

Factors associated with exhaled nitric oxide in children with asthma and allergic rhinitis

Zheng Zhu¹  | Shu Xia² | Xi Chen^{1,3} | Wei-jie Guan² | Zi-jun Guo¹ | Bao-qing Sun¹

¹Department of Allergy and Clinical Immunology, State Key Laboratory of Respiratory Diseases, National Clinical Research Center for Respiratory Disease, Guangzhou Institute of Respiratory Health, the First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China

²State Key Laboratory of Respiratory Diseases, National Clinical Research Center of Respiratory Disease, Guangzhou Institute of Respiratory Health, the First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China

³Guangzhou Panyu Central Hospital, Guangzhou, China

Correspondence

Bao-qing Sun, State Key Laboratory of Respiratory Disease, National Clinical Research Center of Respiratory Disease, Guangzhou Institute of Respiratory Health, The First Affiliated Hospital of Guangzhou Medical University, 151 Yanjiang Road, Guangzhou 510120, China.
Email: sunbaoqing@vip.163.com

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Abstract

Background: Factors attributable to the level of fraction of exhaled nitric oxide (FeNO) in different age groups of asthmatic children are still lack of report.

Objective: To evaluate factors associated with FeNO and the response of FeNO to inhaled steroid in different age groups of asthmatic children with allergic rhinitis.

Methods: Asthmatic children aged 5 to 12 years were recruited. FeNO, lung function and bronchial hyperresponsiveness (BHR) to methacholine, skin prick testing to a panel of aeroallergens, total immunoglobulin E (T-IgE) in serum and eosinophils in blood were tested. Correlations between FeNO and the measured parameters were assessed. FeNO was measured again after the treatment of combined inhaled corticosteroid and long-acting beta-agonist (ICS/LABA) for 4 weeks. Changes in FeNO between different age groups were compared.

Results: A total of 121 eligible subjects were enrolled in and completed this study. Asthmatic children aged 10 to 12 years old had significantly higher FeNO than those between 8 and 9 years and 5 to 7 years of children (both $P < 0.01$). Greater height/age ($P < 0.01$) and higher level of total allergen IgE ($P < 0.01$) are associated with a higher value of FeNO. After 4 weeks of treatment with ICS/LABA, asthma control test scores were significantly increased in all age groups ($P < 0.01$), while the level of FeNO significantly decreased in the elder age group only ($P < 0.01$).

Conclusions: Height and T-IgE are well correlated with FeNO in asthmatic children aged 5 to 12 years. Measurement of FeNO is more suitable for evaluating the efficacy of ICS/LABA in elder asthmatic children.

KEYWORDS

allergy, asthma, children, fraction of exhaled nitric oxide (FeNO)

1 | INTRODUCTION

The prevalence of asthma is estimated to be 300 million globally and still increasing.¹ There has been a rapid increase in the prevalence of asthma among children in China in the past few decades, possibly because of severe air pollution, and altered environmental exposures and dietary patterns.²⁻⁴ Airway inflammation is one main feature of asthma. Airway

eosinophilic inflammation is highly increased as measured by eosinophil cells count in sputum and fraction of exhaled nitric oxide (FeNO) in asthmatics, especially for subjects with atopy, compared to healthy subjects.⁵ FeNO as a noninvasive measurement of airway eosinophilic inflammation marker is commonly used in the diagnosis and management of asthma in both children and adults,⁵ especially for young children who may have difficulty in carrying out a bronchial challenge test. The normative value of FeNO is associated with several

factors, like age, height, gender, and allergen sensitisation in healthy subjects.⁶ The normative value of FeNO was less than 25 ppb for healthy children older than 12 years and less than 20 ppb for the ones younger than 12 years old in the international guideline.⁷

Airway eosinophilic inflammation is sensitive to inhaled corticosteroid (ICS). The percentage of eosinophils and the level of FeNO are significantly decreased when treated with ICS in asthmatics. FeNO measurement is a useful tool to identify steroid-sensitive type asthmatics, to monitor the adherence of treatment drug use and to evaluate the efficacy of steroid therapy in both clinical and study research of asthma.^{8,9} In some studies, the minimal significant changes of FeNO were 10 ppb when the baseline FeNO was higher than 25 ppb or 10% when the baseline FeNO was lower than 25 ppb.¹⁰ But there are also studies with reversals results, in which reported that the changes of FeNO were associated with neither the decrease of eosinophils nor the release of symptoms after the antiasthmatic treatment, including the treatment with steroid.¹⁰

The objective of this study is to evaluate the correlations of demographic characteristics, allergic sensitisation, lung function and bronchial hyperresponsiveness (BHR) with FeNO, and to compare the changes of FeNO after treatment of combined inhaled steroid and long-acting beta-agonist (LABA) for 4 weeks in different age groups of asthmatic children with allergic rhinitis.

