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To cite this article: Qingbin Liu, Wei Wang & Wei Jing (2019) Indoor air pollution aggravates asthma in Chinese children and induces the changes in serum level of miR-155, International Journal of Environmental Health Research, 29:1, 22-30, DOI: [10.1080/09603123.2018.1506569](https://doi.org/10.1080/09603123.2018.1506569)

To link to this article: <https://doi.org/10.1080/09603123.2018.1506569>



Published online: 07 Aug 2018.



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ARTICLE



Indoor air pollution aggravates asthma in Chinese children and induces the changes in serum level of miR-155

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ABSTRACT

Indoor air pollution is associated with childhood asthma but the molecular mechanism remains unclear. We aimed to explore the relationship between indoor air pollution and pediatric asthma, and the potential molecular mechanism.

The serum level of miR-155 was measured by real-time qPCR in 180 Chinese children with asthma caused by air pollution (an asthma group). Meanwhile, 180 healthy subjects were selected as a control group. HCHO, NO₂, and particles (PM₁₀, PM_{2.5}, and PM₁) were measured. Univariate and multivariate logistic regression were analyzed to assess the relationship between air pollutants and asthma risk. A rank correlation test was used to explore the relationship between serum level of miR-155 and the level of PM_{2.5} or HCHO. Serum level of miR-155 was higher in the asthma group than the control group ($p < 0.001$). The history of childhood allergy, breastfeeding, environmental tobacco smoke, PM_{2.5}, and HCHO were significantly different between two groups ($p < 0.05$). Serum level of miR-155 was closely associated with the levels of indoor PM_{2.5} and HCHO in the asthma group ($p < 0.05$) but not in the control group ($p > 0.05$).

Indoor air pollution aggravates the asthma in Chinese children and induces the changes in the serum level of miR-155.

Abbreviation: DEP: Diesel exhaust particles; PAHs: Polycyclic aromatic hydrocarbons; THBS1: thrombospondin 1; ISAAC: International Study of Asthma and Allergies in Childhood; PFTs: Pulmonary Function Tests; FEV1: The first second of forced expiration; EDTA, ethylenediaminetetraacetic acid; RT-qPCR, Reverse transcription quantitative real-time PCR; ETS: environmental tobacco smoke; PAEs: phthalate esters

ARTICLE HISTORY

Received 13 June 2018

Accepted 26 July 2018

KEYWORDS

Air pollution; childhood asthma; indoor air pollution; real-time qPCR; serum miR-155

Introduction

Asthma is a common disease in children and it is estimated 235 million patients have asthma in the world (Saint et al. 2018), and 3.5 million children had at least one asthma attack (Lozier et al. 2018). In order to treat asthma effectively, it is important to understand its cause and the related molecular mechanism. Environmental factors play an important role in the risk of asthmas, such as air pollution (Woodard et al. 2018). Air pollution can cause lower lung function (Bowatte et al. 2017, 2018), cough (Hasunuma et al. 2018), nasal disorder (Hasunuma et al. 2018), current wheeze, rhino conjunctivitis and itchy rash (Altug et al. 2013), all of which may be associated with asthma. Traffic related air pollution can exaggerate respiratory diseases and induce the development of existing asthma (Deng et al. 2016). However, children

spend more time in indoor environment and therefore it is critical to investigate the association between indoor air pollution and asthma development for the treatment of pediatric asthma (Deng et al. 2015). The exposure to air pollutants such as CO, NO₂, SO₂, PM₁₀, and PM_{2.5} plays an important role in the attack of asthma (Guo et al. 2017; Hehua et al. 2017).

Air pollutants aggregate the severity of asthmatic symptoms in pediatric population (Hasunuma et al. 2016). Particles in air pollution are related to exhaled high-concentration NO₂ in children (Altug et al. 2014). Diesel exhaust particles (DEPs) and NO₂ emission from automobile will reduce the pH in children, whereas lower pH can cause airway inflammation (Rinaldi et al. 2017). Other studies also reported that lower pH and high-level epidermal growth factor resulted in the systemic inflammation in asthma patients (Chung et al. 2014). Polycyclic aromatic hydrocarbons (PAHs) are the main constituents of air pollution and more than 30% of PAHs inhalation (Chen et al. 2016). PAH destroys the antioxidant defense system, which may indirectly contribute to the induction of asthma in Children (Wang et al. 2017). Furthermore, controlling oxidative stress caused by air pollution and preventing the injury of respiratory organs will reduce pediatric asthma to air pollutants (Jesenak et al. 2017).

