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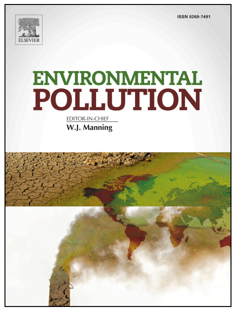

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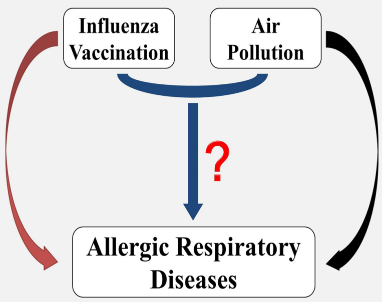
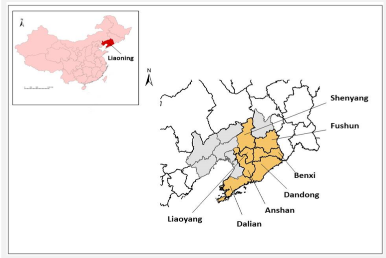
Study Aim



Interaction Effects

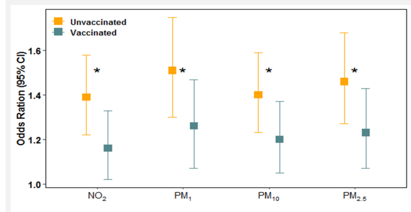
Methods



Northeast China

Cross-sectional Study

Results



Benefits of influenza vaccination on associations between ambient air pollution and allergic respiratory diseases

Benefits of influenza vaccination on the associations between ambient air pollution and allergic respiratory diseases in children and adolescents: New insights from the Seven Northeastern Cities Study in China

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Abstract

Background

Little information exists on interaction effects between air pollution and influenza vaccination on allergic respiratory diseases. We conduct a large population-based study to evaluate the interaction effects between influenza vaccination and long-term exposure to ambient air pollution on allergic respiratory diseases in children and adolescents.

Methods

A cross-sectional study was investigated during 2012-2013 in 94 schools from Seven Northeastern Cities (SNEC) in China. Questionnaires surveys were obtained from 56,137 children and adolescents aged 2-17 years. Influenza vaccination was defined as receipt of the influenza vaccine. We estimated air pollutants exposure [nitrogen dioxide (NO_2) and particulate matter with aerodynamic diameters ≤1μm (PM_1), ≤2.5μm ($PM_{2.5}$) and ≤10μm (PM_{10})] using machine learning methods. We employed two-level generalized linear mix effects model to examine interactive effects between influenza vaccination and air pollution exposure on allergic respiratory diseases (asthma, asthma-related symptoms and allergic rhinitis), after controlling for important covariates.

Results

We found statistically significant interactions between influenza vaccination and air pollutants on allergic respiratory diseases and related symptoms (doctor-diagnosed asthma, current wheeze, wheeze, persistent phlegm and allergic rhinitis). The adjusted ORs for doctor-diagnosed asthma, current wheeze and allergic rhinitis among the unvaccinated group per interquartile range (IQR) increase in PM_1 and $PM_{2.5}$ were significantly higher than the corresponding ORs among the vaccinated group [For PM_1, doctor-diagnosed asthma: OR: 1.89 (95%CI: 1.57-2.27) vs 1.65 (95%CI: 1.36-2.00); current wheeze: OR: 1.50 (95%CI: 1.22-1.85) vs 1.10 (95%CI: 0.89-1.37); allergic rhinitis: OR: 1.38 (95%CI: 1.15-1.66) vs 1.21 (95%CI: 1.00-1.46). For $PM_{2.5}$, doctor-diagnosed asthma: OR: 1.81 (95%CI: 1.52-2.14) vs 1.57 (95%CI: 1.32-1.88); current wheeze: OR: 1.46 (95%CI: 1.21-1.76) vs 1.11 (95%CI: 0.91-1.35); allergic rhinitis: OR: 1.35 (95%CI: 1.14-1.60) vs 1.19 (95%CI: 1.00-1.42)]. The similar patterns were observed for wheeze and persistent phlegm. The corresponding *p* values for interactions were less than 0.05, respectively. We assessed the risks of PM_1-related and $PM_{2.5}$-related current wheeze were decreased by 26.67% (95%CI: 1.04%-45.66%) and 23.97% (95%CI: 0.21%-42.08%) respectively, which was attributable to influenza vaccination (both p for efficiency <0.05).

Conclusions

Influenza vaccination may play an important role in mitigating the detrimental effects of long-term exposure to ambient air pollution on childhood allergic respiratory diseases. Policy targeted at increasing influenza vaccination may yield co-benefits in terms of reduced allergic respiratory diseases.

Keywords: air pollutants, asthma, influenza vaccination, interaction effects, children and adolescents

Introduction

Asthma which is the most common chronic respiratory diseases represents a high burden of disease (Soriano et al. 2017). More than 330 million people are affected, and the prevalence is increasing every year in the world, particularly in developing countries (Campbell-Lendrum et al. 2019; Tong 2019). Strong evidences exist on the detrimental impact of air pollution on asthma and other allergic respiratory diseases (Keet et al. 2018; Thurston et al. 2017; Yang et al. 2018). In general, children are more vulnerable to the adverse respiratory health effects of air pollution exposure compare with adults. This excess vulnerability to air pollution is attributed to children having immature airways and immune systems, inhaling more pollutants relative to their body mass, and spending more time outdoors (Orellano et al. 2017; Pennington et al. 2018). Another important reason is that the maternal exposure to air pollution during pregnancy may lead to childhood asthma and other allergic respiratory diseases (Deng et al. 2016). Thus, exploration of the air pollution-asthma associations in children and the possible preventive and control strategies is of great more significance for decreasing the burden of allergic respiratory diseases.

There are growing concerns about the role of air pollution exposure in infectious diseases of public health relevance (MacIntyre et al. 2014), particularly influenza (CWS Chen et al. 2018). Influenza a global health issue often has severe morbidity and mortality, especially in high-risk populations (Watanabe et al. 2005). It is estimated that up to 85% of acute asthma exacerbations in children are associated with upper respiratory tract infections (Saraya et al.

2014). Influenza infection in patients with asthma may lead to severe influenza complications and even death, due to the swollen and sensitive airways of asthmatic people and serious inflammation of airways and lungs from influenza infection (CDC 2017; Nicholas et al. 2017b). Acute asthma exacerbations due to influenza infections were account for 10% (Iikura et al. 2015), 20.7% (Tan et al. 2003) and as high as 37.9% (Atmar et al. 1998). Though the mechanisms regarding the susceptibility of asthmatic people to virus infection are poorly understood, it has been documented that virus bioaerosols (particulate matter carrying nanoparticle-sized allergens or microorganisms) (Alonso et al. 2015; Jalava et al. 2015; Morakinyo et al. 2016) can deposit in the airways or alveoli of the lower respiratory tract. And then it induce the skewing toward TH2 immunity from TH1 immunity response (Message et al. 2008; Nicholas et al. 2017b; Oliver et al. 2014), which is similar to the mechanisms of the detrimental effects of air pollutants (Guarnieri et al. 2014; Yang et al. 2017). Therefore, air pollution and influenza infection could both increase inflammatory reaction and subsequent immune response, and then cause asthma attack or exacerbation or other serious diseases.

