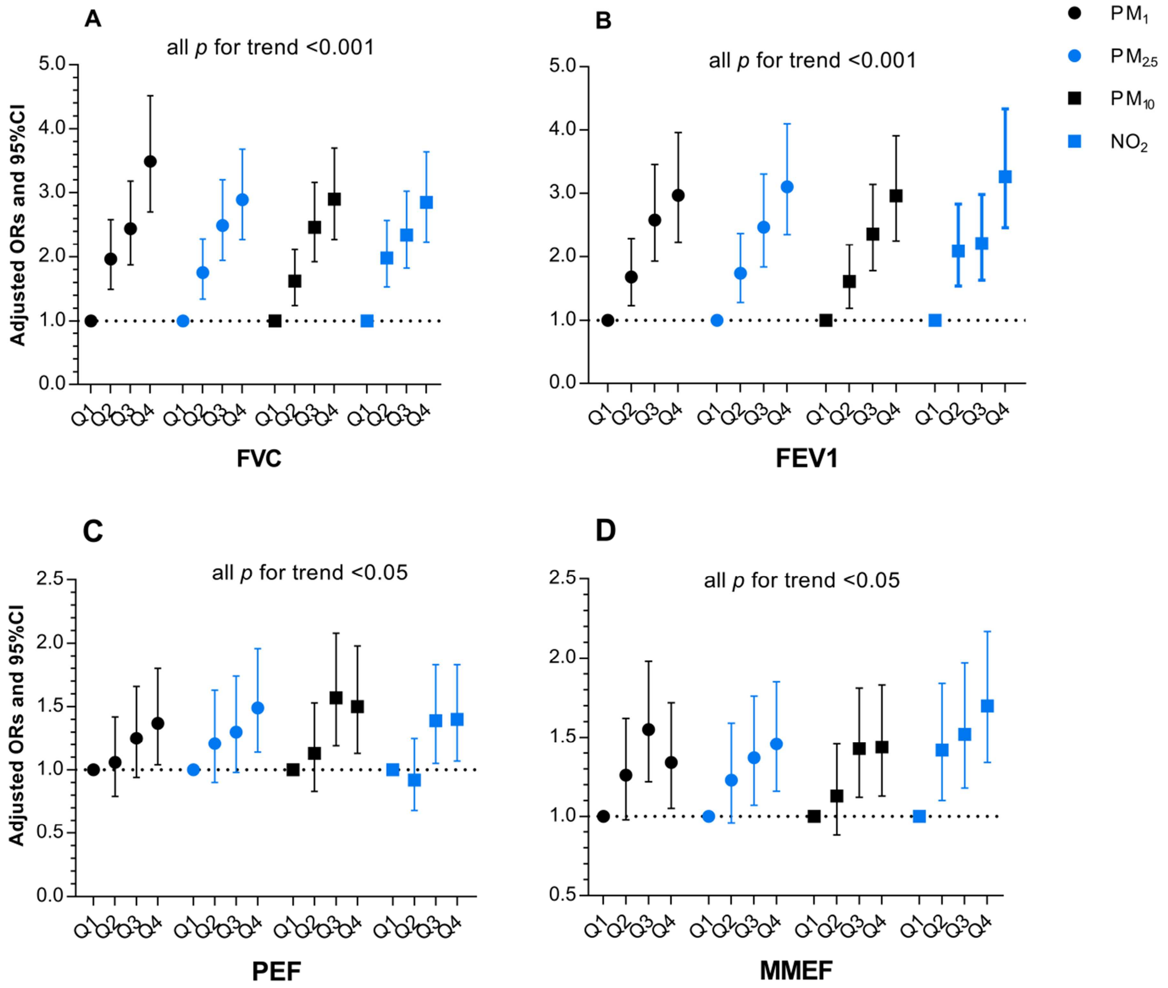


Fig 2 OR (95% CI) for associations between quartiles of ambient air pollution exposure (μg/m^3) concentrations and lung function reduction among children in the China Seven Northeastern Cities (SNEC) Study[ab]. (A) for FVC; (B) for FEV1; (C) for PEF; (D) for MMEF. *p*-Values for trend were calculated using categories representing the median values of corresponding quartiles (Q1: quartile 1 - reference category; Q2: quartile 2; Q3: quartile 3; Q4: quartile 4 with boxes representing the median of each quartile and whiskers representing the 95% confidence interval).

