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Early-life exposure to air pollution associated with food allergy in children: Implications for 'one allergy' concept

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Early-life exposure to air pollution associated with food allergy in children: Implications for 'one allergy' concept

Abstract

Background: The rapid increase of food allergy (FA) has become the "second wave" of allergy epidemic and is now a major global public health concern. Mounting evidence indicates that early life exposure to air pollution is associated with the "first wave" of allergy epidemic (including asthma, allergic rhinitis and eczema) in children, but little is known about its association with FA.
Objectives: We hypothesize FA has triple exposure pathways, gut-skin-airway, and investigate the effects of airway exposure to outdoor and indoor air pollution on childhood FA.
Methods: A cohort study of 2598 preschool children aged 3–6 years old was conducted in Changsha, China. The prevalence of FA was surveyed using a standard questionnaire by International Study of Asthma and Allergies in Childhood (ISAAC). Exposure to indoor air pollution was assessed by four indicators: new furniture, redecora tion, mold or dampness, and window condensation. Exposure to outdoor air pollution was evaluated by the concentrations of PM10, SO2 and NO2, which were obtained from the monitored stations. Both prenatal and postnatal exposure windows were considered. The association between exposure to outdoor/indoor air pollution and childhood FA was estimated by multiple logistic regression models using odds ratio (OR) and a 95% con f idence interval (CI).
Results: A total of 14.9% children reported FA. The prevalence was significantly associated with exposure to indoor air pollution, OR (95% CI) = 1.93 (1.35–2.75) for prenatal exposure to mold/dampness and 1.49 (1.07–2.10) and 1.41 (1.04–1.89) respectively for postnatal exposure to new furniture and window condensation. The prevalence of FA was also associated with prenatal and postnatal exposure to outdoor air pollution, particularly the traffic-related air pollutant NO2, with adjusted ORs (95% Cls) respectively 1.24 (1.00–1.54) and 1.38 (1.03–1.85) per interquartile range (IQR) increase. Sensitivity analysis showed that the association between outdoor/indoor air pollution and childhood FA was significant only in young children aged 3–4 years. Conclusion: Early-life exposure to high levels of outdoor and indoor air pollution in China due to the rapid economic growth and fast urbanization in the past decades may contribute to the rapid increase of food allergy (FA) in children. Our study indicates that, in addition to gut and skin, airway may be a new route of food sensitization. Air pollution leads to the first and second waves of allergy epidemics, suggesting a concept of 'one allergy' disease.

(393 words)

Key words

Allergic diseases, Traffic-related air pollution, Urbanization, Triple exposure hypothesis, One allergy

1.Introduction

Food allergy (FA), a specific immune response to particular foods (Sicherer and Sampson, 2018), has become a major public health issue in the world, affecting 10% of general population and more children (Loh and Tang, 2018). FA is also a common cause of potentially life-threatening hypersensitivity reaction, often called food anaphylaxis, which usually develops rapidly and may even lead to death (Conrado et al., 2021). FA contributes to increased medical expenditure, espe cially emergency treatment, which places a considerable economic burden on patients and society (Gupta et al., 2018). Meanwhile, FA significantly impairs the quality of patients' lives, from limiting partic ipation in social activities to being treated differently by peers, as re ported that bullying, anxiety and depression are common in children living with FA (Khamsi, 2020).

FA, as a type of allergic diseases, plays a key role in the progression of allergic diseases or atopic march (Fig. 1), but it is usually considered to be different from other allergic diseases due to:

● Time lag. Until the beginning of the 21st century, FA has been rising globally, especially the substantial increases in the number of hos pital admissions due to food anaphylaxis. Compared with the "first wave" allergy epidemic (including asthma, allergic rhinitis and eczema) which has increased markedly since 1980s, FA is called the "second wave" allergy epidemic with a time lag of about 30 years (Prescott and Allen, 2011).

● Exposure routes. FA is generally considered to be caused by oral exposure through the gut, whereas eczema is caused by cutaneous exposure through skin contact and asthma or rhinitis is caused by airway exposure through inhalation (Nowak-Wegrzyn et al., 2017). Recently, mounting evidence indicates that food sensitization can also occur through transcutaneous exposure to food allergens, i.e. "gut-skin" dual exposure hypothesis (Brough et al., 2020; Walker et al., 2018).

● Risk factors. There is widespread agreement that exposure to air pollution increased risk of the "first wave" allergy epidemic (Egui luz-Gracia et al., 2020; Paciencia et al., 2022), but its risk on the "second wave" allergy epidemic has been rarely reported.

Genetics and environmental factors have a big impact on how allergic diseases develop. However, the quick increase of FA prevalence should be attributed to environmental determinants (Moran, 2020). Whether being exposed to air pollution leads to the rapid increase in FA in China is the objective of the present work (Fig. 1c).

Recent studies indicate that early-life exposure to air pollution is associated with the increase in the risk of the "first wave" of allergy epidemics, including eczema, rhinitis and asthma in children (Baek et al., 2021; Deng et al. 2015, 2016a, 2016b; Lu et al., 2022), but there are very few studies on its association with food sensitization and there is a high degree of heterogeneity between these rare studies (Ashley et al., 2015; Bowatte et al., 2015). A birth cohort study in the Netherlands found that long-term postnatal exposure to traffic-related air pollutants, including particulate matter less than 2.5 μm (PM2.5) and nitrogen dioxide (NO2), significantly increased the sensitization to food allergens in children at age 4 (Brauer et al., 2007). However, the association was not observed in cohort studies in Sweden (Gruzieva et al., 2012). Recently, a study in US found that prenatal exposure to PM2.5 increased the risk of food sensitization in adolescence at median age of 12.9 years (Sordillo et al., 2019).

The limited knowledge has prompted an urgent need to systematically examine the impact of air pollution exposure on FA.

We hypothesize that airway, in addition to gut and skin, may be a new pathway of food sensitization, i.e. triple (gut-skin-airway) exposure hypothesis (Fig. 1b), and then investigate the association of airway exposure to outdoor and indoor air pollution with FA in children. If this hypothesis is true, it is believed that air pollution has led to the first and second waves of allergy epidemics, which indicates a concept of 'one allergy' disease.