MicroRNA, small non-coding RNA of 18–25 nucleotides, can affect gene expression (Cai et al. 2018) and has been used as biomarkers in human diseases. miR-98 reduces the levels of thrombospondin 1 (THBS1), which plays an important role in regulating cellular immunity activity in allergic asthma (Chen et al. 2017). miR-19b can reduce the levels of oxidative stress by reducing thymic stromal lymphopoietin in an animal asthma model (Ye et al. 2017). MiR-155, one of the most studied miRNAs, has been found to be associated with complex cellular activities. Allergy is often caused by hyperactive CD4⁺ Th2 cells, and miR-155 has a T cell-intrinsic role in cellular immunity. MiR-155 is a potential therapy target to reduce Th2-modulated inflammatory activities (Okoye et al. 2014) and plays an important role in asthma progression (Zhou et al. 2016). Detecting microRNA will be a simple non-invasive way for the diagnosis of pediatric asthma. We seek to explore the relationship between the changes of serum miR-155 and air pollution-induced asthma.

Methods

Participants

All procedures were approved by the human search ethical committee of xxx. From September 2016 to March 2017, the children diagnosed with asthma were recruited at our hospital. The parents or guardians of children conducted a questionnaire survey according to International Study of Asthma and Allergies in Childhood (ISAAC) (Park et al. 2016). The pass rate of the questionnaire was 100%, and all the data were double-checked. The survey questions included: past history of allergy, respiratory symptoms, family genetic information, living environment, living habits, and so on. The severity of asthma was measured by pulmonary function tests (PFTs) according to an earlier report (O'Byrne et al. 2015). All parents of the patients or their guardians signed informed consent in this study.

Inclusion criteria

The asthma symptoms were supposed to be triggered by indoor air pollution if they had both asthma and history of exposure to air pollution via a questionnaire survey according to ISAAC (Park, Lee, Kim, Han, Kim, Chae, Hahm, Lee, Kwon, Park, Park and Ahn 2016). The patients were diagnosed with asthma according to the presence of airflow obstruction (two or more of cough, wheezing, and dyspnea for three or more consecutive days). The first second of forced expiration (FEV1) was increased by > 15% following β -agonist inhalation. The persistent asthma was stable for at least 3 months prior to the present experiment.

Exclusion criteria

The following subjects were excluded from the present experiment: had medical treatment within three months by using vitamin and or antibiotics; had severe organ failure, including heart, renal and other serious disorders.

Patients grouping

From September 2016 to March 2017, 180 children with asthma were selected as an asthma group and 180 healthy controls as a control group in Changchun. Every Chinese person has a government-issued ID card, and thus Han, Man and Meng patients were differentiated by using the ID cards.

Serum preparation

Five-milliliter venous blood was obtained from each subject, placed in a disposable tube containing 2% ethylenediaminetetraacetic acid (EDTA) anticoagulant and fully mixed. The blood was then centrifuged at 1,500 rpm for 15 min at 4°C. Serum was collected, aliquoted, and stored in a –80°C refrigerator.

Total RNA isolation

The RNA was isolated from 500-μL serum by using an RNA isolation Kit (Applied Biosystems, Foster City, CA, USA). RNA concentration and integrity were measured by using a NanoDrop spectrophotometer (NanoDrop Technologies, Wilmington, DE, USA).

Reverse transcription quantitative real-time PCR (RT-qPCR)