Abbreviations: CI, confidence interval; FVC, forced vital capacity; FEV$_1$, forced expiratory volume in 1s; MMEF, maximal mid-expiratory flow; NO$_2$, nitrogen dioxide; PEF, peak expiratory flow; OR, odds ratio; PM$_1$, particles with aerodynamic diameter of no greater than 1.0 μm; PM$_{2.5}$, particles with aerodynamic diameter of no greater than 2.5 μm; PM$_{10}$, particles with aerodynamic diameter of no greater than 10.0 μm.

[a] Adjusted for age, gender, parental education, household income, environmental tobacco smoke exposure, BMI category, annual average temperature and annual average relative humidity.

[b] ORs scaled to IQR (75th%tile–25th%tile) for each air pollutant (13.1 μg/m^3 for PM$_1$; 10.0 μg/m^3 for PM$_{2.5}$; 13.8 μg/m^3 for PM$_{10}$ and 7.3 μg/m^3 for NO$_2$).

Table 1 Characteristics of children participating in the China Seven Northeastern Cities (SNEC) Study, by influenza vaccination.

Variables	Total (n=6740)	Non-Influenza vaccination (n=4562)	Influenza vaccination (n=2178)
Continuous variables	Mean ± SD	Mean ± SD	Mean ± SD
BMI (kg/m^2)	20.01 ± 4.67	20.06±4.34	19.90±5.29
Age (year) [a]	11.56 ± 2.07	11.46 ± 2.04	11.79±2.10
Exercise time per week (hour)	7.58 ± 7.77	7.55 ± 7.34	7.64 ± 8.61
Categorical variables	n (%)	n (%)	n (%)
Girls [a]	3358 (49.82)	2236 (49.01)	1122 (51.52)
Parental education ≥ high school [a]	4211 (62.48)	2592 (64.69)	1260 (57.85)
Household income per year (RMB) [a]			
<10000	1634 (24.24)	1069 (23.43)	565 (25.94)
10,000 – 30,000	2394 (35.52)	1645 (36.06)	749 (34.39)
30,001 – 100,000	2437 (36.16)	1685 (36.94)	752 (34.53)
>100,000	275 (4.08)	163 (3.57)	112 (5.14)
BMI [a]			
Normal weight	4518 (67.03)	3013 (66.05)	1505 (69.1)
Overweight	1068 (15.85)	761 (16.68)	307 (14.1)
Obese	1154 (17.12)	788 (17.27)	366 (16.8)
Environmental Tobacco smoke exposure [a]	3281 (48.68)	2157 (47.28)	1124 (51.61)
Household fuel use [a]	676 (10.03)	435 (9.54)	241 (11.07)
Home mildew [a]	898 (13.32)	639 (14.01)	259 (11.89)
Home renovation in the past 3 years [a]	2416 (35.85)	1573 (34.48)	843 (38.71)
Family history of atopy	1390 (20.62)	926 (20.30)	464 (21.30)
Doctor-diagnosed asthma	460 (6.82)	308 (6.75)	152 (6.97)
Doctor-diagnosed pneumonia	1057 (15.68)	768 (16.83)	289 (13.27)
Doctor-diagnosed bronchitis	196 (2.91)	130 (2.85)	66 (3.03)
Doctor-diagnosed pertussis	44 (0.65)	25 (0.55)	19 (0.87)
Spirometric parameters mean (SD)			
FVC(L)	2.63 ± 0.76	2.63 ± 0.75	2.61 ± 0.76
FEV$_1$ (L)	2.46 ± 0.70	2.46 ± 0.70	2.46 ± 0.70
PEF (L/s)	4.78 ± 1.41	4.78 ± 1.42	4.77 ± 1.40
MMEF (L/s)	3.35 ± 1.05	3.33 ± 1.06	3.39 ± 1.03
Lung function reduction n (%)			
FVC <85% predicted	759 (11.26)	497 (10.89)	262 (12.03)
FEV$_1$ <85% predicted	578 (8.58)	390 (8.55)	188 (8.63)
PEF <75% predicted	458 (6.80)	297 (6.51)	161 (7.39)
MMEF <75% predicted [a]	634 (9.41)	452 (9.91)	182 (8.36)

Abbreviations: BMI: Body Mass Index; FVC, forced vital capacity; FEV$_1$, forced expiratory volume in 1s; MMEF, maximal mid-expiratory flow; PEF, peak expiratory flow; SD: standard deviation;

[a] For difference between vaccinated and unvaccinated, $p<0.05$.