Influenza vaccination greatly contributes to decreased morbidity and mortality due to influenza virus infections (WHO 2012). Although widely recommended for individuals at high risk, such as those with asthma, influenza vaccine uptake has not yet reached the target global coverage rate of 75% (Nair et al. 2011). Recently, a meta-analyses of 126 studies showed that pooled influenza vaccination rate was only 9.4% among general population in mainland China, while higher pooled proportions of 25.1% among children (aged 6 months to17 years) (Wang et al. 2018). It is critical that influenza vaccine is recommended used for preventing influenza and other chronic diseases such as asthma (Carroll et al. 2007; Glezen 2006). In terms of asthma risk, a recent review emphasized that influenza vaccination might effectively protect against the risk of asthma and other respiratory diseases (Suarez-Varela et al. 2018; Vasileiou et al. 2017). In addition, compare with the regions with low-concentration of air pollution, detrimental effects of higher concentrations of air pollution exposure on respiratory health in China cannot be ignored anymore. However, no studies to date evaluated the impact of influenza vaccination on air pollutant-respiratory disease associations in Chinese children. Therefore, we aimed to identify the hypothesis that influenza vaccination modifies the association between long-term exposure to ambient air pollution and allergic respiratory diseases in children and adolescents.

Material and methods

Ethics Statement

Ethical approval for this study was obtained from the Ethical Review Committee of Human Experimentation at Sun Yat-sen University (Ethics Approval Number: 2016016). All potentially identifiable information was removed to protect participants prior to initiation of the retrospective analysis reported here. A written informed consent was collected from the parents/guardians of each participant at the start of the study.

Study Site Selection and Participants Recruitment

The Seven Northeastern Cities (SNEC) study was a cross-sectional study conducted in seven cities in the Liaoning province of China from April 2012 to May 2013. Liaoning is a largely industrial area in China, with the majority of industrial companies located in the seven cities represented in this study. Within the seven cities, we selected 27 administrative districts: six in Shenyang, five in Dalian, four in Fushun, and three each in Anshan, Benxi, Dandong, and Liaoyang. In order to maximize the heterogeneity of the diversity of ambient air pollutants and their concentrations, the air quality monitoring stations were chosen according to the different levels of ambient air pollutant concentrations between 2009 and 2012 (Figure S1). There was one local air quality monitoring station in each administrative district. We defined a 1.5 mile radius around every monitoring station as a buffer area for selecting schools, in order to minimize the error of concentrations of air pollutants exposure. We randomly selected one or two kindergartens, one or two elementary schools, and one or two middle schools which were located within the buffer area of the monitoring station (dependent upon the size of the schools, if the count of students of a school was less than 500, we selected 2 schools). Students were included in the study if they were continuous residents of their current districts for at least four years. Due to Chinese requirements that children must enroll in the school closest to their place of residence, all participants lived within 2 kilometers of their school. We identified 68647 children in 27 administrative districts of the seven cities, of whom 59754 children completed the questionnaire survey. Excluding the missing information of influenza vaccination, 56,137 children were enrolled in this study. For the analysis presented here, we excluded children and adolescents with missing information regarding influenza vaccination. The final sample for the current study consisted of 56,137 children and adolescents (Fig 1).

[Figure 1 is about here]

Assessment of air pollution exposure

We have previously described the exposure assessment in details and a description can also be found in the appendix methods (Dong et al. 2013). Concentrations of nitrogen dioxide (NO_2) and particulate matter with aerodynamic diameters ≤1μm (PM_1), ≤2.5μm ($PM_{2.5}$), and ≤ 10μm (PM_{10}) at school-level during 2009-2012 were assigned to every participant for the pollution exposure evaluation. These estimates were based on machine-learning methods combining satellite remote sensing land use information and meteorological information at a resolution of 0.1° × 0.1° as description in previously studies(G Chen et al. 2018a; G Chen et al. 2018b; G Chen et al. 2018c). Briefly, daily particulate matters concentrations including PM_1, $PM_{2.5}$ PM_{10} were estimated using ground-monitored $PM_{1,}$ $PM_{2.5}$ and PM_{10}, Moderate Resolution Imaging Spectroradiometer (MODIS) products, aerosol optical depth data (AOD), meteorological variables, land use information and other predictors. NO_2 concentrations were estimated using satellite-derived OMI data. The ground measurement technique for pollutants from air monitoring stations was carried out according to standards set by the State Environmental Protection Administration of China (SEPA 1992), which are described in the supplementary materials. We developed a machine learning method (random forests) to link the daily ground measurements of PM_1, $PM_{2.5}$ and $PM_{10.}$ 10-fold cross-validation was performed to validate the estimation ability of the ground-level concentrations of air pollutants, using previously described methods (G Chen et al. 2018b). The results of 10-fold cross-validation were shown in Supplementary Material and Table S1. We assigned the predictive air pollutants data from the 27 districts to each participant according to the home addresses, which were geocoded as geographical longitude and latitude. Then the exposure parameters were calculated by averaging the daily concentration for pollutants during the period 2009-2012. Given the air pollution level is related with the address of the participants, the exposure level of the participants kept stabled within 3-5 years.

Questionnaire survey

Health effects were assessed using a questionnaire from the Epidemiologic Standardization Project Questionnaire of the American Thoracic Society (ATS-DLD-78-A) (Ferris 1978). The ATS questionnaire is available in a Chinese translation and has been effectively utilized in China before (Dong et al. 2011; Yang et al. 2018; Zhang et al. 2002). Before the survey commenced, principals of all selected schools provided permission for the study. Teachers from each school were trained to administrator of the questionnaire and were responsible for obtaining consent from the parents/guardians of student participants. The parents/guardians were encouraged to attend a training session at the school on completing the questionnaires. Alternatively, they could choose to take the questionnaire home and return it in a sealed envelope after completion.

Definitions of allergic respiratory diseases and symptoms

Primary outcomes of interest were defined as follows: (1) doctor-diagnosed asthma: a doctor had diagnosed repeated symptoms (i.e., wheezing, dyspnea, chest tightness, or nighttime or early morning coughing); (2) current asthma: asthma paroxysm, asthma-like symptoms, or asthma treatment in the last two years; (3) persistent cough: cough for more than four days every week for at least three months in the past 12 months; (4) persistent phlegm: phlegm, sputum, or mucus from the chest more than four days every week for at least three months in the past 12 months; (5) wheeze: wheeze or whistling when breathing regardless of whether the child had a cold; (6) current wheeze: more than two episodes of wheezing in the last two years; and (7) allergic respiratory diseases: asthma paroxysm, asthma-like symptoms (including persistent cough, persistent phlegm, or wheeze), or asthma treatment in the past 12 months. All above outcomes were dichotomized into Yes/No answers.