<Fig. 1>

2. Materials and methods

2.1 Study protocol & questionnaire

From September 2011 to January 2012, we conducted a cohort research in Changsha as a part of national "China-Child-Family-Health (CCHH)" research (Zhang et al., 2013a). The Central South University Ethics Committee approved the study's protocol. We used a standard questionnaire of the International Study of Asthma and Allergies in Childhood (ISAAC) to obtain the information about food allergy in children (Asher et al., 2006), and another questionnaire on buildings to investigate the lifestyle and indoor environment of children and their families (Bornehag et al., 2004). All children in 36 kindergartens were randomly selected for questionnaire survey. We asked the parents to fill in the questionnaire and send them back to the kindergarten within a week. A total 2598 children aged 3–6 years old were included in this work.

2.2 Definition of food allergy (FA)

The health outcome was lifetime prevalence of doctor-diagnosed food allergies (FA), which was estimated based on positive responses to the question: "Has your child ever had allergic symptoms such as eczema, hives, diarrhea, swollen lips or eyes caused by foods?"

2.3 Exposure to outdoor air pollution

Ambient air pollution was represented by three types of air pollut ants, sulfur dioxide (SO2), nitrogen dioxide (NO2), and particulate matter with diameter ≤10 μm (PM10), which were used as indicators of industry-related air pollution (IRAP), traffic-related air pollution (TRAP), and mixed air pollution respectively (Deng et al., 2015; Sram, 2020). The daily average concentration of air pollutants was obtained from seven monitoring stations of Changsha, which was used to estimate each child's daily exposure by an inverse distance weighted (IDW) method (Deng et al., 2015).

2.4 Exposure to indoor air pollution

We selected four indicators of the indoor air pollution: new furniture, redecoration, mold/damp stains, and window condensation. New furniture and redecoration are main sources for indoor air pollution, especially for the new buildings. Mold/damp

stains and window condensation are main indicators for ventilation of buildings, which is a key factor affecting the level of indoor air pollution. The exposure to above four indicators of indoor air pollution was obtained by ques tionnaire (the detailed information shown in Table S1). The answers “A little”, “A lot”, and “Yes” were defined as “with exposure”, while the answer “No” was defined as “without exposure”, and the answer “Don’t know” was considered to be missing data in the statistical analysis.

<Table 1>

2.5 Exposure windows

We considered both pre- and post-natal exposure windows for each child. Prenatal window is defined as the period from the first to the last month of pregnancy, and further divided into three gestational periods: 1st-3rd month (the first trimester), 4th-6th month (the second trimester), and 7th-last month (the third trimester), respectively. The postnatal window is from the first month of birth to the last month before the survey.

2.6 Confounding covariates

Potential confounding variables include personal and indoor envi ronmental factors. Personal factors included the child’s sex, age, birth season, breastfeeding, time to kindergarten, parental atopy and socio economic status (SES) indicated by housing size. Covariates related to the indoor environment included environmental tobacco smoke (ETS), household pets (keeping dogs) and cleaning habits. In our previous studies, these confounding factors were associated with childhood allergic diseases and thus may affect outcome estimates (Deng et al., 2015).

2.7 Statistical analysis

We used a multiple logistic regression model to evaluate the asso ciation between outdoor/indoor air pollution and childhood FA during different exposure windows by adjusting for covariates. All statistical analyses were performed using SPSS software (version 16.0, SPSS Inc, Chicago, USA). Results were interpreted by odds ratios (OR) with 95% confidence intervals (95% CI), where p-value less than or equal to 0.05 was considered statistically significant. Outdoor air pollutants were entered into the logistic regression model as continuous variables and their risks were estimated by per interquartile range (IQR) increase in their exposure levels. Indoor air pollution was entered into the logistic regression model as categorical variables, and their associations with health outcomes were estimated by setting no exposure cases as the reference (OR =1).

3.Rsults

Of 2598 children, 388 children (14.9%) had a history of FA. Table 1 displays the prevalence of FA stratified by covariates. We found that the prevalence in male children (16.7%), children aged 3–4 years (16.1%), children with atopic parents (31.8%) and children living in seldom cleaning houses (18.9%) were significantly

higher than female children (12.8%), children aged 5–6 years (13.1%), children with no atopic parents (12.4%) and children living in clean houses (13.9%).

Children's exposure to indoor air pollution and the corresponding prevalence of food allergies during prenatal and postnatal periods are shown in Table 2. As expected, we found that families who redecorated their houses less frequently during maternal pregnancy (prenatal period) than after birth (postnatal period), as indicated by the presence of less number of pieces of new furniture in comparison (338 vs 980) and house decoration (139 vs 499), but kept their houses less ventilated as indicated by more window condensation during winter (1222 vs 869) and mold/dampness (435 vs 308). The FA prevalence was higher in children exposed to higher level of indoor air pollution with new furniture, house decoration, window condensation and mold/dampness.

<Table 2>

Table 3 shows that prenatal exposure to mold/dampness signifi cantly increases the risk of FA with adjusted OR (95% CI) =1.93 (1.35–2.75), but exposure to new furniture and window condensation was significant during postnatal period with adjusted ORs (95% CIs) = 1.49 (1.07–2.10) and 1.41 (1.04–1.89), respectively.

<Table 3>

Children are exposed to high levels of outdoor air pollutants, including PM10, SO2 and NO2, as shown in Table S2. We found that exposure to outdoor air pollution is significantly associated with child hood FA (Table 4). Traffic-related air pollutant (TRAP), NO2, signifi cantly increased the risk during both pre- and post-natal periods with the adjusted ORs (95% Cls) respectively 1.24 (1.00–1.54) and 1.38 (1.03–1.85) for IQR increase in exposure level. PM10 and SO2 signifi cantly increased the risk of childhood FA only during postnatal period with adjusted ORs (95% CIs) respectively 1.42 (1.08–1.86) and 1.34 (1.07–1.70). The detailed exposure-response relationships shown in Fig. 2 also highlighted that the high level of exposure to PM10, SO2, and NO2 significantly increased the risk of FA during both prenatal and postnatal periods. However, the "U" shaped exposure-response curve also indicated the risk of low level of exposure, especially NO2 during both prenatal and postnatal periods and PM10 during prenatal period.