Table 2 Distributions of predicted air pollutant exposures among children participating in the China Seven Northeastern Cities (SNEC) Study.

Air pollutant(μg/m^3)	Mean ± SD	Median (Min/Max)	IQR	NAAQS[a]	WHO guideline[b]
PM_1	46.8 ± 6.5	45.2 (41.0/54.1)	13.1	NA	NA
$PM_{2.5}$	54.0 ± 6.1	52.1 (48.8/58.8)	10.0	35.0	10.0
PM_{10}	95.6 ± 9.8	94.6 (89.3/103.1)	13.8	100.0	20.0
NO_2	33.6 ± 4.7	32.3 (20.6/42.5)	7.3	40.0	40.0
Temperature (°C) [c]	8.4 ± 1.1	7.82 (6.7/10.7)	1.3	NA	NA
Relative humidity [d]	62.0 ± 3.4	62.0 (52.0/68.0)	1.0	NA	NA

Abbreviations: IQR: interquartile range (range from 25th to 75th percentile of district-specific concentrations); NO_2, nitrogen dioxide; PM_1, particles with aerodynamic diameter of no greater than 1.0 μm; $PM_{2.5}$, particles with aerodynamic diameter of no greater than 2.5 μm; PM_{10}, particles with aerodynamic diameter of no greater than 10.0 μm; SD: standard deviation.

[a] NAAQS: Annual National Ambient Air Quality Standards of China in 2012; NA: no guidelines for PM_1.

[b] World Health Organization’s 2005 air quality guidelines; no guidelines for PM_1.

[c] Temperature: annual average temperature during 2009-2012; no guidelines for temperature.

[d] Relative humidity: annual average relative humidity; no guidelines for relative humidity.

Table 3 Differences (95% CI) in lung function measures associated with a one IQR greater ambient air pollutant concentration (μg/m^3) among children in the northeast of China, by influenza vaccination.

Variables	**Total** **β (95% CI)** [a]	**Non-influenza vaccination** **β (95% CI)** [ab]	**Influenza vaccination** **β (95% CI)** [ab]	***p*-value for interaction**[c]
FVC (mL)				
PM$_1$	-222.97 (-259.17, -186.77)	-283.44 (-327.04, -239.83)	-108.24 (-174.88, -41.60)	0.002
PM$_{2.5}$	-173.29 (-203.26, -143.33)	-204.87 (-240.25, -169.50)	-97.40 (-152.25, -42.57)	0.037
PM$_{10}$	-130.03 (-155.26, -104.79)	-136.17 (-165.09, -107.25)	-111.73 (-161.25, -62.19)	0.775
NO$_2$	-123.27 (-149.01, -97.54)	-122.20 (-152.00.99, -92.39)	-152.05 (-205.39, -98.71)	0.448
FEV$_1$ (mL)				
PM$_1$	-154.52 (-186.89, -122.16)	-195.86 (-235.23, -156.50)	-67.90 (-126.55, -9.24)	0.002
PM$_{2.5}$	-123.22 (-150.00, -96.45)	-145.26 (-177.17, -113.35)	-64.54 (-112.82, -16.25)	0.022
PM$_{10}$	-95.61 (-118.12, -73.10)	-101.00 (-127.02, -74.98)	-74.60 (-118.19, -31.01)	0.350
NO$_2$	-93.18 (-116.12, -70.24)	-94.07 (-120.84, -67.31)	-101.43 (-148.32, -54.55)	0.778
PEF (mL/s)				
PM$_1$	-209.42 (-281.62, -137.22)	-253.84 (-342.28, -165.40)	-133.00 (-261.84, 4.16)	0.351
PM$_{2.5}$	-168.77 (-228.48, -109.06)	-178.70 (-250.40, -107.02)	-139.18 (-244.99, -33.37)	0.726
PM$_{10}$	-137.58 (-187.77, 88.39)	-133.54 (-192.00, -75.08)	-138.43 (-233.36, -43.51)	0.910
NO$_2$	-118.63 (-169.82, -67.44)	-121.86 (-181.98, -61.73)	-115.53 (-217.09, -13.96)	0.942
MMEF (mL/s)				
PM$_1$	-41.25 (-95.98, 13.49)	-46.12 (-114.07, 21.84)	-33.82 (-126.46, 58.82)	0.421
PM$_{2.5}$	-38.89 (-84.18, 6.42)	-34.80 (-89.96, 20.34)	-36.36 (-112.60, 39.89)	0.618
PM$_{10}$	-39.80 (-77.86, -1.74)	-34.93 (-79.89, 10.03)	-33.65 (-102.18, 34.88)	0.840
NO$_2$	-35.43 (-74.17, 3.32)	-32.54 (-78.71, 13.62)	-16.64 (-89.75, 56.48)	0.671