Influenza vaccination exposure

During the study period, the trivalent inactivated influenza vaccine had been approved and widely used for prevention of seasonal influenza infection in China. In the present study, children and adolescents were regarded as vaccinated if parents answered “yes” to the following survey question: “have you received influenza vaccine in the past three years?”

Potential confounders

Selection of covariates was guided by existing literature and the potential socioeconomic confounding (Castro-Rodriguez et al. 2016; Civelek et al. 2011; Just et al. 2010). Thus, covariates included: age (years), gender (boy/girl), low birth weight (Yes/No, defined as birth weight < 2500 g), BMI (Body mass index, defined as weight in kilograms divided by height in meters squared, kg/m^2), average temperature during period of the investigation (℃), premature birth (<37 weeks/≥37 weeks), breast-feeding (defined as having breastfed more than 3 months; Yes/No), exercise time per week (hours/week), area of residence per person (m^2/person), household income per year of the family (RMB), education of parents (>senior high school/≤senior high school), environmental tobacco smoke exposure (Yes/No, defined as living with families who smoke cigarettes daily in the house), and family history of allergic diseases (Yes/No). We selected the covariates in the final model as confounders according to the estimated effects for air pollutants in unvaccinated and vaccinated groups on the health outcomes changed by at least 10% upon in the base model.

A positive family history of allergies or asthma was defined as children and adolescents' biological parents or grandparents reporting a diagnosis of hay fever, allergic conjunctivitis, eczema, allergic rhinitis, or asthma. Children and adolescents with family history of allergies or asthma were categorized as having an "allergic predisposition."

Statistical Analysis

We conducted the Shapiro-Wilk W test to examine the normality distribution and Bartlett test for unequal variances of the dataset. We described mean and standard deviation (SD) for continuous variables and frequency percentages for categorical variables respectively. Student's t-tests and Chi-square test for continuous and categorical variables, respectively to compare the differences between the vaccinated group children and unvaccinated group children. A two-level generalized linear mix effects model was used to evaluate associations between health outcomes and PM_1, $PM_{2.5}$, PM_{10}, and NO_2 (Witte et al. 2000). Because of the high correlations between air pollutants ($r > 0.70$), only the single-pollutant models were used in order to avoid multi-collinearity. We treated participants as the first-level units and the school as the second-level units. The school was as a cluster for random intercept in the modeling. The details of this model are provided in the Supplementary Material and previous studies (Dong et al. 2013). Influenza vaccination status was used to examine the modified effects on the associations between ambient air pollution and allergic respiratory diseases. The covariates including age, gender, obesity, low birth weight, premature birth, breast-feeding status, exercise time per week, area of residence per person, household income, education of parents, environment tobacco smoke exposure, family history of asthma, average temperature during the time of investigation and districts for adjusting in the models.

In order to explore the interactive effects between each air pollutant and influenza vaccination status on children's respiratory allergic outcomes, a series of two-level logistic regression models were built. These placed random effects on each air pollutant at the school-level, fixed effects on influenza vaccination at the individual level, and adjusted for the aforementioned covariates (Dong et al. 2013). We incorporated cross-product terms between air pollutants and influenza vaccination to investigate the two-level interaction on the multiplicative scale. Results are presented as odds ratios (ORs) and their corresponding 95% confidence intervals (95% CIs) to describe the adjusted associations. Meta-regression models with fixed-effects within the study were built for assessing the efficiency of influenza vaccine for modifying the risk of air pollutants on allergic respiratory diseases.

To evaluate the robustness of the key findings, a series of sensitivity analysis including stratification by gender, allergic predisposition status, excluding indoor air pollution exposure and excluding one of the districts were conducted. The details of the modeling are described in the appendix methods ("Statistical analysis"). Mixed effects modeling was carried out by the GLIMMIX procedure in SAS v9.4 (SAS Institute Inc., Cary, NC). Meta-regression modeling was carried out in R ver3.5.2. For all the tests, a two-tailed value of $p < 0.05$ was used to determine statistical significance, except for interaction terms and meta-regression analysis (where $p < 0.10$ was used).

Results

The distributions of baseline characteristics of the study participants with and without influenza vaccination are shown in Table 1. A total of the 56,137 children and adolescents included in this analysis, 50.37% of them were boys and the average age of the participants was 10.31 years (ranged 2-17 years). Within the sample, 6.95% of children and adolescents had a family history of asthma and 22.42% reported an allergic predisposition. There were statistically significant differences in crude prevalence rates of allergic respiratory diseases outcomes between vaccinated and unvaccinated participants, with the exception of wheeze and allergic rhinitis (Table 2).

[Table 1 is about here]

[Table 2 is about here]

Distribution of estimated air pollutants levels are summarized in Table 3. The 4-year annual average PM_1, $PM_{2.5}$, PM_{10}, and NO_2 concentrations were 47.21μg/m^3, 55.08μg/m^3, 98.75μg/m^3 and 35.43μg/m^3, respectively.

[Table 3 is about here]

Overall, the positive associations between air pollutants and allergic respiratory diseases and related symptoms were observed among all the participants, boys and girls (Table 4, supplementary Table S8 and Table S9). We found statistically significant interactions between influenza vaccination and ambient long-term air pollutants on allergic respiratory diseases and related symptoms (doctor-diagnosed asthma, current wheeze, wheeze, persistent phlegm, and allergic rhinitis) (Table 4). Compared to children and adolescents who received influenza vaccine, those without influenza vaccination had higher estimated ORs for all associations between air pollutants and health outcomes (Table 4). The adjusted ORs for doctor-diagnosed asthma, current wheeze and allergic rhinitis among the unvaccinated group per interquartile range (IQR) increase in PM_1 and $PM_{2.5}$ were significantly higher than the corresponding ORs among the vaccinated group [For PM_1, doctor-diagnosed asthma: OR: 1.89 (95%CI: 1.57-2.27) vs 1.65 (95%CI: 1.36-2.00); current wheeze: OR: 1.50 (95%CI: 1.22-1.85) vs 1.10 (95%CI: 0.89-1.37); allergic rhinitis: OR: 1.38 (95%CI: 1.15-1.66) vs 1.21

(95%CI: 1.00-1.46). For $PM_{2.5}$, doctor-diagnosed asthma: OR: 1.81 (95%CI: 1.52-2.14) vs 1.57 (95%CI: 1.32-1.88); current wheeze: OR: 1.46 (95%CI: 1.21-1.76) vs 1.11 (95%CI: 0.91-1.35); allergic rhinitis: OR: 1.35 (95%CI: 1.14-1.60) vs 1.19 (95%CI: 1.00-1.42)]. The similar patterns were observed for wheeze and persistent phlegm. The corresponding *p* values for interactions were less than 0.05, respectively. We assessed the risks of PM_1-related and $PM_{2.5}$-related current wheeze were decreased by 26.67% (95%CI: 1.04%-45.66%) and 23.97% (95%CI: 0.21%-42.08%) respectively, which was attributable to influenza vaccination (both *p* for efficiency <0.05).