2 | METHODS

2.1 | Study design

Children with mild to moderate intermittent asthma were recruited. Disease history was assessed by questionnaires. After a washout period, demographic characteristics, FeNO, allergic sensitisation (allergen skin prick testing [SPT], total IgE in serum), lung function and BHR to methacholine were measured. Then combined ICS and LABA (budesonide [80 ug] and formoterol [4.5 ug]) were used for 4 weeks, and either inter-nasal corticosteroids or nasally applied cellulose powder (nasal mucosal allergen avoidance) were used to release the symptoms of allergic rhinitis. After 4 weeks of treatment, FeNO and lung function were measured again. FeNO values were used as dependent variables to test associations of demographic, allergic sensitisation and lung function BHR.

2.2 | Participants

Children with mild to moderate intermittent asthma of either gender, aged 5 to 12 years were recruited from the outpatient of paediatric respiratory medicine of the first affiliated hospital of Guangzhou Medical University between July 2015 and

September 2016. The included criteria were as follows: patients had doctor diagnosed asthma with allergic rhinitis, were sensitive to at least one kind of a panel aeroallergens, had recurrent asthma symptoms in the preceding year and were not treated with any antihistamine or antiasthmatic drugs one month prior to the enrollment. Patients with acute upper and lower airway infections within 4 weeks prior to the study were excluded. All of the asthmatic children were divided into little (5 to 7), middle (8 to 9) and elder (10 to 12) age groups, and the differences between groups were compared.

The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University. Written informed consent was obtained from the parents of each child prior to the study.

2.3 | Fractional exhaled nitric oxide measurement

Fractional exhaled nitric oxide measurements were performed in the morning prior to the lung function tests using a chemiluminescence analyser (NIOX MINO, Aerocrine, Sweden), according to the international guideline.⁷

2.4 | Lung function and methacholine bronchial challenge testing

Lung function and methacholine bronchial challenge tests were performed using spirometers (Jaeger, Germany) according to the recommendations of the American Thoracic Society/European Respiratory Society.¹¹ Briefly, at least three (no more than eight) manoeuvres were performed with a variation between the best two manoeuvres of less than 5% or 150 mL in forced vital capacity and forced expiratory volume in 1 s. Then the methacholine bronchial challenge tests were performed based on the dosimeter method. The control and methacholine diluents were delivered by an automated APS pro system (Jaeger, Germany).

2.5 | Allergen SPT and immunoglobulin E (IgE) measurement

Allergic sensitisation was determined by the SPT and the levels of allergen-specific IgE in serum. SPT was carried out with a panel of common aeroallergens, including *Dermatophagoides pteronyssinus*, *Dermatophagoides farina*, dogs, cats, *Alternaria alternata*, *Blattella germanica*, mixed tree pollen, mixed grass, and a positive (histamine) and a negative (diluent) control (ALK-Abello, Hørsholm, Denmark). A wheal of at least 3 mm is needed for a positive result. Atopy was defined as the presence of at least one positive SPT finding. Blood samples were collected in a heparin-containing venipuncture tube and the serums were separated by centrifuges. Total plasma IgE was measured by means of the UniCAP 100 assay.