Abbreviations: CI, confidence interval; FVC, forced vital capacity; FEV$_1$, forced expiratory volume in 1s; MMEF, maximal mid-expiratory flow; NO$_2$, nitrogen dioxide; PEF, peak expiratory flow; PM$_1$, particles with aerodynamic diameter of no greater than 1.0 μm; PM$_{2.5}$, particles with aerodynamic diameter of no greater than 2.5 μm; PM$_{10}$, particles with aerodynamic diameter of no greater than 10.0 μm.

[a] Models were adjusted for age, gender, parental education, household income, environmental tobacco smoke exposure, BMI category, annual average temperature and annual average relative humidity.

[b] β were scaled to the interquartile range (75th %tile – 25th %tile) for the concentration of each air pollutant (13.1 μg/m^3 for PM$_1$; 10.0 μg/m^3 for PM$_{2.5}$; 13.8 μg/m^3 for PM$_{10}$ and 7.3 μg/m^3 for NO$_2$).

[c] *p*-value for cross-product term air pollutant × vaccination, $p<0.10$.

Table 4 Adjusted ORs (95%CI) for lung function reduction associated with a one IQR greater ambient air pollutant concentration (μg/m^3) among children in the northeast of China, by influenza vaccination.

Variables	**Total OR (95% CI)^{ab}**	**Non-influenza vaccination OR (95% CI)^{ab}**	**Influenza vaccination OR (95% CI)^{ab}**	***p*-value for interaction^c**
FVC <85% predicted value				
PM_1	1.98 (1.57,2.51)	2.33 (1.79,3.03)	1.65 (1.20,2.28)	0.058
$PM_{2.5}$	1.75 (1.43,2.15)	1.91 (1.53,2.39)	1.57 (1.20,2.06)	0.183
PM_{10}	1.58 (1.30,1.92)	1.60 (1.29,1.98)	1.55 (1.20,2.01)	0.814
NO_2	1.54 (1.24,1.92)	1.49 (1.18,1.89)	1.64 (1.22,2.20)	0.525
FEV_1 <85% predicted value				
PM_1	2.04 (1.60,2.59)	2.23 (1.69,2.94)	1.76 (1.23,2.51)	0.246
$PM_{2.5}$	1.88 (1.55,2.27)	2.00 (1.61,2.49)	1.66 (1.25,2.21)	0.260
PM_{10}	1.70 (1.42,2.03)	1.75 (1.43,2.14)	1.60 (1.23,2.09)	0.556
NO_2	1.69 (1.36,2.10)	1.72 (1.35,2.18)	1.64 (1.20,2.22)	0.766
PEF <75% predicted value				
PM_1	1.31 (0.99,1.73)	1.56 (1.13,2.14)	0.98 (0.67,1.44)	0.033
$PM_{2.5}$	1.28 (1.02,1.61)	1.45 (1.12,1.87)	1.04 (0.76,1.43)	0.061
PM_{10}	1.25 (1.03,1.53)	1.37 (1.09,1.71)	1.06 (0.80,1.42)	0.107
NO_2	1.21 (0.98,1.50)	1.34 (1.05,1.71)	0.99 (0.72,1.36)	0.085
MMEF <75% predicted value				
PM_1	1.02 (0.78,1.33)	1.06 (0.79,1.42)	0.94 (0.64,1.36)	0.515
$PM_{2.5}$	1.07 (0.86,1.33)	1.12 (0.88,1.42)	0.97 (0.71,1.32)	0.386
PM_{10}	1.11 (0.91,1.34)	1.14 (0.93,1.41)	1.02 (0.77,1.35)	0.429
NO_2	1.14 (0.93,1.40)	1.18 (0.94,1.47)	1.04 (0.77,1.42)	0.461