<Table 4>

Sensitivity analysis indicates that the association between outdoor/ indoor air pollution and childhood FA was significant in young children aged 3–4 years only.

<Fig. 2>

4.Discussion

We added the evidence that exposure to indoor and outdoor air pollution significantly increased the risk of food allergy (FA) in children, especially prenatal exposure. Our study indicates that airway is a new pathway of FA and verifies the "gut-skin-airway" triple exposure hy pothesis. Air pollution leads to the first and second waves of

allergy epidemics, suggesting a concept of ‘one allergy’ disease, which provides new implications for the control and prevention of the rapidly increasing of FA in children worldwide.

Our study indicates that the rapid increase of childhood FA in China is linked with the development during the past decades (Cai et al., 2020; Hu et al., 2010). With the rapid economic growth in the past few de cades, China has witnessed a high level of ambient air pollution; meanwhile the fast urbanization has resulted in many citizens moving to new buildings where the new furniture and redecoration are contrib uting causes to serious indoor air pollution (Gao et al., 2014; Zhang et al., 2013b). Our study indicated that high level of outdoor and indoor air pollution due to rapid economic growth and fast urbanization may lead to a high risk of FA in China, as reported that FA prevalence in infants aged 0–24 months in Chongqing had increased substantially from 3.5% in 1999 to 7.7% in 2009 (Hu et al., 2010). This finding was also supported by the increasing FA prevalence reported in highly urbanized and developed countries including the US (from 3.3% in 1997 to 3.9% in 2007) (Branum and Lukacs, 2009), Canada (from 1.5% in 2000 to 1.62% in 2005 for peanut allergy) (Ben-Shoshan et al., 2009), UK (from 0.24% in 2001 to 0.51% in 2005 for peanut allergy) (Kotz et al., 2011), and Australia (food anaphylaxis increased 5.5-fold in children aged 0–4 years between 1994-1995 and 2004–2005) (Poulos et al., 2007). It can be expected that FA will further increase in the near future, particularly in low- and middle-income countries where eco nomic growth and urbanization are the main manifestations of national development (Loh and Tang, 2018).

We found that early-life exposure to outdoor air pollution, especially TRAP (NO2), had a significant effect on FA in children. This finding was demonstrated in a mouse model that airway exposure to TRAP and other air pollutants lead to peanut allergy sensitization (Moran et al., 2021). Several birth cohort studies also supported our findings. A Swedish birth cohort study observed that an excess risk of food sensitization at 8 years was related to NOx exposure in the first year of life (OR =2.30, 95% CI:1.10–4.82) (Gruzieva et al., 2012). A multicenter study in Canada found that the NO2 concentration was associated with peanut sensiti zation (OR =1.07, 95% CI:1.03–1.11) in children at one year of age (Sbihi et al., 2015). A meta-analysis concluded that exposure to NO2 significantly increased the risk of sensitization to food allergens in early childhood at the age of 4 years and exposure to PM2.5 during early childhood increased the risk at 4 and 8 years of life (Bowatte et al., 2015). Recently, prenatal exposure to black carbon (OR =1.4, 95% CI:1.1–1.7) and PM2.5 (OR =1.3, 95% CI:1.1–1.7) was found to in crease the risk of sensitization to food in a US birth cohort of 996 mother-child pairs (Sordillo et al., 2019).

The risk of exposure to indoor air pollution to health is of great concern because children spend most of their time in indoor environ ment (Gabriel et al., 2021), but the effects of indoor air pollution on childhood FA are very limited. The prevalence of allergy were found to be associated with indoor environmental factors, mainly due to the exposure to indoor allergens, such as house dust mites, pets, insects, moulds and chemical agents (Carrer et al., 2001). Exposure to low levels of indoor allergens in early childhood was found to be associated with incidence of sensitization (Munir et al., 1997). Our study found that prenatal exposure to mold or postnatal exposure to new furnitur e/window condensation was significantly associated with childhood FA. New furniture and decorative materials continuously release gaseous pollutants

including volatile organic compounds (VOCs). It was reported that children exposed to VOCs had 5 to 11 times higher risk of sensiti zation to either egg or milk compared to unexposed children (Lehmann et al., 2001). A case-control study of 400 Swedish pre-school children found that exposure to propylene glycol and glycol ethers (PGEs, a class of VOCs) in bedroom increased the risk of IgE sensitization (OR =1.8, 95% CI: 1.1–2.8) (Choi et al., 2010). Several studies also observed that early-life exposure to environmental tobacco smoke (ETS) was a risk factor for food allergen sensitization, for example, the BAMSE cohort of 3316 children found that ETS exposure during infancy increased the risk of food allergen sensitization at 4 years of age (OR 1.47, 95% CI 1.1–2.0) and persistent sensitization at 16 years of age (OR 2.2, 95% CI 1.3–3.6) (Thacher et al., 2016).

Our findings provide the evidence to support "gut-skin-lung" triple exposure hypothesis for FA. The dual exposure hypothesis has been widely accepted, i.e., both oral and cutaneous exposure to allergens can lead to the development of FA (Brough et al., 2020; Du Toit et al., 2016; Walker et al., 2018). Our research suggested that the airway or lungs may be the third exposure route, which is consistent with the recent mouse models and human cell–based studies (Kulis et al., 2021; Peters et al., 2022). This finding indicates that FA is actually an allergic disease similar to other allergic diseases and indicates a common mechanism underlying eczema, asthma, allergic rhinitis, and FA (Olbrich et al., 2020). Recently, mounting evidence has highlighted that damage to the epithelium of the lungs, gut, and skin by an altered microbiome, air pollution or food allergens leads to various manifestations of allergic diseases (Dalton et al., 2022; Kemter and Nagler, 2019; Krempski et al., 2020; Olbrich et al., 2020). Recently, similarities and interactions be tween allergic diseases have been widely observed; people with one disease are more likely to suffer from other allergic diseases (Ching-Wei et al., 2022; Chiu et al., 2020; Miyaji et al., 2020; Ziyab, 2019).