Serum miRNAs were quantified in by using RT-PCR. cDNA was synthesized by using a MicroRNA Assay Kit (Invitrogen, Carlsbad, CA, USA). The RT reaction was performed in a 20-μL reaction volume with 5-μL RNA extract, 0.2-μL 100-mM dNTPs, 1.5-μL reverse transcriptase (50 U/μL), 2-μL 10 × buffer, 0.2-μL RNase inhibitor (20 U/μL), 0.5-μL primers (20 μM, forward primer, 5'-GCGGTTAATGCTAATCGTGAT-3', and reverse primer, 5'-GTGCAGGGTCCGAGGT-3') and 9.6-μL ddH₂O. The mixtures were incubated at 16°C for half an hour, 42°C for 30 min, and 90°C for 5 min. In addition, 5-μL cDNA solution was amplified by using 12-μL Master Mix, 1.2-μL primers and 6.8-μL RNA-free ddH₂O in final 25 μL. qPCR was carried out on a 7500 Real-Time PCR System (Thermo Fisher Scientific, Waltham, MA, USA) at 94°C for 5 min, and 45 cycles of 94°C for 10 s and 66°C for 45 s. Relative levels of miR-155 to small nuclear U6 RNA (internal control, forward primer, 5'-CTCGCTTCGGCAGCAC-3'; reverse primer, 5'-AACGCTTCACGAATTTGCGT-3') were calculated according to a $\Delta\Delta$ CT method.

Measurement of indoor air pollutants

According to indoor air quality standard (GB/T1883–2002) in China (Lu et al. 2010), sampling points should be 1.0–1.5 m above ground, and all doors and windows were closed for 12 h before sampling. A handheld particle counter (Lighthouse 3016-IAQ, Fremont, CA, USA) was used to measure indoor particles (PM₁₀, PM_{2.5}, and PM₁) concentration. CI counters are calibrated based on ISO 10,012–1 and the relevant parts of ISO 14,644, and Federal standards 209 (Lappalainen et al. 2013). The analyzed particle sizes were ≥ 0.1 μm. Several particle samples were obtained taken from living room and bedroom. The results were presented as particle concentrations per liter. The sampling rate was set at 2.83 L/min, and sampling time was 1 h daily from 19:00 to 20:00 within Monday to Friday during normal living time of family members in house. HCHO and NO₂ samples were collected by using an atmospheric sampler (QC-2B; Beijing Municipal Institute of

Labor Protection, Beijing, China), and measured by using the *N*-(1-Naphthyl)ethylene diamine dihydrochloride spectrophotometric method(China standard, GB/T15516–1995) (Liu and Hu 2012). Air pollutants were measured in both living room and bedroom at the same time and the whole period was 2 months.

Statistical analyses

A *t*-test was used to compare the data difference between asthma and control groups. Chi-square test was used to explore the difference for the number data between two groups. Mann–Whitney *U* nonparametric test would be used if the data did not meet the normal distribution. Univariate and multivariate regression analysis was performed to assess possible risks of asthma. Spearman's rank correlation test was used to explore the relationship between serum levels of miR-155 and the levels of indoor air pollution. The statistical difference was significant if $p < 0.05$.

Results

Clinical characteristics

The statistical difference for age and sex was insignificant between the two groups (Table 1, $p > 0.05$). The statistical differences for all other parameters were insignificant either between two groups ($p > 0.05$, Table 1).

Relative levels of serum mir-155 in asthma and control groups

In the present study, 0.05 to 0.29 $\mu\text{g}/\mu\text{L}$ of the total RNA could be isolated from 500 μL of serum. As compared with healthy children, serum levels of miR-155 were significantly higher than in the

Table 1. Demographic characteristics of selected participants.

Parameters	Asthma group	Control group	χ^2 and <i>t</i> -value	<i>p</i> -value
Gender, male/female	101/79	98/82	0.256	0.613
Age, years	10.83 $\pm$ 3.06	10.13 $\pm$ 2.65	−1.380	0.124
Body mass index, weight (kg)/height (m) ²	25.61 $\pm$ 4.82	24.73 $\pm$ 4.91	0.659	0.407
Severity of asthma scores	4.28 $\pm$ 1.25	Not Applicable	–	–
Races				
Han, cases (percent)	150(83.33)	145(80.56)	0.839	0.657
Man, cases (percent)	25(13.89)	31(17.22)		
Meng, cases (percent)	5(2.78)	4(2.22)		

Note: all participants were from Changchun city. $n = 180$ for each group. * $p < 0.05$ vs. a control group.

Table 2. The comparison for the concentrations of indoor air pollutants between asthma and control groups.