Abbreviations: CI, confidence interval; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1s; MMEF, maximal mid-expiratory flow; NO_2, nitrogen dioxide; OR, odds ratio; PEF, peak expiratory flow; PM_1, particles with aerodynamic diameter of no greater than 1.0 μm; $PM_{2.5}$, particles with aerodynamic diameter of no greater than 2.5 μm; PM_{10}, particles with aerodynamic diameter of no greater than 10.0 μm.

[a] ORs scaled to IQR (75th%tile–25th%tile) for each air pollutant (13.1 μg/m^3 for PM_1; 10.0 μg/m^3 for $PM_{2.5}$; 13.8 μg/m^3 for PM_{10} and 7.3 μg/m^3 for NO_2).

[b] Models were adjusted for age, gender, parental education, household income, environmental tobacco smoke exposure, BMI category, annual average temperature and annual average relative humidity.

[c] *p*-value for cross-product term air pollutant × vaccination, $p<0.10$.

Table 5 Differences (95% CI) in lung function measures associated with a one IQR greater ambient air pollutant concentration (μg/m^3) among children in the northeast of China, by influenza vaccination status and gender.

Variables	**Total** **β (95% CI)** ^{ab}	**Non-influenza vaccination** **β (95% CI)** ^{ab}	**Influenza vaccination** **β (95% CI)** ^{ab}	***p*-value for interaction** ^{c}
Boys (n=3382)				
FVC (mL)				
PM$_1$	-255.61 (-312.00,-199.22)	-325.77 (-392.37, -259.17)	-107.01 (-213.18, -0.84)	0.052
PM$_{2.5}$	-193.86 (-240.06,-147.65)	-229.02 (-282.57, -175.47)	-111.96 (-198.57, -25.35)	0.396
PM$_{10}$	-137.40 (-176.03,-98.78)	-145.09 (-188.65, -101.52)	-136.60 (-214.09, -59.12)	0.490
NO$_2$	-122.97 (-162.48,-83.46)	-127.11 (-172.22, -82.01)	-172.81 (-255.75, -89.87)	0.237
FEV$_1$ (mL)				
PM$_1$	-170.89 (-220.13,-121.65)	-218.90 (-277.87, -159.92)	-70.16 (-160.47, 20.15)	0.056
PM$_{2.5}$	-134.05 (-174.39,-93.70)	-158.83 (-206.21, -111.45)	-78.01 (-151.78, -4.23)	0.312
PM$_{10}$	-97.66 (-131.35,-63.98)	-104.79 (-143.25, -66.33)	-91.87 (-157.93, -25.81)	0.831
NO$_2$	-88.48 (-122.91,-54.05)	-92.96 (-132.72, -53.20)	-112.50 (-183.20, -41.81)	0.643
PEF (mL/s)				
PM$_1$	-166.35 (-272.44,-60.26)	-211.48 (-338.47, -84.50)	-65.57 (-257.94, 126.78)	0.676
PM$_{2.5}$	-139.38 (-226.31,-52.45)	-137.32 (-239.45, -35.19)	-132.83 (-289.62, 23.96)	0.630
PM$_{10}$	-109.43 (-182.06,-36.80)	-94.98 (-177.98, -11.97)	-152.88 (-292.52, -13.23)	0.279
NO$_2$	-79.96 (-154.32,-5.61)	-79.83 (-165.68, 6.00)	-103.46 (-252.68, 45.75)	0.504
MMEF (mL/s)				
PM$_1$	-30.09 (-111.35,51.15)	-23.11 (-122.46, 76.23)	-29.52 (-168.04, 109.00)	0.410
PM$_{2.5}$	-25.37 (-91.98,41.22)	-5.65 (-85.57, 74.26)	-51.77 (-165.27, 61.71)	0.864
PM$_{10}$	-17.54 (-73.16,38.07)	-2.92 (-67.81, 61.95)	-44.11 (-145.39, 57.17)	0.769
NO$_2$	-4.40 (-61.20,52.38)	3.54 (-63.41, 70.50)	-3.90 (-111.33, 103.52)	0.929
Girls (n=3358)				
FVC (mL)				
PM$_1$	-184.82 (-225.99,-143.65)	-225.85 (-276.03, -175.68)	-103.19 (-173.35, -33.04)	0.025
PM$_{2.5}$	-148.71 (-183.16,-114.27)	-171.27 (-212.35, -130.19)	-79.80 (-138.12, -21.48)	0.052
PM$_{10}$	-118.58 (-147.93,-89.23)	-121.20 (-155.10, -87.30)	-80.73 (-133.59, -27.87)	0.353
NO$_2$	-118.45 (-148.53,-88.37)	-110.76 (-145.66, -75.85)	-113.03 (-171.08, -54.97)	0.866
FEV$_1$ (mL)				
PM$_1$	-129.04 (-167.25,-90.82)	-156.69 (-203.25, -110.14)	-55.60 (-121.64, 10.43)	0.022
PM$_{2.5}$	-105.26 (-137.21,-73.32)	-120.63 (-158.74, -82.52)	-44.85 (-99.57, 9.86)	0.033
PM$_{10}$	-87.20 (-114.35,-60.04)	-89.38 (-120.82, -57.95)	-50.39 (-99.82, -0.97)	0.158