[Table 4 is about here]

In stratified analysis by gender, significant interactions were mainly found for air pollutants and influenza vaccination on allergic outcomes including doctor-diagnosed asthma, current wheeze, wheeze and allergic rhinitis in boys (Table S8-S9). For example, the significant association for doctor-diagnosed asthma with PM_{10} in the unvaccinated group (OR: 1.74, 95%CI: 1.46-2.07) was stronger than in the vaccinated group (OR: 1.39, 95%CI: 1.16-1.66) ($p_{\text{for interaction}}$ <0.05). In contrast with the associations seen in boys, the interaction effects of influenza vaccination exposure and air pollutants for girls were only statistically significant for current wheeze (Table S9). Furthermore, the results from stratified analyses in age and allergic predisposition status indicated that younger children and children with allergic predisposition were sensitivity to modification effects of influenza vaccination on the associations between ambient air pollution and allergic respiratory diseases (Table S10-S14).

We did additional sensitivity analyses using di□erent definitions of allergic respiratory diseases in the past three years and excluding one of 27 districts for sensitivity analysis, respectively, which indicated the similar patterns (Table S7, S15-S41).

Table 5 shows the interactions between air pollutants exposure and influenza vaccination states on allergic respiratory diseases in the past 12 months (Table 5). The interactions among all the participants were statistical significant for all air pollutants and influenza vaccination with allergic respiratory diseases in the past 12 months. The ORs and 95%CIs for the associations between air pollutant concentrations and allergic respiratory diseases were consistently greater in the unvaccinated group than those in the vaccinated group. Meta-regression analysis assessed the risks of the $PM_{2.5}$-related allergic respiratory diseases were reduced 15.75% (95%CI: -3.04%-31.13%) attributable to influenza vaccine (Table 5) ($p_{\text{for efficiency}}$<0.10). In further stratified analyses by allergic predisposition, gender and excluding indoor air pollution exposure, the patterns of the associations and interactions on the allergic respiratory diseases in the past 12 months persisted in all the subgroups (Fig 2, Table S42-S44).

[Table 5 is about here]

[Figure 2 is about here]

Discussion

This study provides new evidence on the potential benefits of influenza vaccination against the detrimental health effects of long-term ambient air pollution exposure on allergic respiratory diseases. We found stronger associations of long-term exposure to air pollution with allergic respiratory diseases and related symptoms among children and adolescents who were not vaccinated against influenza compared to those were vaccinated against influenza, indicating that vaccination could decrease the detrimental effects of air pollution on allergic respiratory diseases.

In this study, we observed the prevalence rates of most of respiratory and allergic symptoms were higher among vaccinated group than those among unvaccinated group. Regarding the results, the possible explanations were as following: Firstly, Given the large sample size (56137 participants) in this study, it is likely to observe the statistically significant differences in the prevalence rates between the two groups. Secondly, influenza infection is associated with asthma attack or severe complications (Feldman et al. 2019; Nicholas et al. 2017a). The asthmatic children's parents, especially the parents' with the history of asthma, were more likely to be more concerns and prevent influenza infection by vaccination than those whose children without asthma. While, asthma a complicated allergic disease is influenced by many factors, especially hereditary factor. Though influenza vaccine may prevent asthmatic children from influenza infection or asthma attack, the effectiveness of vaccine may not enough to protect the children against hereditary factor. Thirdly, at the same time, we found many studies explored the effectiveness of influenza vaccination on asthmatic people and the impacts on asthma attack or other clinical outcomes, but the results were not fully consistent. Recently a system review carried out by Eleftheria Vasileiou et al evaluated the effectiveness and safety of influenza vaccine in asthmatic patients (Vasileiou et al. 2017). Three cohort studies found the greater protective effects on asthma attacks in vaccinated group than unvaccinated group (Jaiwong et al. 2015; Kramarz et al. 2001; Watanabe et al. 2005). Observational studies demonstrated that influenza vaccines effectiveness prevented 59%–78% of emergency visits and/or hospitalizations from asthma attacks or influenza infections (Abadoglu et al. 2004; Sugaya et al. 1994). However, several epidemic and experimental studies found there were no relationships between influenza vaccination and asthma attack or exacerbations (Kmiecik et al. 2007; Miller et al. 2003; Redding et al. 2002). A retrospective cohort study of 800 children showed that the significantly higher risks of asthma in emergency department visits and clinical visits among vaccinated group than those among unvaccinated group (OR: 3.4 vs 1.9) (Christy et al. 2004). As the inconsistent results of these studies, further epidemical or experimental studies are warranted.

The independent effects of air pollution or influenza vaccination on childhood allergic respiratory diseases have been extensively investigated (Dong et al. 2011; Goodman et al. 2017; Herbert et al. 2017; Ray et al. 2017; Yang et al. 2018). However, few studies have investigated potential effect modification by vaccination for high risk populations. A case-crossover study conducted in Taiwan, China, found that older people who were exposed to CO, NO_2, PM_{10}, or $PM_{2.5}$ and did not receive the influenza vaccine were at greater risk of acute coronary syndrome (ACS) compared to those who had received the vaccine (Huang et al. 2016). A case-control study with 117 children from Tanzania showed that a higher risk for severe pneumonia was associated with higher household air pollution exposure (OR: 5.5, 95% CI: 1.4-22.1) and with delayed measles vaccination (OR: 3.9, 95% CI: 1.1-14.8) (PrayGod et al. 2016). Although the previous studies and our study have different study designs, participant' characteristics, vaccine types, and health outcomes, findings from the previous studies provide indirect support for our findings that vaccine might modify the adverse effects of air pollution on allergic respiratory diseases. Overall, our findings provided the new some evidence on supporting the increase in influenza vaccine use for allergic respiratory diseases in Chinese children and adolescents who expose to ambient air pollution.