TABLE 1 The anthropometric parameters, baseline lung function, bronchial hyperresponsiveness, ACT scores, T-IgE and eosinophils count in peripheral blood

Parameters	All patients (<i>n</i> = 121)	Male (<i>n</i> = 88)	Female (<i>n</i> = 33)
Age, y	8.4 ± 1.8	8.4 ± 1.9	8.5 ± 1.6
Height, cm	131.2 ± 11.9	130.9 ± 12.6	132.1 ± 10.1
Weight, kg	29.0 ± 9.0	29.1 ± 9.4	28.8 ± 8.0
FEV ₁ %Pred	91.0 ± 15.3	91.8 ± 15.7	88.9 ± 14.1
FEV ₁ /FVC	82.9 ± 8.5	82.9 ± 7.9	82.8 ± 10.1
MMEF%Pred	67.6 ± 22.7	69.3 ± 22.7	63.5 ± 22.5
PEF (L/min)	239.2 ± 69.2	239.1 ± 73.1	239.4 ± 58.6
PD ₂₀ Mch (mg)	0.4 ± 0.6	0.4 ± 0.6	0.3 ± 0.5
ACT	19.1 ± 4.4	19.1 ± 4.4	18.9 ± 4.3
T-IgE (KU/L)	710.8 ± 592.1	674. ± 554.6	870.1 ± 767.2
Eos count (10 ⁹)	0.6 ± 0.5	0.6 ± 0.5	0.6 ± 0.4
Eos (%)	7.8 ± 6.2	8.2 ± 6.6	7.0 ± 5.4

TABLE 2 Comparisons of the anthropometric parameters, lung function, ACT scores, T-IgE and eosinophils count in peripheral blood between different age groups

Parameters	Little age group (<i>n</i> = 38)	Middle age group (<i>n</i> = 48)	Elder age group (<i>n</i> = 35)
Age, y	6.3 ± 0.7	8.5 ± 0.5	10.7 ± 0.8
Height, cm	119.5 ± 6.2	131.2 ± 6.6	143.9 ± 9.2
Weight, kg	22.7 ± 4.7	28.4 ± 6.7	36.7 ± 9.6
FEV ₁ %Pred	96.0 ± 14.1	88.1 ± 16.6	89.3 ± 13.7
FEV ₁ /FVC	95.6 ± 14.1	88.6 ± 16.7	89.3 ± 13.7
MMEF%Pred	71.4 ± 23.0	65.5 ± 22.4	66.5 ± 23.1
PEF (L/min)	182.6 ± 33.4	241.5 ± 47.0	297.4 ± 74.8
PD ₂₀ Mch (mg)	0.38 ± 0.55	0.25 ± 0.45	0.45 ± 0.74
ACT	18.9 ± 4.3	19.3 ± 3.8	18.9 ± 5.1
T-IgE (KU/L)	569.6 ± 503.3	788.1 ± 627.2	765.3 ± 624.3
Eos count (10 ⁹)	0.6 ± 0.3	0.6 ± 0.5	0.7 ± 0.5
Eos (%)	7.6 ± 5.1	7.6 ± 7.6	8.3 ± 5.2

Note: Little age group: 5 to 7 years, middle age group: 8 to 9 years, elder age group: 10 to 12 years.

2.6 | Statistical analyses

Data analyses were performed by SPSS 16.0 (SPSS Inc., USA). Normal distributed data were expressed as mean ± standard deviation otherwise median (interquartile range). The loge FeNO values were used as dependent variables to test the associations of demographic and covariates. Multivariable regression models were used to assess the independent effect and covariate-adjusted contribution of the factors to FeNO. A *P* value of less than 0.05 was considered as statistically significant.

3 | RESULTS

A total of 121 allergic asthma children were enrolled in and completed this study. No significant differences of anthropometric parameters, lung function, BHR, T-IgE and eosinophils in peripheral blood and asthma control test (ACT)

scores were found between male and female children (shown in Table 1). Anthropometric and lung function parameters increased with the age, while no significant differences of the BHR to Mch, T-IgE, eosinophils in blood and ACT scores were found between different age groups (table 2).

Most of the asthmatic children (114/121) were sensitive to dust mites, followed by *B. germanica* (57/121) and Dogs dander (52/121), while much lower percentage of children were sensitive to tested food allergens and tree and grass pollen. The sensitisation profiles of different age groups of asthmatic children are shown in Table 3. There are no significant differences of the percentages of sensitisations to the tested allergens between different age groups. Subjects aged 8 to 9 years had higher level of FeNO than those aged 5 to 7 years (geometric mean 28.0 (18.4) vs. 20.6 (17.5) ppb, *P* = 0.189), but had a significant lower level of FeNO than those aged between 10 and 12 years (geometric mean 28.0 (18.4) vs 53.0 (39.4) ppb, *P* = 0.000). Overall, greater age, height/weight, peak expiratory flow (PEF)