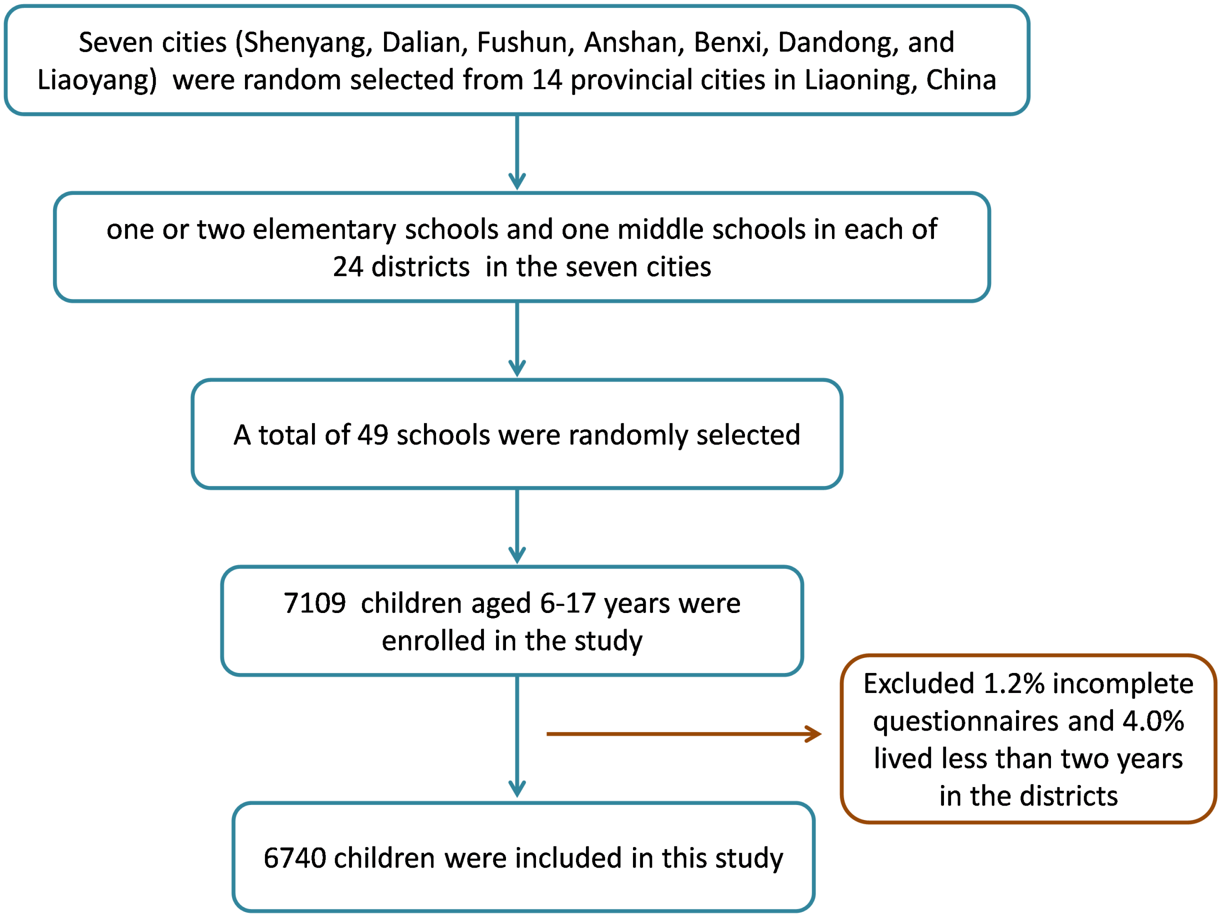
NO_2	-90.97 (-118.78,-63.16)	-87.04 (-119.39, -54.70)	-74.01 (-127.86, -20.17)	0.493
PEF (mL/s)				
PM_1	-226.20 (-315.93,-136.46)	-259.01 (-369.81, -148.21)	-142.71 (-292.45, 7.02)	0.379
$PM_{2.5}$	-180.34 (-255.19,-105.49)	-197.32 (-288.02, -106.62)	-113.92 (-236.99, 9.15)	0.374
PM_{10}	-153.06 (-216.61,-89.52)	-157.16 (-231.83, -82.48)	-105.27 (-215.39, 4.85)	0.440
NO_2	-143.64 (-208.63,-78.64)	-145.89 (-222.52, -69.26)	-102.74 (-222.00, 16.52)	0.572
MMEF (mL/s)				
PM_1	-30.65 (-98.02,36.70)	-46.36 (-130.85, 38.13)	-17.42 (-121.90, 87.05)	0.740
$PM_{2.5}$	-34.63 (-90.97,21.70)	-47.22 (-116.68, 22.23)	-11.17 (-97.02, 74.67)	0.627
PM_{10}	-47.77 (-95.75,0.20)	-54.57 (-111.95, 2.79)	-15.52 (-92.23, 61.19)	0.590
NO_2	-52.23 (-101.33,-3.13)	-55.83 (-114.67, 2.99)	-11.48 (-94.76, 71.78)	0.645