Parameters	Groups	Range	P25	P50	P75	Z	<i>p</i> values
PM ₁₀	Asthma	60.42–507.31	138.95	208.77	308.18	−2.451	0.004**
	Control	26.53–466.64	109.45	159.42	248.47		
PM ₂₅	Asthma	14.95–159.02	28.61	43.58	55.12	−4.467	0.001**
	Control	12.61–98.05	18.97	26.39	37.68		
PM ₁	Asthma	6.76–77.18	9.84	15.31	27.17	−3.078	0.001**
	Control	4.52–40.43	7.61	12.42	17.19		
HCHO	Asthma	12.04–142.12	22.03	38.35	57.33	−1.691	0.018*
	Control	12.26–94.34	15.32	25.11	45.57		
NO ₂	Asthma	11.58–233.74	20.39	30.07	45.06	−2.935	0.004**
	Control	10.62–119.6	16.47	21.73	32.45		

Note: Mann–Whitney *U* test, * $p < 0.05$ vs. a control group and ** $p < 0.01$ vs. a control group.

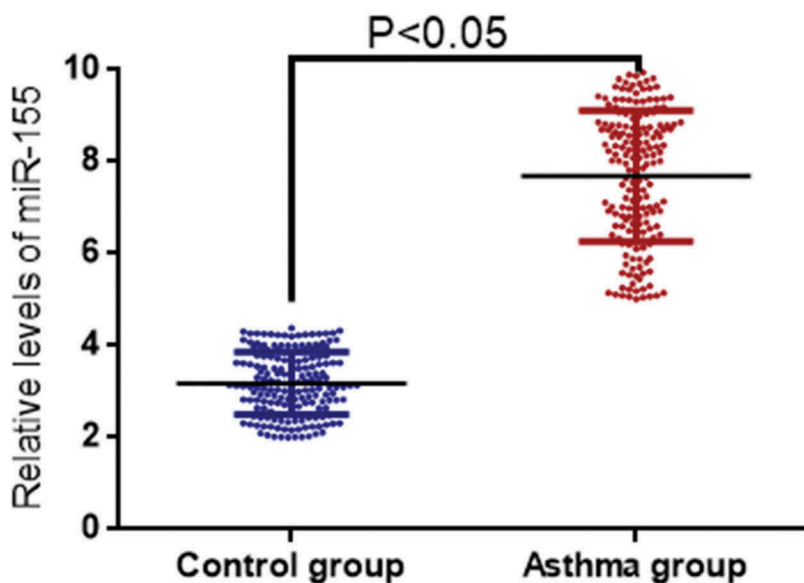


Figure 1. Serum level of miR-155 in different groups. $n = 180$ for each group. The statistical difference for serum level of miR-155 was highly significant if $p < 0.001$.

asthma group (3.26 ± 1.21 vs. 7.56 ± 2.49 , $p < 0.001$, Figure 1). The results suggest that miR-155 is associated with the risk of pediatric asthma.

The concentration of indoor air pollutants between asthma and control groups

The results showed that the concentrations of indoor PM_{10} , $PM_{2.5}$, PM_1 , HCHO, and NO_2 were higher in the asthma group than in the control group (Table 2, $p < 0.05$). The results of univariate analysis showed that the concentrations of PM_{10} , $PM_{2.5}$, PM_1 , and NO_2 in the asthma group were significantly different from those in the controls (Table 2, $p < 0.01$). The concentrations of HCHO were significantly higher in the asthma group than the control group (Table 2, $p < 0.05$).

The risks causing pediatric asthma

Univariate analysis showed that children’s history of allergy, children’s history of rhinitis, breast-feeding, ETS (environmental tobacco smoke) exposure and indoor plant were associated with asthma risk ($p < 0.05$, Table 3). Among these factors, PM_{10} , $PM_{2.5}$, PM_1 , HCHO, and NO_2 concentration quartiles were introduced into the multivariate regression model, and significantly different between the two groups ($p < 0.05$), whereas breastfeeding showed protective function for childhood asthmas (Table 4). Serum level of miR-155 was associated with the five factors in asthma group but not in control group (Table 5).

Table 3. The risks causing pediatric asthma between two groups.

Parameters	Asthma group, cases (percent)	Control group, cases (percent)	χ^2	p -value
History of allergy	93(51.67)	32(17.78)	45.602	0.000**
History of rhinitis	45(25)	36(20)	1.166	0.280**
0.28.Breastfeeding	89(49.44)	132(73.33)	21.669	0.000**
ETS exposure	128(71.11)	75(41.67)	31.729	0.000**
Indoor plant	135(75)	167(92.78)	21.046	0.000**

Note: Chi-square test. ** $p < 0.01$ vs. a control group.