The biological mechanisms underlying the modifying effects of influenza vaccination on associations between air pollution exposure and asthma are not clear. One possible explanation is the protection offered by influenza vaccination against asthma from influenza virus infection. Given the respiratory repercussions of an influenza virus infection, protection from infection may also serve to protect from asthma and allergic respiratory triggers. Another possibility is that particulate matters and NO_2 might induce oxidative stress, immune response, and airway inflammation in asthmatic patients (Gruzieva et al. 2017; Saygin et al. 2017). The mechanism of immune response caused by air pollutant exposure may be similar to that caused by respiratory virus infections (Nicholas et al. 2017b). Particulate matter carries allergens or other microorganisms, including viruses, which are the smallest common airborne aerosols with diameters less than 20 nanometers(Mentese et al. 2012). Viruses are unable to survive independently without attaching to other particles, such as $PM_{2.5}$ or PM_1 (Yang et al. 2011). These virus-carrying particles can be inhaled into the lower respiratory tract, which triggers an immune response and increases secretion and expression of inflammatory cytokines. When the Th1 immune response skews towards to the Th2 immune response, the virus could exacerbate inflammation, resulting in chronic airway diseases, asthma exacerbation, or virus infection complication(Guarnieri and Balmes 2014; Nicholas et al. 2017b). If influenza vaccine was inoculated into the body especially for high risk individual, the antibody against for influenza virus will be produced. Meanwhile, antibody-mediated immunity balance could be through the pathway of Th1/Th2, which might be the same pathway of the immune response triggered by air pollutants. Then, influenza vaccine may be against the detrimental effects of particulate matters by the pathway of immunity response. Therefore, influenza vaccination might play a role in mitigating the detrimental effects of particulate matter on asthma and other allergic respiratory diseases.

Gender stratified analysis indicated that boys appeared to have greater effects interactions between influenza vaccination and air pollution on asthma, asthma-related symptoms, and allergic rhinitis compared to girls. The reason for the gender differences in the present study is not clear. One possible explanation is that sex hormones may play an important role in regulating the inflammatory response, as demonstrated in the mouse model(Blacquiere et al. 2010). Boys have a higher prevalence of asthma than girls during the prepubescent period due to dysanapsis, smaller airway diameters resulting in immature lung function, and allergic inflammation (Borish et al. 2005). Asthma in girls increases after puberty because of increasing estrogen (Zein et al. 2015). Increasing sex hormones in girls may influence type 2-mediated or IL-17a-mediated airway inflammation. Influenza vaccination might decrease the inflammatory response due to air pollution exposure (Zein and Erzurum 2015). Another possible factor is that genes related to lipid metabolism may be modulated by levels of testosterone in response to the influenza vaccine, leading to the differences between girls and boys (Furman et al. 2014).

Our study has several strengths. We had a large sample size and, therefore, adequate power to detect modest effects. Additionally, we utilized a robust estimation of air pollution exposure, with measures of environmental exposure for both home and school settings. Prior work has typically only estimated environmental exposure either at home or at school. Finally, we evaluated the interaction effects of PM_1 exposure and influenza vaccination status on asthma, asthma-related symptoms, and allergic rhinitis. It is reported that PM_1 particles are recognized as high surface area to volume ratio, which might result in the greater effects on respiratory tissues and adverse health outcomes (Mei et al. 2018). Thus, PM_1 exposure may play an important role in asthma and other lower respiratory diseases.

However, we should be cautious for some potential limitations of this study. First, this is a cross-sectional study and we are unable to determine the temporality, i.e., whether the health effect occurred after the pollution exposures or vaccination, which is a key criteria to assess causality. Second, the ambient air pollution exposure data are assessed with machine learning modeling, which may influence the precision of pollutant concentrations at the individual level. This could lead to potential non-differential misclassification of exposure and the related bias would be towards the null. Third, there is the possibility of recall biases from self-reported data on smoking, physical activity, physician diagnosis of asthma, asthma symptom history, and influenza vaccination status. However, we believe that any such misclassification would be non-differential and the results may have been under-estimated. Fourth, information regarding some potential confounding, such as asthma type, severity of asthma (mild, moderate, or severe) and type of vaccine, was not available, and so residual or unmeasured confounding is also a possibility. Last, the present study was conducted in areas with high concentrations of air pollution in China. Thus, the findings may not be generalizable to high-income countries with lower air pollutant concentrations. Nevertheless, our results could provide reference values for countries with similar air pollution levels as well as a large sample with high pollution level to detect the pollution-vaccination interaction. Given the above limitations of this study, further researches are warranted with better study designs, more precise air pollution measurements, and adequately controlling for potential confounders.

Conclusion

Our findings suggest that influenza vaccination could act as a buffer for the detrimental effects of air pollution on allergic respiratory diseases in children and adolescents. Policy targeted at increasing influenza vaccination may yield co-benefits in terms of reduced allergic respiratory diseases.

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Declaration of interests

We declare no competing interests.

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Table 1 Distribution of basic characteristics and potential confounders among children in northeast China stratified by influenza vaccination status.

Variables	Total	Unvaccinated	Vaccinated
Continuous Variables	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
Age	10.31±3.59	10.77±3.35	9.62±3.81
Height (cm)	143.96±21.68	146.73±20.25	139.86±23.03
Weight (kg)	39.99±16.15	41.57±15.75	37.65±16.44
Exercise time per week (hours/week)	6.71±8.01	6.70±7.91	6.40±8.15
Area of residence per person (m^2/person)	23.74±12.19	23.73±11.75	23.75±12.82
Categorical variables	**n (%)**	**n (%)**	**n (%)**
Gender			
Boys	28275 (50.37)	16848 (50.29)	11427 (50.48)
Girls	27862 (49.63)	16653 (49.71)	11209 (49.52)
Breast feeding*	37755 (67.26)	22898 (68.35)	14857 (65.63)
Low birth weight	2071 (3.69)	1193 (3.56)	878 (3.88)
Premature birth*	3049 (5.43)	1660 (4.96)	1389 (6.14)
Caesarean birth*	27491 (48.97)	16182 (48.30)	11309 (49.96)
Education level of parents*			
>Senior high school	41563 (74.04)	25149 (75.07)	16414 (72.51)
≤Senior high school	14574 (25.96)	8352 (24.93)	6222 (27.49)
Household income per year (RMB)*			
<10 000	11602 (20.67)	6699 (20.00)	4903 (21.66)
10 000 – 30 000	20578 (36.66)	12339 (36.83)	8239 (36.40)
30 000 – 100 000	19999 (35.63)	12366 (36.91)	7633 (33.72)
>100 000	3958 (7.05)	2097 (6.26)	1861 (8.22)
Environmental tobacco smoke exposure *	26512 (47.23)	15584 (46.52)	10928 (48.28)
Family history of asthma	3899 (6.95)	2289 (6.83)	1610 (7.11)
Allergic predisposition*	12585 (22.42)	7707 (23.01)	4878 (21.55)

Abbreviations: RMB, Chinese Renminbi; SD: standard deviation.

*Indicates statistically significant different between children and adolescents with and without influenza vaccination at p<0.05.

Table 2 Distribution of health outcomes among children and adolescents in northeast China stratified by influenza vaccination status.