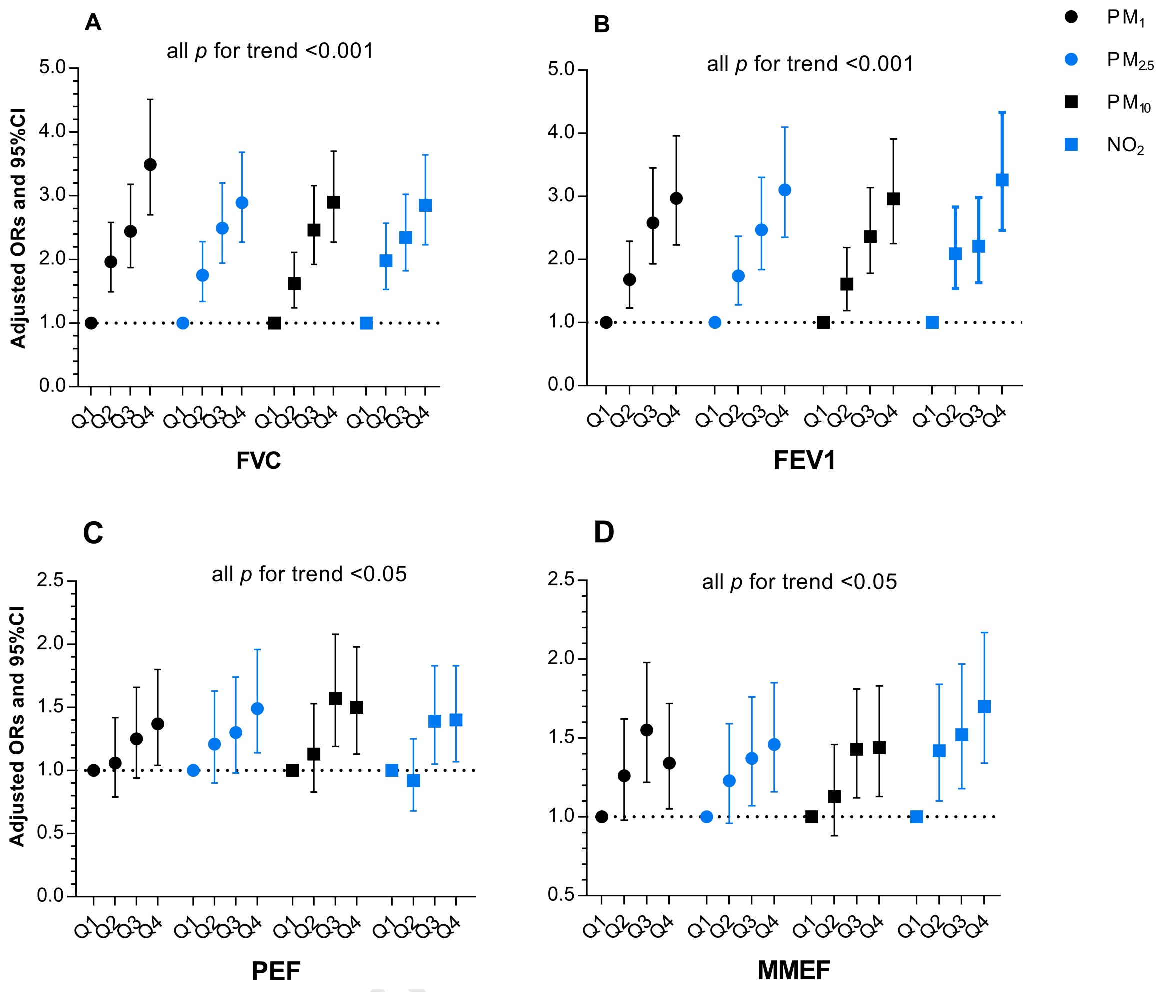
Abbreviations: CI, confidence interval; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1s; MMEF, maximal mid-expiratory flow; NO_2, nitrogen dioxide; PEF, peak expiratory flow; PM_1, particles with aerodynamic diameter of no greater than 1.0 µm; $PM_{2.5}$, particles with aerodynamic diameter of no greater than 2.5 µm; PM_{10}, particles with aerodynamic diameter of no greater than 10.0 µm.