Table 4. Multiple logistic regression analysis for the environment risks causing pediatric asthma.

	<i>B</i>	S.E.	Wald	<i>p</i>	OR	95% CI
A history of allergy	1.883	0.482	15.393	0.001**	5.593	2.578–17.915
Breast feeding	−0.862	0.425	4.152	0.043*	0.361	0.186–0.928
ETS	1.151	0.426	7.265	0.006**	3.568	1.170–7.425
PM _{2.5}	0.754	0.270	7.709	0.003**	2.029	1.049–4.630
HCHO	0.553	0.186	8.495	0.001**	2.736	1.098–5.516

Note: Mann–Whitney *U* test, **p* < 0.05 vs. a control group and ***p* < 0.01 vs. a control group.

Table 5. The relationship between the factors affecting pediatric asthma and serum miR-155 levels.

Parameters	Asthma group		Control group		50% cutoff point
	OR (95%CI)	<i>p</i> -values	OR (95%CI)	<i>p</i> -values	
A history of allergy	2.31 (0.29, 4.61)	0.027*	1.15 (0.38, 1.99)	0.165	1.27 ± 0.11
Breast feeding	0.26 (0.05, 0.73)	0.001**	0.92 (0.17, 1.85)	0.084	0.73 ± 0.06
ETS	1.63 (0.53, 2.72)	0.035*	1.29 (0.83, 1.87)	0.068	0.99 ± 0.07
PM _{2.5}	1.38 (0.61, 2.84)	0.024*	1.22 (0.58, 2.39)	0.121	1.08 ± 0.16
HCHO	2.47 (0.39, 5.20)	0.019	1.47 (0.53, 3.18)	0.076	1.92 ± 0.23

Note: Up arrow showed the protecting function of breast feeding. Mann–Whitney *U* test. **p* < 0.05 vs. a control group and ***p* < 0.01 vs. a control group.

Serum mir-155 level was positively related with the levels of main components of indoor air pollution in the asthma group

Spearman's rank correlation test showed that the increase of serum miR-155 was not associated with the levels of indoor PM_{2.5} (Figure 2a) and HCHO (Figure 2c) in a control group (*P* > 0.05), but associated with that (Figure 2(b–d)) in an asthma group (*P* < 0.05).

Discussion

In this study, PM₁₀, PM_{2.5}, PM₁, HCHO, and NO₂ were detected in 360 patient homes in Changchun. The indoor PM concentration was high, which may be associated with traffic emission and industrial development. Cooking and smoking are two important indoor factors associated with PM_{2.5} sources in China. Higher indoor particles could be observed in households using coal when compared with using gas and electricity with a reduction of PM_{2.5} in the kitchen by 40–70% (Li et al. 2016). PM_{2.5} was found at indoor public places just like smoking lounges and mainly contained organic carbon, elemental carbon, PAHs, and phthalate esters (PAEs) (Li et al. 2017). Indoor smoking, cooking, ETS, and home decoration increased the concentration of indoor particles, which triggered pediatric asthma.

Asthma severity covariates were adjusted by using multiple logistic regression. Multivariate logistic analysis showed that there was a significant correlation between indoor PM_{2.5} exposure and childhood asthma (Table 4). HCHO is one of the major indoor air pollutants and has a strong irritating odor. The present study showed that there was a significant difference for indoor HCHO concentration between asthma and control groups (*P* < 0.05). Breast milk contains large amounts of IgA, cytokines, long-chain fatty acids and oligosaccharides, and other substances, and can improve the baby's immune system (Friedman and Zeiger 2005). This study found that breast-feeding was a protective factor in childhood asthma (Table 4).

miR-155 shows a relatively broad expression in the mammalian respiratory system and plays a signaling regulatory role in asthma. This study found that miR-155 may be associated with increased risk of childhood asthma. The present results confirmed the relationship between miR-155 and childhood asthma. On the other hand, the concentrations of indoor PM_{2.5} and HCHO were found to be associated with serum miR-155 level the in asthma group (Figure 2). This finding has provided a theoretical basis for gene therapy and environmental factors control in childhood asthma, but further work needs to confirm the supposed mechanism.

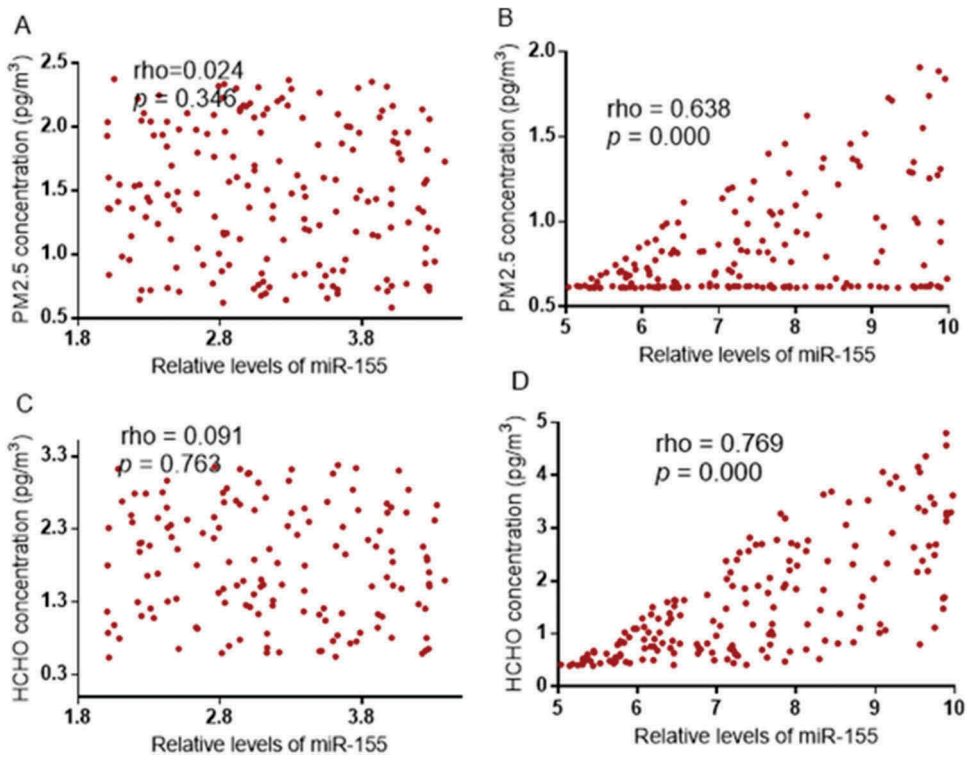


Figure 2. Spearman's rank correlation coefficients between serum levels of miR-155 and indoor air pollution. (A) Spearman's rank correlation coefficients between serum levels of miR-155 and the levels of indoor PM_{2.5} in a control group. (B) Spearman's rank correlation coefficients between serum levels of miR-155 and the levels of indoor PM_{2.5} in an asthma control group. (C) Spearman's rank correlation coefficients between serum levels of miR-155 and the levels of indoor HCHO in a control group. (D) Spearman's rank correlation coefficients between serum levels of miR-155 and the levels of indoor HCHO in an asthma group. $n = 180$ for each group. There will be a strong positive relation between the two variables if rho falls within 0.5 and 1.

The concentration of indoor pollutants was higher in the asthma group than that of the control group; a history of allergy, breastfeeding, PM_{2.5}, HCHO, and in-house plants were the main factors affecting asthma risk. Air pollution aggravating asthma may be associated with the changes of serum level of miR-155.

There were some limitations for the present work: the present results confirmed the relationship between miR-155 and childhood asthma, but the related molecular mechanism remained unclear. Furthermore, the molecular mechanism for air pollution affecting the serum levels of miR-155 was unknown, either. The exact factors for causing the indoor pollutants were not explored in the present work. Regarding for the impact of indoor sources, cooking may be the main factor for increasing indoor particles when compared with smoking. Further work is highly demanded to address these issues in the future.

What is already known?

Indoor air pollution is associated with childhood asthma.

The serum level of miR-155 is an indicator of asthma.

What this study adds

Serum level of miR-155 was closely associated with the levels of indoor PM_{2.5} and HCHO in the asthma children.

Indoor air pollution aggravates the asthma in Chinese children and induces the changes in the serum level of miR-155.

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