Variables	Unvaccinated n=33501, n (%)	Vaccinated n=22636, n (%)	*p*-value
Doctor-diagnosed asthma			
No	31048 (92.68)	20744 (91.64)	<0.001
Yes	2453 (7.32)	1892 (8.36)	
Current asthma			
No	32651 (97.46)	21936 (96.91)	<0.001
Yes	850 (2.54)	700 (3.09)	
Current wheeze			
No	32263 (96.30)	21607 (95.45)	<0.001
Yes	1238 (3.70)	1029 (4.55)	
Wheeze			
No	29594 (88.34)	19988 (88.30)	0.897
Yes	3907 (11.66)	2648 (11.70)	
Persistent cough			
No	31489 (93.99)	20887 (92.27)	<0.001
Yes	2012 (6.01)	1749 (7.73)	
Persistent phlegm			
No	32613 (97.35)	21763 (96.14)	<0.001
Yes	888 (2.65)	873 (3.86)	
Allergic rhinitis			
No	30314 (90.49)	20428 (90.25)	0.341
Yes	3187 (9.51)	2208 (9.75)	

Table 3 Description of ambient air pollution concentrations (μg/m^3) in northeast China.

Air pollutants	Mean	SD	Median	Minimum	Maximum	IQR	NAAQS*	WHO guideline†
PM_1	47.21	5.76	48.97	38.15	56.20	11.45	--	--
$PM_{2.5}$	55.08	6.19	56.23	46.04	65.58	11.53	35	10
PM_{10}	98.75	9.91	101.02	75.90	114.56	17.09	100	20
NO_2	35.43	4.43	37.11	20.57	42.59	7.70	40	40
Temperature (°C)‡	15.95	5.41	17.00	1.50	27.50	7.00	--	--

Abbreviations: PM_1, airborne particulates with aerodynamic diameter < 1μm; $PM_{2.5}$, airborne particulates with aerodynamic diameter < 2.5μm; PM_{10}, airborne particulates with aerodynamic diameter < 10μm; NO_2, nitrogen dioxide; SD: standard deviation; IQR: interquartile range (range from 25th to 75th percentile of district-specific concentrations); NAAQS: National Ambient Air Quality Standards of China.

*Annual National Ambient Air Quality Standards of China in 2012; no guidelines for PM_1.

†World Health Organization's 2005 air quality guidelines; no guidelines for PM_1.

‡Temperature during time of investigation.

Table 4 Adjusted ORs and 95%CIs for the associations between ambient air pollutants and asthma, asthma-related symptoms and allergic rhinitis stratified by influenza vaccination status.

Variables	Total OR (95% CI) †*	Unvaccinated OR (95% CI) †	Vaccinated OR (95% CI) †	$p_{interaction}$ value *	Efficiency (%)	$p_{efficiency}$ value
Doctor-diagnosed asthma						
PM_1	1.78 (1.49,2.13)	1.89 (1.57,2.27)	1.65 (1.36,2.00)	0.048	12.70 (-13.98,33.14)	0.318
$PM_{2.5}$	1.70 (1.45,2.01)	1.81 (1.52,2.14)	1.57 (1.32,1.88)	0.025	13.26 (-10.92,32.18)	0.257
PM_{10}	1.60 (1.38,1.86)	1.71 (1.46,2.01)	1.46 (1.24,1.72)	0.007	14.62 (-7.31,32.08)	0.176
NO_2	1.58 (1.36,1.84)	1.70 (1.44,1.99)	1.43 (1.21,1.69)	0.006	15.88 (-6.13,33.33)	0.145
Current asthma						
PM_1	1.78 (1.39,2.28)	1.86 (1.43,2.42)	1.67 (1.26,2.22)	0.368	10.22 (-32.14,39.00)	0.585
$PM_{2.5}$	1.72 (1.37,2.15)	1.80 (1.42,2.29)	1.61 (1.25,2.07)	0.267	10.56 (-26.59,36.81)	0.529
PM_{10}	1.65 (1.34,2.03)	1.73 (1.39,2.16)	1.54 (1.22,1.95)	0.262	10.98 (-22.80,35.48)	0.479
NO_2	1.64 (1.34,2.02)	1.74 (1.39,2.18)	1.51 (1.19,1.93)	0.201	13.22 (-20.73,37.63)	0.400
Current wheeze						
PM_1	1.32 (1.09,1.60)	1.50 (1.22,1.85)	1.10 (0.89,1.37)	0.001	26.67 (1.04,45.66)	0.043
$PM_{2.5}$	1.30 (1.09,1.54)	1.46 (1.21,1.76)	1.11 (0.91,1.35)	0.002	23.97 (0.21,42.08)	0.048
PM_{10}	1.28 (1.10,1.50)	1.44 (1.21,1.72)	1.10 (0.92,1.32)	0.001	23.61 (1.72,40.63)	0.036
NO_2	1.29 (1.10,1.51)	1.47 (1.23,1.75)	1.09 (0.91,1.31)	0.001	25.85 (4.46,42.45)	0.021
Wheeze						
PM_1	1.25 (1.11,1.41)	1.35 (1.18,1.53)	1.11 (0.96,1.27)	0.001	17.78 (0.48,32.07)	0.044
$PM_{2.5}$	1.24 (1.11,1.38)	1.33 (1.18,1.50)	1.10 (0.97,1.25)	<0.001	17.29 (1.52,30.54)	0.033
PM_{10}	1.21 (1.10,1.34)	1.30 (1.17,1.45)	1.09 (0.97,1.23)	<0.001	16.15 (1.60,28.55)	0.031
NO_2	1.19 (1.08,1.32)	1.27 (1.14,1.42)	1.09 (0.97,1.22)	0.003	14.17 (-0.58,26.77)	0.059
Persistent cough						
PM_1	1.35 (1.13,1.60)	1.38 (1.13,1.68)	1.32 (1.08,1.61)	0.665	4.35 (-26.72,27.81)	0.757
$PM_{2.5}$	1.32 (1.12,1.54)	1.36 (1.13,1.63)	1.28 (1.06,1.54)	0.514	5.88 (-22.25,27.55)	0.650
PM_{10}	1.26 (1.09,1.46)	1.28 (1.08,1.51)	1.25 (1.06,1.48)	0.806	2.34 (-23.70,22.91)	0.844
NO_2	1.24 (1.07,1.44)	1.24 (1.05,1.47)	1.24 (1.04,1.47)	0.986	0.00 (-27.28,21.44)	1.000
Persistent phlegm						
PM_1	1.38 (1.17,1.62)	1.46 (1.23,1.74)	1.28 (1.07,1.53)	0.066	12.33 (-12.46,31.66)	0.301
$PM_{2.5}$	1.34 (1.16,1.56)	1.42 (1.21,1.66)	1.26 (1.07,1.48)	0.070	11.27 (-11.28,29.25)	0.301
PM_{10}	1.29 (1.12,1.47)	1.34 (1.16,1.56)	1.22 (1.05,1.42)	0.112	8.96 (-12.48,26.31)	0.385
NO_2	1.26 (1.10,1.44)	1.32 (1.14,1.53)	1.19 (1.02,1.39)	0.097	9.85 (-11.60,27.18)	0.341
Allergic rhinitis						
PM_1	1.31 (1.10,1.56)	1.38 (1.15,1.66)	1.21 (1.00,1.46)	0.024	12.32 (-14.12,32.64)	0.328
$PM_{2.5}$	1.28 (1.09,1.51)	1.35 (1.14,1.60)	1.19 (1.00,1.42)	0.026	11.85 (-12.48,30.93)	0.311
PM_{10}	1.23 (1.06,1.43)	1.30 (1.11,1.52)	1.15 (0.98,1.35)	0.015	11.54 (-10.70,29.32)	0.284
NO_2	1.22 (1.05,1.42)	1.30 (1.11,1.52)	1.12 (0.95,1.31)	0.005	13.85 (-7.86,31.19)	0.194