[a] Adjusted for age, gender, parental education, household income, environmental tobacco smoke exposure, BMI category, annual average temperature and annual average relative humidity.

[b] β were scaled to the interquartile range (75th %tile – 25th %tile) for the concentration of each air pollutant (13.1 µg/m^3 for PM_1; 10.0 µg/m^3 for $PM_{2.5}$; 13.8 µg/m^3 for PM_{10} and 7.3 µg/m^3 for NO_2).

[c] *p*-value for cross-product term air pollutant × vaccination, $p<0.10$.


Seven cities (Shenyang, Dalian, Fushun, Anshan, Benxi, Dandong, and Liaoyang) were random selected from 14 provincial cities in Liaoning, China
one or two elementary schools and one middle schools in each of 24 districts in the seven cities
A total of 49 schools were randomly selected
7109 children aged 6-17 years were enrolled in the study
Excluded 1.2% incomplete questionnaires and 4.0% lived less than two years in the districts
6740 children were included in this study


A
all p for trend <0.001
Adjusted ORs and 95%CI
0.0
1.0
2.0
3.0
4.0
5.0
Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4
FVC
B
all p for trend <0.001
0.0
1.0
2.0
3.0
4.0
5.0
Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4
FEV1
● PM$_1$
● PM$_{2.5}$
■ PM$_{10}$
■ NO$_2$
C
all p for trend <0.05
Adjusted ORs and 95%CI
0.0
0.5
1.0
1.5
2.0
2.5
Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4
PEF
D
all p for trend <0.05
0.5
1.0
1.5
2.0
2.5
Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4
MMEF

Highlights

- No study on interactions between flu vaccine and air pollution on lung function
- Flu vaccine may mitigate the detrimental effects of air pollution on lung function
- The interactions appeared to be more substantial in girls than in boys