Air pollution leads to the first and second waves of allergy epidemics, suggesting a concept of 'one allergy' disease. The concept of ''One Airway, One Disease'' for asthma and allergic rhinitis has been widely accepted due to their link (Zou et al., 2022). It has been indicated that a high proportion of new patients have upper and lower airway diseases that coexist (Giovannini-Chami et al., 2018). Our studies suggest that both the first wave of allergy epidemic (including eczema, asthma and allergic rhinitis) and the second wave of allergy epidemic are sensitive to the same environmental exposures, especially air pollutants (Table S3 in the Supplemental Materials).

The 'one allergy' means that successful control measures for asthma, such as reducing exposure to air pollution, will provide a good reference for prevention of FA. At present, the main measure to prevent FA is to avoid food allergens or to increase the food tolerance (Gonzalez-Visiedo et al., 2022; Liu et al., 2022; Yang et al., 2022). For example, the American Academy of Pediatrics (AAP) advises parents to avoid giving their children peanuts to prevent them from having allergic reactions, and even advises expectant mothers not to eat peanuts during pregnancy to reduce the chance of infant allergy (Brzozowska et al., 2022). Recently, the dual exposure hypothesis indicates that the skin is also a key target to prevent and treat childhood food allergies (Martin et al., 2015). Our work suggests novel prevention or intervention strategies for FA, i.e. to reduce exposure to air pollution.

We acknowledge that our study has several limitations. Firstly, the results based on the questionnaire/parental report may have had some recall bias. Our study may underestimate FA prevalence, because many individuals with food allergy may naturally overcome it over time. In longitudinal studies, most food allergies that develop early in life, such as allergies to eggs and cow's milk, usually resolve with time (Sicherer et al., 2020). Secondly, our retrospective cohort study used question naire to ask the lifetime prevalence of food allergy of the children without exact diagnosis date, and thus the analysis on the association of postnatal air pollution exposure with risk of food allergy may lead to a possibility of 'reverse causation' (i.e. food allergy occurred before the exposure). Therefore, a prospective cohort study is needed in the future to confirm the observed evidence in our study. Thirdly, we have only investigated several types of outdoor and indoor air pollution. Addi tional research will be conducted to learn explore the impacts of addi tional types of air pollutants.

5.Conclusions

Our study added the evidence that exposure to outdoor as well as indoor air pollution is significantly linked with the prevalence of food allergy (FA) in children, suggesting that airway may be a new food sensitization pathway in addition to gut and skin. Air pollution leads to the first and second waves of allergy epidemics, suggesting a concept of 'one allergy' disease. This means that successful control measures for asthma, such as reducing exposure to air pollution, will provide a good reference for prevention of FA, thereby reversing the rapid increase of FA.

Credit authors statement

Xin Zhang: Data analysis, Methodology, Writing-Original draft preparation. Chan Lu: Data analysis, Methodology, Writing-Original draft preparation. Yuguo Li: Supervision, Reviewing. Dan Norb¨ack: Supervision, Reviewing. Padmini Murthy: Supervision, Reviewing. Radim J. Sram: Supervision, Reviewing. Qihong Deng: Conceptuali zation, Supervision, Writing - Review & Editing.

Declaration of competing interest

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

Data availability

The data that has been used is confidential.

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Appendix A. Supplementary data

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References

Asher, M.I., Montefort, S., Björkstén, B., Lai, C.K.W., Strachan, D.P., Weiland, S.K., et al., 2006. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet 368, 733-743.

Ashley, S., Thanh, D., Koplin, J., Martino, D., Prescott, S., 2015. Food for thought: Progress in understanding the causes and mechanisms of food allergy. Curr. Opin. Allergy Clin. Immunol. 15, 237-242.

Baek, J.-O., Choo, J., Roh, J.-Y., 2021. Associations between ambient air pollution and medical care visits for atopic dermatitis. Environ. Res. 195, 110153.

Ben-Shoshan, M., Kagan, R.S., Alizadehfar, R., Joseph, L., Turnbull, E., St Pierre, Y., et al., 2009. Is the prevalence of peanut allergy increasing? A 5-year follow-up study in children in Montreal. J. Allergy Clin. Immunol. 123, 783-788.

Bornehag, C.G., Sundell, J., Sigsgaard, T., 2004. Dampness in buildings and health (DBH): Report from an ongoing epidemiological investigation on the association between indoor environmental factors and health effects among children in Sweden. Indoor Air 14, 59-66.

Bowatte, G., Lodge, C., Lowe, A.J., Erbas, B., Perret, J., Abramson, M.J., et al., 2015. The influence of childhood traffic-related air pollution exposure on asthma, allergy and sensitization: A systematic review and a meta-analysis of birth cohort studies. Allergy 70, 245-256.

Branum, A.M., Lukacs, S.L., 2009. Food allergy among children in the United States. Pediatrics 124, 1549-1555.

Brauer, M., Hoek, G., Smit, H.A., De Jongste, J., Gerritsen, J., Postma, D.S., et al., 2007. Air pollution and development of asthma, allergy and infections in a birth cohort. Eur. Respir. J. 29, 879-888.

Brough, H.A., Nadeau, K.C., Sindher, S.B., Alkotob, S.S., Chan, S., Bahnson, H.T., et al., 2020. Epicutaneous sensitization in the development of food allergy: What is the evidence and how can this be prevented? Allergy 75, 2185-2205.

Brzozowska, A., Podlecka, D., Jankowska, A., Król, A., Kaleta, D., Trafialek, E., et al., 2022. Maternal diet during pregnancy and risk of allergic diseases in children up to 7–9 years old from Polish Mother and Child Cohort Study. Environ. Res. 208, 112682.

Cai, J., Li, B., Yu, W., Yao, Y., Wang, L., Li, B., et al., 2020. Associations of household dampness with asthma, allergies, and airway diseases among preschoolers in two cross-

sectional studies in Chongqing, China: Repeated surveys in 2010 and 2019. Environ. Int. 140, 105752.

Carrer, P., Maroni, M., Alcini, D., Cavallo, D., 2001. Allergens in indoor air: environmental assessment and health effects. Sci. Total Environ. 270, 33-42.

Ching-Wei, L., Yi-Pen, T., Yu-Tong, S., Hong-Ren, Y., Heing-Jung, L., Chiu-Hsing, H., et al., 2022. Prenatal and perinatal risk factors of food allergy in Taiwanese young children. World Allergy Organization Journal 15, 100663.

Chiu, C.-Y., Yang, C.-H., Su, K.-W., Tsai, M.-H., Hua, M.-C., Liao, S.-L., et al., 2020. Early-onset eczema is associated with increased milk sensitization and risk of rhinitis and asthma in early childhood. J. Microbiol. Immunol. Infect. 53, 1008-1013.

Choi, H., Schmidbauer, N., Sundell, J., Hasselgren, M., Spengler, J., Bornehag, C.-G., 2010. Common household chemicals and the allergy risks in pre-school age children. PLoS One 5, e13423.

Conrado, A.B., Ierodiakonou, D., Gowland, M.H., Boyle, R.J., Turner, P.J., 2021. Food Anaphylaxis in the United Kingdom: Analysis of National Data, 1998-2018. BMJ 372, n251.

Dalton, K.R., Pándifo-Del-Río, M., Louis, L.M., Garza, M.A., Quirós-Alcalá, L., Davis, M.F., 2022. Microbiome alterations associated with phthalate exposures in a US-based sample of Latino workers. Environ. Res. 214, 114126.

Deng, Q., Lu, C., Norbäck, D., Bornehag, C.G., Zhang, Y., Liu, W., et al., 2015. Early life exposure to ambient air pollution and childhood asthma in China. Environ. Res. 143, 83-92.

Deng, Q., Lu, C., Li, Y., Sundell, J., Norbäck, D., 2016. Exposure to outdoor air pollution during trimesters of pregnancy and childhood asthma, allergic rhinitis, and eczema. Environ. Res. 150, 119-127.

Deng, Q., Lu, C., Wu, C., Chen, L., Yuan, H., 2016. Preconceptional, prenatal and postnatal exposure to outdoor and indoor environmental factors on allergic diseases' symptoms in preschool children. Chemosphere 152, 459-467.

Du Toit, G., Tsakok, T., Lack, S., Lack, G., 2016. Prevention of food allergy. J. Allergy Clin. Immunol. 137, 998-1010.

Eguiluz-Gracia, I., Mathioudakis, A.G., Bartel, S., Vijverberg, S.J.H., Fuertes, E., Comberiati, P., et al., 2020. The need for clean air: The way air pollution and climate change affect allergic rhinitis and asthma. Allergy 75, 2170-2184.

Gabriel, M.F., Felgueiras, F., Batista, R., Ribeiro, C., Ramos, E., Mourão, Z., et al., 2021. Indoor environmental quality in households of families with infant twins under 1 year of age living in Porto. Environ. Res. 198, 110477.

Gao, Y., Zhang, Y., Kamijima, M., Sakai, K., Khalequzzaman, M., Nakajima, T., et al., 2014. Quantitative assessments of indoor air pollution and the risk of childhood acute leukemia in Shanghai. Environ. Pollut. 187, 81-89.

Giovannini-Chami, L., Paquet, A., Sanfiorenzo, C., Pons, N., Cazareth, J., Magnone, V., et al., 2018. The "one airway, one disease" concept in light of Th2 inflammation. Eur. Respir. J. 52, 1800437.

Gonzalez-Visiedo, M., Kulis, M.D., Markusic, D.M., 2022. Manipulating the microbiome to enhance oral tolerance in food allergy. In: Cellular Immunology.

Gruzieva, O., Bellander, T., Eneroth, K., Kull, I., Melén, E., Nordling, E., et al., 2012. Traffic-related air pollution and development of allergic sensitization in children during the first 8 years of life. J. Allergy Clin. Immunol. 129, 240-246.

Gupta, R.S., Warren, C.M., Smith, B.M., Blumenstock, J.A., Jiang, J., Davis, M.M., et al., 2018. The public health impact of parent-reported childhood food allergies in the United States. Pediatrics 142, e20181235.

Hu, Y., Chen, J., Li, H., 2010. Comparison of food allergy prevalence among Chinese infants in Chongqing, 2009 versus 1999. Pediatr. Int. 53, 820-824.

Kemter, A.M., Nagler, C.R., 2019. Influences on allergic mechanisms through gut, lung, and skin microbiome exposures. J. Clin. Investig. 129, 1483-1492.

Khamsi, R., 2020. Food allergies: The psychological toll. Nature 588, S4-S6.

Kotz, D., Simpson, C.R., Sheikh, A., 2011. Incidence, prevalence, and trends of general practitioner-recorded diagnosis of peanut allergy in England, 2001 to 2005. J. Allergy Clin. Immunol. 127, 623-630.

Krempski, J.W., Dant, C., Nadeau, K.C., 2020. The origins of allergy from a systems approach. Ann. Allergy Asthma Immunol. 125, 507-516.

Kulis, M.D., Smeekens, J.M., Immormino, R.M., Moran, T.P., 2021. The airway as a route of sensitization to peanut: An update to the dual allergen exposure hypothesis. J. Allergy Clin. Immunol. 148, 689-693.

Lehmann, I., Rehwagen, M., Diez, U., Seiffart, A., Rolle-Kampczyk, U., Richter, M., et al., 2001. Enhanced in vivo IgE production and T cell polarization toward the type 2 phenotype in association with indoor exposure to VOC: Results of the LARS study. Int. J. Hyg. Environ. Health 204, 211-221.

Liu, Q., Lin, S., Sun, N., 2022. How does food matrix components affect food allergies, food allergens and the detection of food allergens? A systematic review. Trends Food Sci. Technol. 127, 280-290.

Loh, W., Tang, M.L.K., 2018. The epidemiology of food allergy in the global context. Int. J. Environ. Res. Public Health 15, 2043.

Lu, C., Liu, Z., Yang, W., Liao, H., Liu, Q., Li, Q., Deng, Q., 2022. Early life exposure to outdoor air pollution and indoor environmental factors on the development of childhood allergy from early symptoms to diseases. Environ. Res. 216, 114538.

Martin, P.E., Eckert, J.K., Koplin, J.J., Lowe, A.J., Gurrin, L.C., Dharmage, S.C., et al., 2015. Which infants with eczema are at risk of food allergy? Results from a population-based cohort. Clin. Exp. Allergy 45, 255-264.

Miyaji, Y., Yang, L., Yamamoto-Hanada, K., Narita, M., Saito, H., Ohya, Y., 2020. Earlier aggressive treatment to shorten the duration of eczema in infants resulted in fewer food allergies at 2 years of age. J. Allergy Clin. Immunol. Pract. 8, 1721-1724.

Moran, T., Smeekens, J., Immormino, R., Allen, Z., Chio, A., Kulis, M., 2021. Air pollutant exposure induces peanut allergy in an animal model. J. Allergy Clin. Immunol. 147, AB174.

Moran, T.P., 2020. The external exposome and food allergy. Curr. Allergy Asthma Rep. 20, 1-9.

Munir, A.K., Kjellman, N.I., Björkstén, B., 1997. Exposure to indoor allergens in early infancy and sensitization. J. Allergy Clin. Immunol. 100, 177-181.

Nowak-Węgrzyn, A., Szajewska, H., Lack, G., 2017. Food allergy and the gut. Nat. Rev. Gastroenterol. Hepatol. 14, 241-257.

Olbrich, C.L., Bivas-Benita, M., Xenakis, J.J., Maldonado, S., Cornwell, E., Fink, J., et al., 2020. Remote allergen exposure elicits eosinophil infiltration into allergen nonexposed mucosal organs and primes for allergic inflammation. Mucosal Immunol. 23, 777-787.

Paciência, I., Hulo, J.C., Moreira, A., 2022. Environmental inequality: Air pollution and asthma in children. Pediatr. Allergy Immunol. 33, e13818.

Peters, R.L., Mavoa, S., Koplin, J.J., 2022. An overview of environmental risk factors for food allergy. Int. J. Environ. Res. Public Health 19, 722-733.

Poulos, L.M., Waters, A.M., Correll, P.K., Loblay, R.H., Marks, G.B., 2007. Trends in hospitalizations for anaphylaxis, angioedema, and urticaria in Australia, 1993-1994 to 2004-2005. J. Allergy Clin. Immunol. 120, 878-884.

Prescott, S., Allen, K.J., 2011. Food allergy: Riding the second wave of the allergy epidemic. Pediatr. Allergy Immunol. 22, 155-160.

Sbihi, H., Allen, R.W., Becker, A., Brook, J.R., Mandhane, P., Scott, J.A., et al., 2015. Perinatal exposure to traffic-related air pollution and atopy at 1 year of age in a multi-center Canadian birth cohort study. Environ. Health Perspect. 123, 902-908.

Sicherer, S.H., Sampson, H.A., 2018. Food allergy: A review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. J. Allergy Clin. Immunol. 144, 885-898.

Sicherer, S.H., Warren, C.M., Dant, C., Gupta, R.S., Nadeau, K.C., 2020. Food allergy from infancy through adulthood. J. Allergy Clin. Immunol. Pract. 8, 1854-1864.

Sordillo, J.E., Rifas-Shiman, S.L., Switkowski, K., Coull, B., Gibson, H., Rice, M., et al., 2019. Prenatal oxidative balance and risk of asthma and allergic disease in adolescence. J. Allergy Clin. Immunol. 144, 1534-1541.

Sram, R.J., 2020. Impact of air pollution on the health of the population in parts of the Czech Republic. Int. J. Environ. Res. Public Health 17, 6454.

Thacher, J.D., Gruzieva, O., Pershagen, G., Neuman, Å., van Hage, M., Wickman, M., et al., 2016. Parental smoking and development of allergic sensitization from birth to adolescence. Allergy 71, 239-248.

Walker, M.T., Green, J.E., Ferrie, R.P., Queener, A.M., Kaplan, M.H., Cook-Mills, J.M., 2018. Mechanism for initiation of food allergy: Dependence on skin barrier mutations and environmental allergen costimulation. J. Allergy Clin. Immunol. 141, 1711-1725.

Yang, H., Qu, Y., Gao, Y., Sun, S., Ding, R., Cang, W., et al., 2022. Role of the dietary components in food allergy: A comprehensive review. Food Chem. 386, 132762.

Zhang, Y., Li, B., Huang, C., Yang, X., Qian, H., Deng, Q., et al., 2013. Ten cities cross-sectional questionnaire survey of children asthma and other allergies in China. Chin. Sci. Bull. 58, 4182-4189.

Zhang, Y., Mo, J., Weschler, C.J., 2013. Reducing health risks from indoor exposures in rapidly developing urban China. Environ. Health Perspect. 121, 751-755.

Ziyab, A.H., 2019. Prevalence of food allergy among schoolchildren in Kuwait and its association with the coexistence and severity of asthma, rhinitis, and eczema: A cross-sectional study. World Allergy Organization Journal 12, 100024.

Zou, M.-L., Huang, C.-B., Chen, Y.-H., Wu, C.-D., Candice Lung, S.-C., Chien, L.-C., et al., 2022. Frequent occurrence of respiratory symptoms in children is associated with exposure to air pollution, land use types, and parental mental health in the greater Taipei area. Environ. Res. 206, 112567.

Fig.1. (a) Allergic march or progression of allergic diseases; (b) Exposure routes of allergic diseases; (c) The effects of exposure to air pollution on the first and second waves of allergy epidemics.

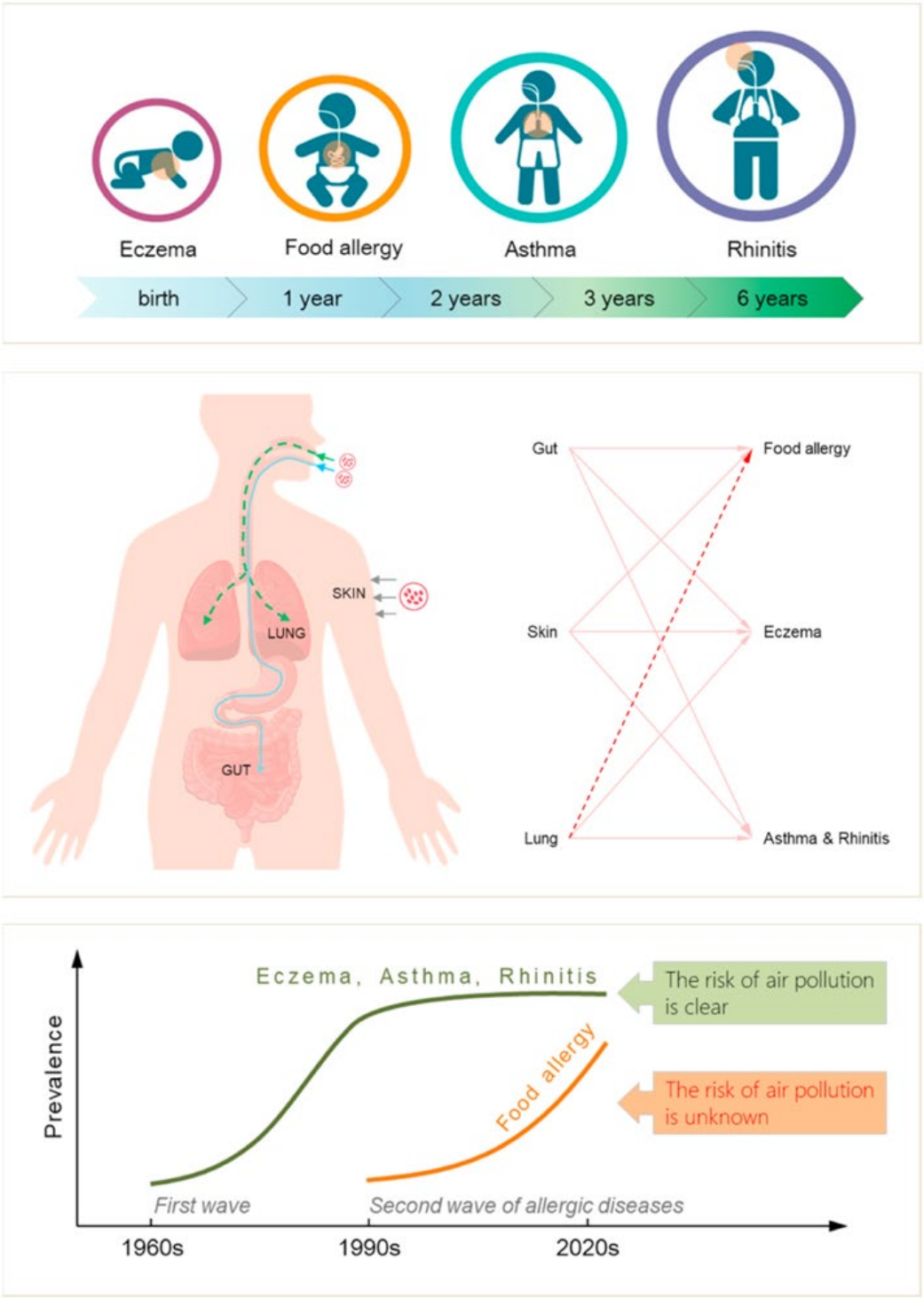

Fig. 2. Concentration-response curves (smoothing restricted cubic spline function) between pre- and post-natal exposure to air pollutants (PM10, SO2, NO2) and the risk of food allergy in children.

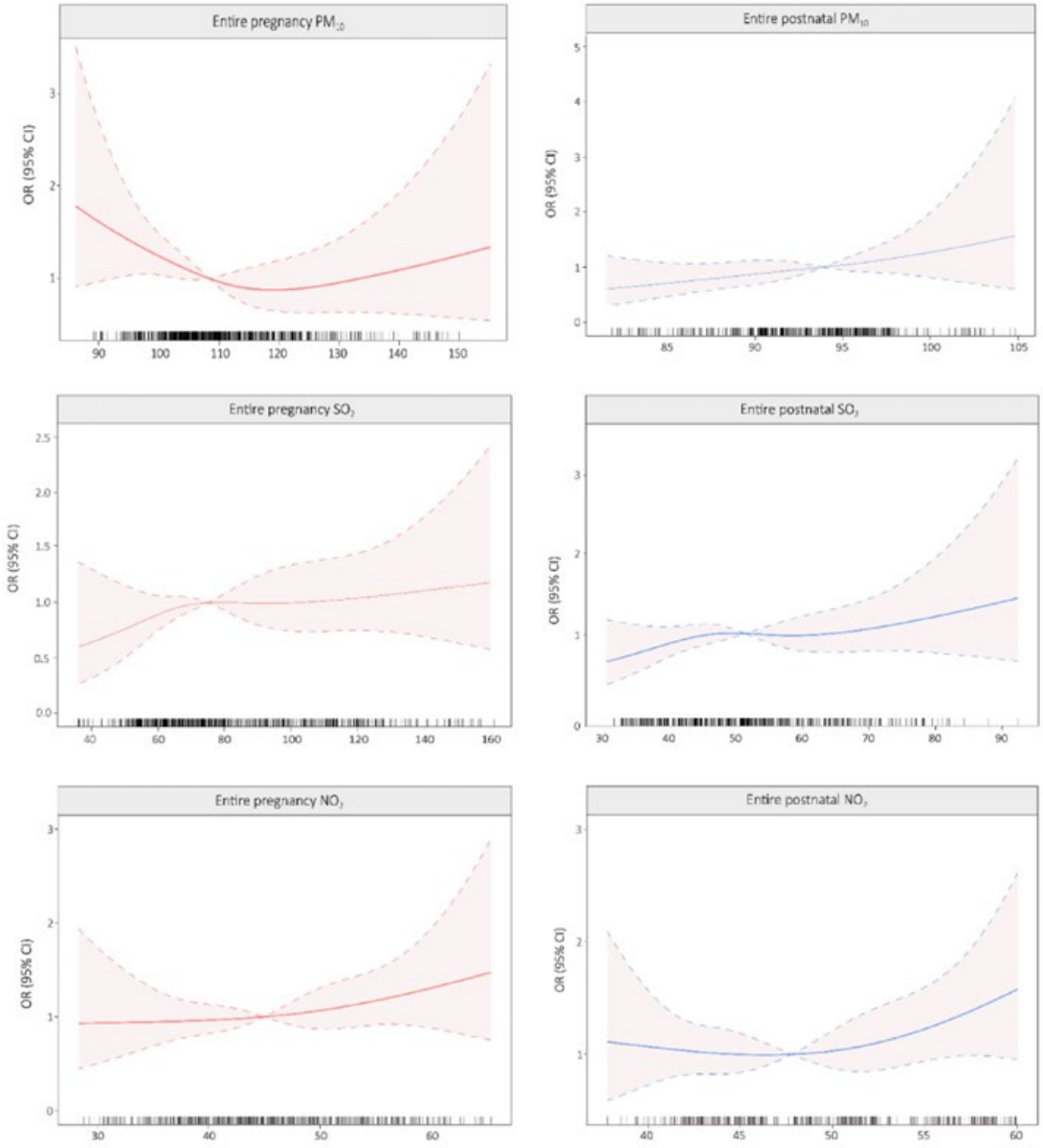

Table 1 Demographic information and prevalence of food allergy among children (n = 2598).

	Total	Cases	(%)	P-value
Total	2598	388	(14.9)	–
Sex				
Boys	1399	234	(16.7)	0.003
Girls	1199	154	(12.8)	
Age (years old)				
3–4	1617	260	(16.1)	0.038
5–6	981	128	(13.1)	
Birth season				
Warm (May–September)	666	173	(15.0)	0.996
Cold (October–April)	590	215	(14.9)	
Breast-feeding				
No	222	25	(11.3)	0.226
Yes	2376	363	(15.3)	
Time to kindergarten				
<3 yeas	615	97	(15.8)	0.666
≥3 years	1971	289	(14.7)	
Parental atopy				
No	2214	274	(12.4)	<0.001
Yes	340	108	(31.8)	
House size (m2)				
≤75	836	114	(13.6)	0.104
>75	1732	272	(15.7)	
Environmental tobacco smoke (ETS) at home				
Yes	1734	257	(14.8)	0.896
No	864	131	(15.2)	
Mosquito incense used				
Yes	1811	262	(14.5)	0.661
No	764	121	(15.8)	
Household pets (dogs)				
Yes	167	23	(13.8)	0.828
No	2427	365	(15.0)	
Cleaning frequency				
Frequently	2089	291	(13.9)	0.005
Seldom	498	94	(18.9)	

Table 2 Descriptive statistics of the indicators for exposure to indoor air pollution and the prevalence of food allergy in children during prenatal and postnatal periods (n = 2598).

		Prenatal				Postnatal			
		Total	Cases	(%)	P-value	Total	Cases	(%)	P-value
New furniture	Yes	338	57	(16.9)	0.252	980	180	(18.4)	<0.001
	No	1768	263	(14.9)		1545	206	(13.3)	
Redecoration	Yes	139	24	(17.3)	0.390	499	88	(17.6)	0.052
	No	1920	282	(14.7)		1944	283	(14.6)	
Mold/damp stains	Yes	435	87	(20.0)	<0.001	308	54	(17.5)	0.131
	No	2137	299	(14.0)		2142	315	(14.7)	
Window condensation	Yes	1222	188	(15.4)	0.334	869	156	(18.0)	0.006
	No	1308	189	(14.4)		855	117	(13.7)	

Table 3 Odds ratio (95%CI) of childhood food allergy due to exposure to indoor air pollution during prenatal and postnatal periods (n =2598).

	OR (95% CI)			
	Crude	Adjusted	3–4 years old	5–6 years old
Prenatal				
New furniture	1.21 (0.87, 1.67)	1.12 (0.72, 1.74)	1.10 (0.64, 1.90)	1.14 (0.52, 2.51)
Redecoration	1.23 (0.77, 1.97)	1.06 (0.57, 1.96)	0.70 (0.31, 1.57)	2.25 (0.80, 6.36)
Mold/damp stains	1.65 (1.26, 2.18) ***	1.93 (1.35, 2.75) ***	1.98 (1.26, 3.12) **	1.98 (1.06, 3.68) *
Window condensation	1.12 (0.89, 1.40)	0.98 (0.74, 1.31)	1.00 (0.70, 1.42)	1.01 (0.61, 1.67)
Postnatal				
New furniture	1.53 (1.22, 1.91) ***	1.49 (1.07, 2.10) *	1.45 (1.00, 2.09) *	1.59 (0.87, 2.90)
Redecoration	1.31 (1.00, 1.71) *	1.03 (0.68, 1.55)	1.11 (0.66, 1.88)	0.92 (0.47, 1.81)
Mold/damp stains	1.29 (0.93, 1.78)	1.09 (0.70, 1.71)	0.94 (0.54, 1.65)	1.54 (0.71, 3.34)
Window condensation	1.45 (1.11, 1.89) **	1.41 (1.04, 1.89) *	1.55 (1.07, 2.24) *	1.19 (0.71, 2.00)

Table 4 Odds ratio (95%CI) of childhood food allergy due to exposure to outdoor air pollution during prenatal and postnatal periods (n =2598).

	Crude	Adjusted[a]	3–4 years old[a]	5–6 years old[a]
Prenatal				
PM10	0.87 (0.76, 0.99) *	0.87 (0.70, 1.07)	0.65 (0.45, 0.94) *	1.00 (0.76, 1.32)
SO2	1.00 (0.85, 1.17)	1.07 (0.87, 1.33)	1.31 (0.97, 1.79)	0.89 (0.65, 1.22)
NO2	1.18 (0.99, 1.39)	1.24 (1.00, 1.54) *	1.25 (0.92, 1.69)	0.86 (0.56, 1.32)
Postnatal				
PM10	1.01 (0.87, 1.18)	1.42 (1.08, 1.86) *	1.45 (1.07, 1.97) *	1.44 (0.78, 2.68)
SO2	1.04 (0.90, 1.21)	1.34 (1.07, 1.70) *	1.49 (1.06, 2.10) *	1.27 (0.92, 1.76)
NO2	1.21 (0.97, 1.51)	1.38 (1.03, 1.85) *	1.49 (1.03, 2.16) *	1.25 (0.76, 2.05)