*Adjusted by age, gender, obesity, low birth weight, premature birth, breast-feeding status, exercise time per week, area of residence per person, household income, education of parents, smoking exposure, family history of asthma, average temperature during investigation and districts.

†ORs were scaled to the interquartile range for each pollutant (11.45 $\mu g/m^3$ for PM_1; 11.53 $\mu g/m^3$ for $PM_{2.5}$; 17.09 $\mu g/m^3$ for PM_{10}; and 7.70 $\mu g/m^3$ for NO_2).

Table 5 Adjusted ORs and 95%CIs for the associations between ambient air pollution and allergic respiratory diseases attack in the past 12 months among children and adolescents in northeast China.

Variables	Total †*	Unvaccinated OR (95% CI) †	Vaccinated OR (95% CI) †	$p_{interaction}$ value *	Efficiency (%)	$p_{efficiency}$ value
PM_1	1.30 (1.11,1.51)	1.51 (1.30,1.75)	1.26 (1.07,1.47)	0.001	16.56 (-3.71,32.87)	0.103
$PM_{2.5}$	1.26 (1.10,1.46)	1.46 (1.27,1.68)	1.23 (1.07,1.43)	0.001	15.75 (-3.04,31.13)	0.095
PM_{10}	1.23 (1.08,1.40)	1.40 (1.23,1.59)	1.20 (1.05,1.37)	0.002	14.29 (-3.11,28.75)	0.102
NO_2	1.23 (1.08,1.40)	1.39 (1.22,1.58)	1.16 (1.02,1.33)	< 0.001	16.55 (-0.43,30.66)	0.056

*Adjusted by age, gender, obesity, low birth weight, premature birth, breast-feeding status, exercise time per week, area of residence per person, household income, education of parents, smoking exposure, family history of asthma, average temperature during investigation and districts.

†ORs were scaled to the interquartile range for each pollutant (11.45 μg/m^3 for PM_1; 11.53 μg/m^{3}for $PM_{2.5}$; 17.09 μg/m^{3}for PM_{10}; and 7.70 μg/m^{3}for NO_2).

Allergic respiratory diseases: asthma paroxysm, asthma-like symptoms (including persistent cough, persistent phlegm, or wheeze), or asthma treatment in the past 12 months.