TABLE 3 The sensitisation allergen of the asthmatic children

Allergens	Little age group (<i>n</i> = 38)	Middle age group (<i>n</i> = 48)	Elder age group (<i>n</i> = 35)	Total (<i>n</i> = 121)
Dust mites	37	44	33	114 (94.2%)
<i>Blattella germanica</i>	18	22	17	57 (47.1%)
Dogs	18	16	18	52 (43.0%)
Cats	5	9	7	21 (17.4%)
Albumen	4	3	2	9 (7.4%)
Milk	3	1	1	5 (4.1%)
Shrimp	2	3	6	11 (9.1%)
Crab	4	4	2	10 (8.3%)
Polymycetes	2	1	1	4 (3.3%)
<i>Aspergillus fumigatus</i>	1	4	1	6 (5.0%)
<i>Alternaria alternata</i>	3	3	3	9 (7.4%)
Birch	3	4	5	12 (9.9%)
Plane tree	2	2	2	6 (5.0%)
Timothy	2	2	2	6 (5.5%)

Note: There are no significant statistical differences between groups of the tested allergens.

and higher level of total IgE ($P < 0.001$) are related to higher FeNO levels (Figure 1).

The significant coefficients from multiple linear regression models of the log FeNO are shown in Table 4. Due to the colinearity of age and height in children and adolescents, age was not included in the models. Height and blood total IgE were independent predictors of FeNO values. Gender (male) was not associated with higher FeNO among all patients or three different age groups ($P < 0.05$).

Overall, after 4 weeks of treatment with combined ICS and LABA, ACT score significantly increased (from 19.06 ± 4.36 to 23.96 ± 2.95 , $P < 0.01$), while the level of FeNO decreased (from 30.51 (30.39) to 23.94 (23.28) ppb, $P < 0.01$). When analysed with different age groups, the decrease of FeNO was significantly more in the elder age group than the other two groups ($P < 0.01$), while no significant difference in the increase of ACT score was found between different age groups ($P > 0.05$, Table 5).

4 | DISCUSSION

In this study, we have evaluated the distribution of FeNO in asthmatic children aged 5 to 12 years, and have analysed the correlations of demographic, lung function and BHR, and allergen sensitisation with FeNO values, and have also compared the changes of FeNO after the treatment of combined ICS and LABA between different age groups. Children little than 5-year-old may have difficulty in finishing the measurement of FeNO, and children larger than 12 years old are more likely with adults, so we enrolled the children aged range from 5 to 12 years. The data show that FeNO increases with

age, with highest geometric mean value of FeNO in the elder age group ($P < 0.05$).

Studies have reported that besides age, height and weight, the value of PEF and T-IgE also correlate with FeNO.⁸ As height, weight and PEF increase with the growth of age, we used multiple linear regression models of the log FeNO, the results showed that only height and T-IgE were independent predictors of FeNO values. Allergen exposure may induce an increase in airway eosinophilic inflammation. In this study, most of the children were sensitive to house dust mites, which are perennial allergen, and there is no significant difference in the sensitisation between different age groups, so the effects of the allergen exposure on FeNO are not so great as seasonal allergens that changed with seasons.¹² So, when we compare the differences in FeNO of subjects with different sensitisations, especially to seasonal and perennial allergens, we should take into account the impact of the seasonal allergen exposure on FeNO.

Due to the colinearity of age and height in children and adolescents, age was not included in the models. In healthy subjects (both children and adults), gender (male) was also associated with higher FeNO.⁶ But in this study, there were no significant differences in FeNO between male and female children. Higher levels of FeNO were reported in larger age/height group children, may be because the larger area of airway epithelia, especially large bronchia epithelia produced more FeNO. As it is more easy for the diffusion and delivery of the FeNO through a larger airway.¹²

The measurement of FeNO is a very useful tool in diagnosing and management of asthma in children.^{5,13} The geometric mean FeNO of the studied asthmatic children is higher than the normative value of healthy children.^{6,14} Only in the elder age group, the geometric mean value of FeNO is larger

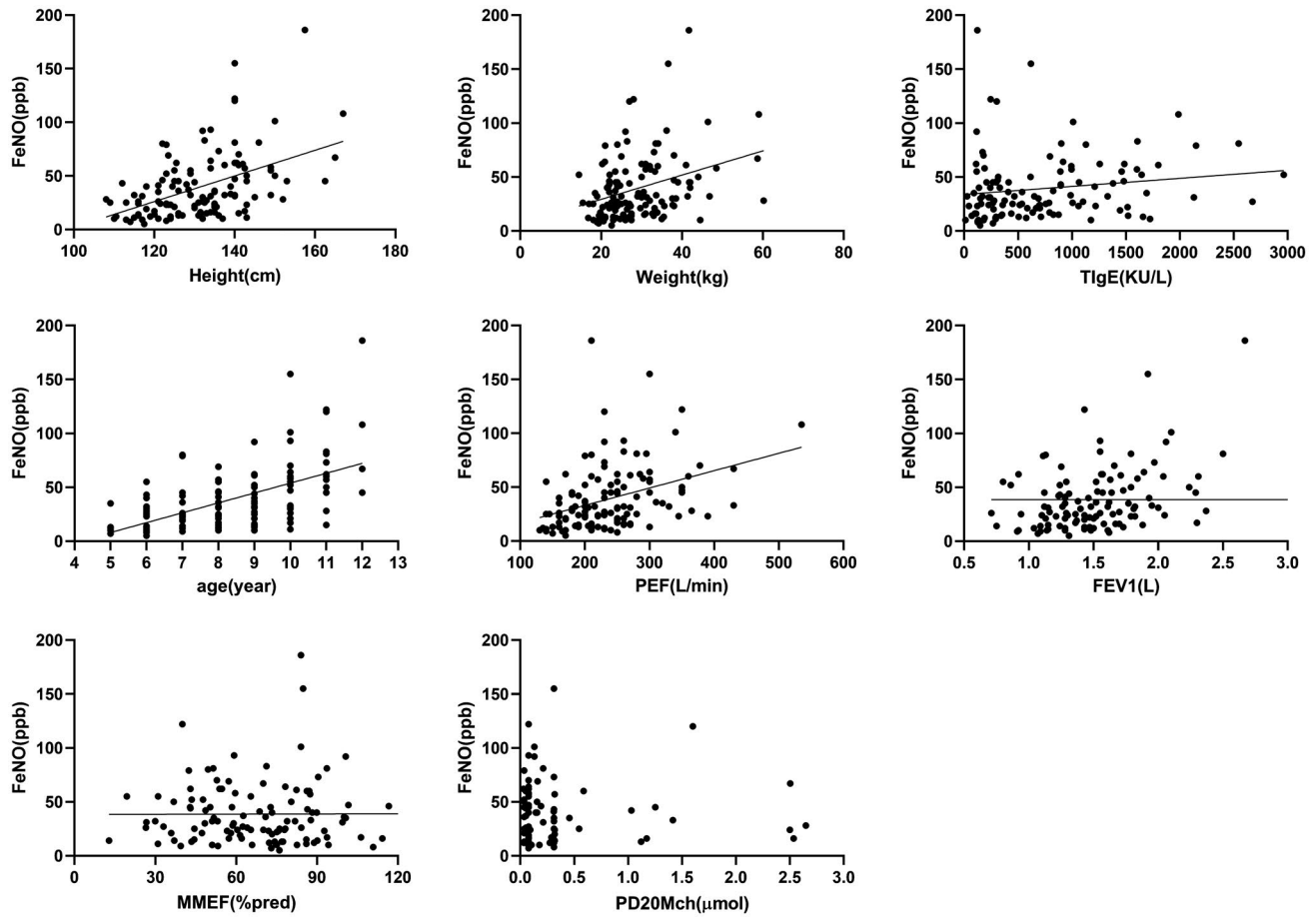


FIGURE 1 Correlations of FeNO with demographic, lung function parameters and allergen T-IgE. Greater age, height/weight, peak expiratory flow and higher level of total IgE are related to higher FeNO levels

TABLE 4 Coefficients from multiple regression models of Log FeNO at baseline and after treatment

	Constant	Height (cm)	T-IgE (KU/L)	R^2
FeNO (baseline)	−0.228	0.012	0.000	0.328
FeNO (after treatment)	−0.042	0.010	0.000	0.265

Note: At baseline: $\text{Lg(FeNO)} = -0.228 + 0.012 \times \text{Height}$, After treatment: $\text{Lg(FeNO)} = -0.042 + 0.01 \times \text{Height}$.

TABLE 5 Values of lung function, ACT score and FeNO at baseline and after treatment

Parameters	FEV ₁ %Pred (%)		PEF (L/min)		ACT		FeNO (ppb)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
All patents	91.0 ± 15.3	96.5 ± 14.9*	239.2 ± 69.2	264.5 ± 67.2*	19.1 ± 4.4	24.0 ± 2.9*	30.5 (30.4)	23.9 (23.3)*
Little age	96.0 ± 14.1	103.3 ± 13.1*	182.8 ± 33.0	216.0 ± 35.7*	19.1 ± 4.4	24.3 ± 2.2*	20.6 (17.5)	17.4 (13.2)
Middle age	88.1 ± 16.6	95.8 ± 12.1*	242.6 ± 46.9	263.4 ± 48.9*	19.2 ± 3.8	23.9 ± 3.3*	28.0 (18.4)	23.8 (25.3)
Elder age	89.3 ± 13.7	90.2 ± 17.0	297.4 ± 74.8	319.9 ± 73.6*	18.9 ± 5.1	23.7 ± 3.3*	53.0 (39.4)	34.4 (25.5)*

* $P < 0.05$, compared between the baseline and post treatment values.

than the cutoff values reported in some studies for diagnosing asthma.^{5,12} So, the results of our study partially support the theory that measurement of FeNO can be used for diagnosing asthma in children, at least for children 10 years old or elder.

There are also studies reported that FeNO for assessing the efficacy of antiasthma treatment, especially with ICS in both children and adults.¹⁵ At baseline, the ACT scores were comparable between different age groups,

while higher FeNO values were found in larger age group asthmatic children, as well as PEF, which consists of trends in healthy children.^{6,14} So, the levels of FeNO may not accurately reflect the control or severity of asthma, which consists of a previous study.¹⁶ After 4 weeks of treatment with combined ICS and LABA, a significant decrease of FeNO was found in the elder age group only, although ACT scores significantly increased in all age groups. FeNO is well correlated with the percentage of eosinophilia cells in sputum,⁵ which reflect the airway eosinophilic inflammation. Inhaled steroid can greatly decrease the eosinophils in airways, so the values of FeNO may also significantly decrease after the treatment with inhaled steroid alone or inhaled steroid combined with bronchial dilators. In some clinical studies that evaluated the efficacy of the treatment of asthma, significant efficacy was obtained if the decrease of FeNO was larger than 10 ppb (baseline FeNO higher than 25 ppb) or higher than 10% (the baseline FeNO was lower than 25 ppb).^{10,16,17} In this study, a significant decrease of FeNO was found only in the elder age group (decrease larger than 10 ppb). There are also studies with controversial results about the use of FeNO for evaluating the treatment of asthma.¹⁶ As the value of FeNO may vary greatly in different phenotypes of asthma, the measurement of FeNO can be better used in some subgroup asthmatics, especially for allergic asthma patients.

There are several limitations that should be mentioned in this study. First, more boys were included in this study, which may partially explain the result that no significant differences in the FeNO were found between male and female children. Second, not all of the possible factors that may affect FeNO were assessed. Third, as atopy and allergic rhinitis were well associated with higher levels of FeNO, all of the children in this study were combined with AR, so the differences of FeNO between the atopy and nonatopy, asthmatics with AR and without AR were not compared.

In conclusion, height and T-IgE are well associated with the levels of FeNO in asthmatic children 5 to 12 years old. The measurement of FeNO to evaluate the efficacy of treatment with ICS/LABA should be better used in larger-age group children.

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CONFLICT OF INTEREST

All authors declared that they have no relationships with or financial interests in any commercial company related to this study and article. All authors declared no conflict of interest.

AUTHOR CONTRIBUTIONS

Designed the study: Zhu, Guan, Sun

Steered literature search, data collection and analysis: Xia, Chen

Performed the study: Zhu, Xia, Chen, Guo

Drafted the manuscript: Zhu, Xia, Chen, Guan

Reviewed and approved the submission of the manuscript: Zhu, Xia, Chen, Guan, Guo, Sun

ETHICS

The study protocol was approved by the ethics committee of the First Affiliated Hospital of Guangzhou Medical University, and parents signed informed consent.

ORCID

Zheng Zhu  <https://orcid.org/0000-0002-6949-3785>

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