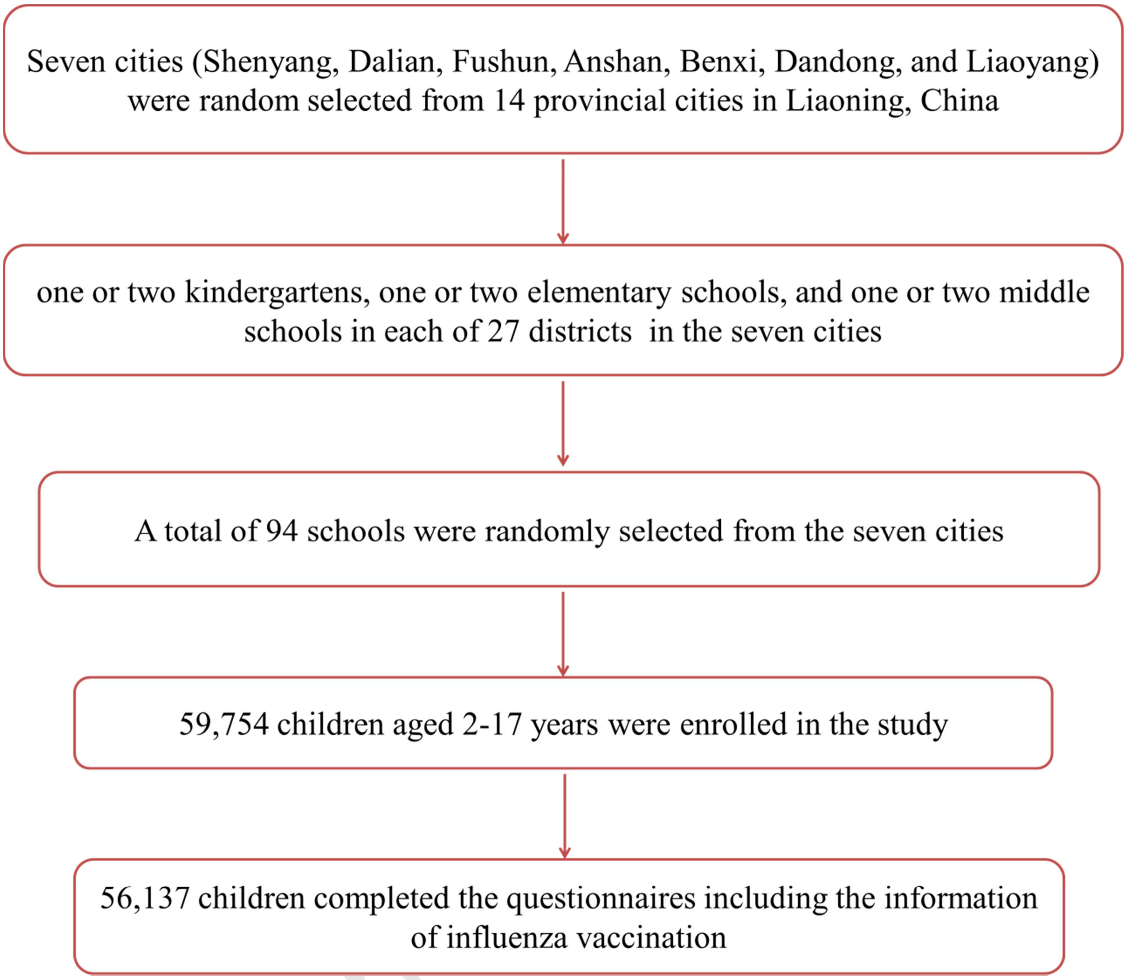

Fig 1 Sampling process for Seven Northeast Cities Study in China

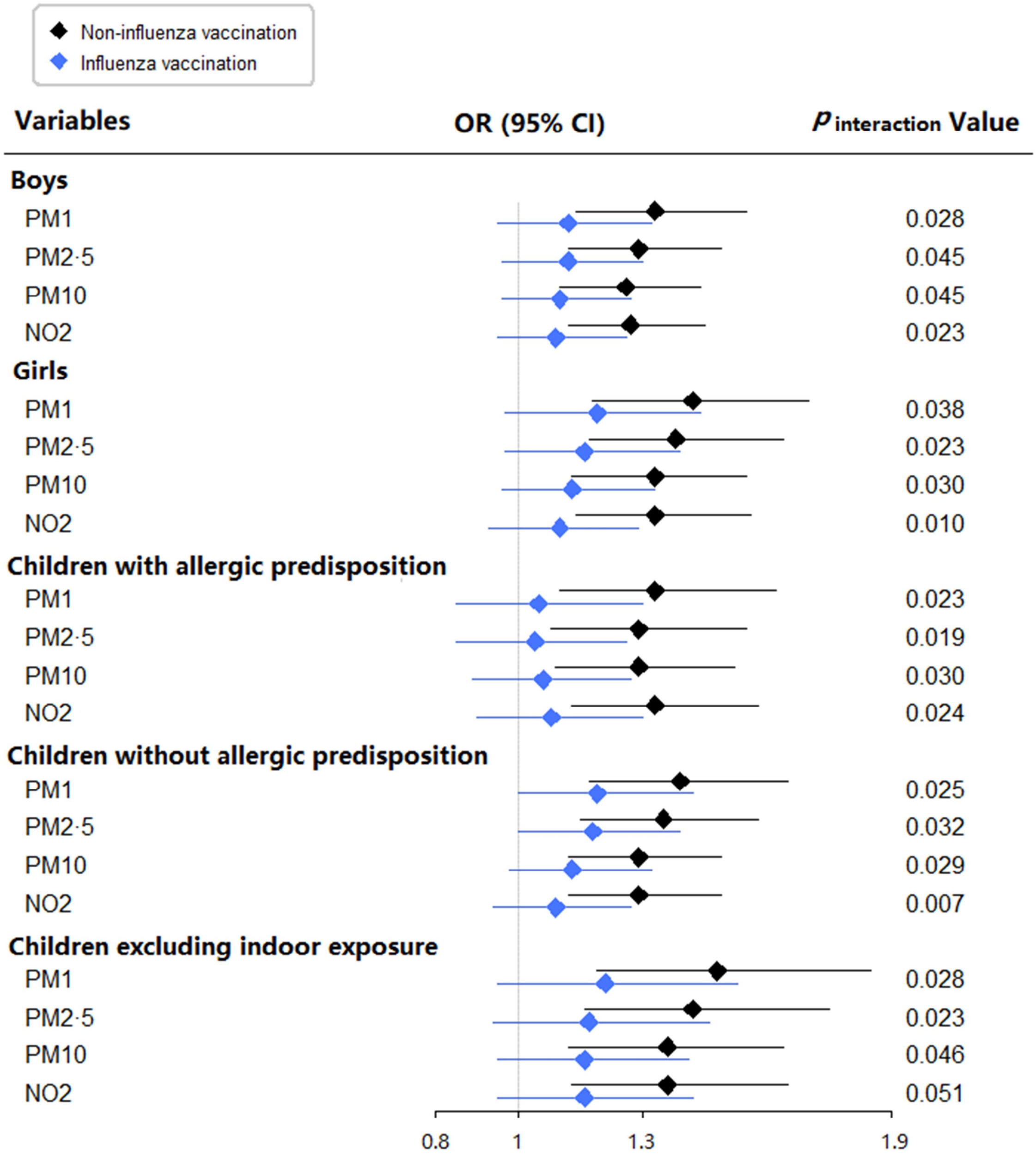

Fig 2 Adjusted ORs and 95%CIs for the associations between ambient air pollutants and allergic respiratory diseases in the past 12 month residing in northeast China , stratified by allergic predisposition and gender, respectively.

Adjusted by age, gender, obesity, low birth weight, premature birth, breast-feeding status, exercise time per week, area of residence per person, household income, education of parents, smoking exposure, family history of asthma, average temperature during investigation and districts.

ORs were scaled to the interquartile range for each pollutant (11.45 μg/m^3 for PM_1; 11.53 μg/m^{3}for $PM_{2.5}$; 17.09 μg/m^{3}for PM_{10}; and 7.70 μg/m^{3}for NO_2).

Allergic predisposition: any biological parent or grandparent with diagnosed hay fever or allergies (including allergic dermatitis, allergic conjunctivitis, and eczema).

Figure legends

Fig 1 Sampling process for Seven Northeast Cities Study in China.

Fig 2 Adjusted ORs and 95%CIs for the associations between ambient air pollutants and allergic respiratory diseases in the past 12 month in northeast China, stratified by allergic predisposition, gender and excluding indoor air pollution exposure, respectively.

Adjusted by age, gender, obesity, low birth weight, premature birth, breast-feeding status, exercise time per week, area of residence per person, household income, education of parents, smoking exposure, family history of asthma, average temperature during investigation and districts. ORs were scaled to the interquartile range for each pollutant (11.45 μg/m^3 for PM_1; 11.53 μg/m^3 for $PM_{2.5}$; 17.09 μg/m^{3}for PM_{10}; and 7.70 μg/m^{3}for NO_2).

Allergic predisposition: any biological parent or grandparent with diagnosed hay fever or allergies (including allergic dermatitis, allergic conjunctivitis, and eczema).

Table 1 Distribution of basic characteristics and potential confounders among children in northeast China stratified by influenza vaccination status.

Footnotes: Abbreviations: RMB, Chinese Renminbi; SD: standard deviation.

[*]Indicates statistically significant different between children and adolescents with and without influenza vaccination at p<0.05.

Table 2 Distribution of health outcomes among children and adolescents residing in northeast China stratified by influenza vaccination status.

Table 3 Description of 4-year ambient air pollution concentrations (μg/m^3) in northeast China.

Table 4 Adjusted ORs and 95%CIs for the associations between ambient air pollutants and asthma, asthma-related symptoms and allergic rhinitis stratified by influenza vaccination status.

Table 5 Adjusted ORs and 95%CIs for the associations between ambient air pollution and allergic respiratory diseases attack in the past 12 months among children and adolescents in northeast China.

Highlights

- Few studies on interaction between air pollution and influenza vaccine on asthma.
- A large population-based study to assess these interaction effects in China.
- Influenza vaccine may mitigate the detrimental effects of air pollution on asthma.
- Boys seem to be more sensitive to these interaction effects than girls.

Declaration of interests

☒ 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.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: