Associations of Sleep Problems With Asthma/wheeze and Allergic Rhinitis Among Chinese Children Aged 0-6 Years: a Cross-sectional Study

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Abstract

Background: Asthma/wheeze and allergic rhinitis are common among pre-school age children, which urgently need to identify more modifiable risk factors for prevention. The aim of this study was to examine the associations of sleep problems with asthma/wheeze and allergic rhinitis among Chinese children aged 0-6 years.

Methods: This cross-sectional survey, a part of the National Survey on Physical Growth and Development of Children in nine cities of China (NSPGDC), was conducted in Guangzhou, China. Children aged 0-6 years were randomly selected from 29 communities and 32 kindergartens. Asthma/wheeze, allergic rhinitis and sleep problem were evaluated by a valid questionnaire which was completed by participants' parent(s). Binary logistic regression models were employed to estimate the odds ratios (OR) and 95% confidence intervals (CI) for asthma/wheeze and allergic rhinitis according to short sleep duration, late bedtime and frequent nocturnal awakening.

Results: We included 13376 children aged 0~6 years. Of these, 371 (2.8%) diagnosed as asthma/wheeze, and 610 (4.6%) diagnosed as allergic rhinitis. Frequent nocturnal awakening was associated with asthma/wheeze and allergic rhinitis, adjusted OR were 1.53 (95% CI: 1.20~1.94) and 1.39(1.14-1.71), respectively. Further subgroup analysis showed the association of frequent nocturnal awakening with asthma/wheeze and allergic rhinitis differed by age. No significant associations of short duration and late bedtime with asthma/wheeze and allergic rhinitis were identified.

Conclusions: Our data suggested that frequent nocturnal awakening was associated with asthma/wheeze and allergic rhinitis, but this association differed by age. Further studies are warranted to confirm its' causal association and to understand the underlying mechanisms.

Background

Allergic respiratory diseases (ARDs), primarily asthma and allergic rhinitis, are important clinical and public concerns all over the world. Globally, asthma and allergic rhinitis affect 4-10% and 10-30% of the whole population [1], respectively. Among children, the prevalence of ARDs is disparity across regions and countries, but the overall prevalence increases year by year [2–4]. ARDs not only increase health and care costs, but also reduce the life quality of the suffers [5, 6], which, therefore calling for more preventive measures to minimize its harmful fundamentally.

ARDs are associated with a broad range of environmental factors and lifestyles other than genetic factors [7], which are not fully understood. Recently, associations between sleep problems and ARDs have gained increasing attention. Sleep problems, such as difficulty in settling to sleep, nocturnal awakening, and irregular sleep patterns and short-duration sleep, are common in children. Approximately 25% of children experience some forms of sleep problem during childhood [8]. To date, several studies have examined the association between sleep problems and ARDs. However, there were few studies have been conducted among pre-school age children with a narrow range of age or a small sample size [9, 10]. In addition, previous studies have suggested that residency in urban areas and prenatal smoking are associated with an increased risk of wheeze and asthma [11, 12], however, no study that examined the association between sleep problems and ARDs has adjusted for such confounders. Therefore, the association of sleep problems with asthma and allergic rhinitis among pre-school aged children remains unclear. To identify the association among pre-school age children is substantially important, since pre-school age a critical period for developing the physique and immune system and forming a healthy lifestyle, include developing a good sleep habit [10, 13].

The present study aimed to examine the associations of sleep problems with asthma and allergic rhinitis among Chinese children aged 0-6 years. We hypothesized that sleep problems, include frequent nocturnal awakening, short duration and late bedtime would be associated with ARDs even after adjustment for potential confounders.

Methods

Study design and participants

We conducted a cross-sectional survey of children aged 0-6 years in Guangzhou between July to October in 2015, which was a part of the National Survey on Physical Growth and Development of Children in nine cities of China (NSPGDC) [14]. The NSPGDC used the identical methodology to collect data from nine cities, thus data collected in each city could be analyzed to produce a general

conclusion for the local population. The study design, organization, and implementation of the NSPGDC have been published previously [15]. Briefly, in each study city, a cluster random sampling method based on age groups (there were 22 age groups and 150-200 subjects for each sex-age subgroup) for both urban and rural areas was employed to produce a random sample [16]. Children under 3 years in a community was classified as a minimum cluster unit, and children aged 3 and above in kindergarten regarded as a unit. Exclusion criteria included temporary residents, acute illness within a month, chronic illness (such as cardiopathy, chronic nephrosis, tuberculosis, persistent hepatitis), obviously malnourished and physically handicapped.

In Guangzhou, we selected 12798 participants below the age of 3 years from 16 communities across three urban administrative districts (Yuexiu, Liwan and Haizhu) and 13 communities across four rural administrative districts (Conghua, Huadu, Panyu and Baiyun); 6707 participants aged 3 to 6 years were selected from 16 kindergartens in urban administrative districts, and 16 kindergartens in rural administrative districts. We excluded 6129 participants after reviewing the completeness of the questionnaire (with missing data >15%). Therefore, the remain 13376 participants were included in the final analysis, with an effective response rate of 68.6% (13376/19505). Data was collected by local trained physicians with a structured questionnaire, which include participants' demographic characteristics, mother's health conditions during pregnancy, delivery model, feeding patterns in the first 6 months, sleep problems and ARDs of the participants. Body weight and height (supine length if under 3 years) were also measured by calibrated instruments and standard specifications, and body mass index (BMI) was calculated by dividing the weight in kg by the square of length in m.

Ethics

The study was approved by the Ethical Committee for Biomedical Research in Guangzhou Women and Children's Medical Center (reference number : 2018052407). A written informed consent was obtained from all the participants' parents before starting of the survey.

Measurement

Asthma/wheeze and allergic rhinitis was diagnosed by the parental questionnaire based on the International Study of Asthma and Allergy in Children Questionnaire (ISAACQ) (*"Has your baby had wheezing or whistling in the chest during the past 12 months?"*, *"Has your baby had a problem with sneezing, or a runny, or a blocked nose when he/she did not have a cold or the flu during the past 12 months?"* and *"Has this nose problem been accompanied by itchy-watery eyes during the past 12 months?"*) [22].

We measured short sleep duration, late bedtime and frequent night waking in the present study. Sleep duration was calculated based on 2 questions (*"How many hours did your baby sleep during the night in the past 2 weeks?"* and *"How many hours did your baby sleep during the daytime in the past 2 weeks?"*) derived from the Pittsburgh sleep quality index [18]. According to the National Sleep Foundation's recommendation, infants (0-11 months) who sleep less than 12 hours, toddlers (1-2 years) who sleep less than 11 hours for and preschoolers (3-6years) who sleep less than 10 hours were defined as short sleep duration [19]. Bedtime was classified into 2 groups: at or before 11:00 PM, and after 11:00 PM. Participants whose bedtime later than 11:00 PM was considered as a late bedtime [20, 21]. The nocturnal awakening frequency was also classified into 3 groups: none or seldom, once per night, and twice or more per night. According to the previous study by the National Sleep Foundation [22], children who wakened twice or more per night among infants (0-11 months) and toddlers (1-2 years), and once per night among preschoolers (3-6 years) were defined as frequent nocturnal wakening.

Previous studies suggested a broad range of demographic characteristic and environmental factors that are associated with Asthma/wheeze and allergic rhinitis [9, 10, 23, 24]. Therefore, we adjusted for these potential confounders in our analysis as much as we could, which included resident area, age group, gender, family annual income, ethnicity, mother's education and occupation, delivery model, gestational age, birth weight, maternal smoking, passive smoking and maternal alcohol consumption during pregnancy, feeding patterns in the first 6 months, passive smoking and BMI of children.

Statistical analysis

Mean and standard deviation were reported for continuous variables. Frequencies and percentage were reported for categorical variables. T tests and Chi-square tests were used for comparing continuous and categorical variables, respectively. Binary logistic regression models were employed to estimate the odds ratios (OR) and 95% confidence intervals (CI) for asthma/wheeze and allergic rhinitis according to short sleep duration, late bedtime and frequent nocturnal awaking, respectively. In each logistic regression model, four models were fitted.

In model 1, we estimated the crude ORs. In model 2, we adjusted for demographic characteristics, included region (urban/rural), sex (male/female), age group (≤12 months/1-2 years/3-6years), family annual income (below 50000 RMB/50000-100000 RMB/100000-300000 RMB/above 300000 RMB) [25], mother's educational level (college or above/senior high school/junior high school or below) and occupation (farmers/workers/service/others). In model 3, we additionally adjusted for factors related to pregnancy, including delivery models (vaginal delivery/cesarean delivery), preterm birth (≤37 weeks/ >37-42 weeks), birth weight (<2500 g/2500-3900g/ ≥4000 g), maternal smoking (yes/no) and maternal alcohol consumption (yes/no). In mode 4, we additionally adjusted for feeding patterns in the first 6 months of the participants (breastfeeding/artificial feeding/mixed feeding), passive smoking (yes/no) and BMI (continuous data) of children. We further conducted subgroup analysis to examine whether age influence the associations of asthma/wheeze and allergic rhinitis with frequent nocturnal awaking where significant associations were found. Missing data of continuous covariables was inputted based on means and categorical covariables was inputted by the median. Significance level was set at $P<0.05$ and all tests were 2-sided. Statistical analyses were conducted using SPSS Statistics, version 25.0 (IBM Corp).

Results

Participants' characteristics

We included 13376 children in the current analysis. Of them, 6718 (50.2%) were boys and 6010 (44.9%) were from the urban areas. The age of the participants ranged from 0 to 6 years (mean $\pm$ SD: 1.92 $\pm$ 1.98 years), 4895 (36.6%) were aged between 0 to 12 months and 4781 (36.4%) were aged between 3 to 6 years. The other characteristics of the participants were summarized in Table 1.

Table 1
The characteristics of the participants

Characteristics		Total	Asthma/Wheeze		Allergic rhinitis	
		(n=13376)	Yes(n=371)	No(n=13005)	Yes(n=610)	No(n=12766)
Region*	Urban	6010(44.9)	223(60.1)	5787(44.5)	352(57.7)	5658(44.3)
	Rural	7366(55.1)	148(39.9)	7218(55.5)	258(42.3)	7108(55.7)
Age group*	<12 months	4895(36.6)	112(30.2)	4783(36.8)	51(8.4)	4844(37.9)
	1-2 years	3610(27.0)	77(20.8)	3533(27.2)	46(7.5)	3564(27.9)
	3-6 years	4871(36.4)	182(49.1)	4689(36.1)	513(84.1)	4358(34.1)
Gender*	Male	6718(50.2)	225(60.6)	6493(49.9)	348(57.0)	6370(49.9)
	Female	6658(49.8)	146(39.4)	6512(50.1)	262(43.0)	6396(50.1)
Ethnicity	Han	13160(98.4)	366(98.7)	12794(98.4)	600(98.4)	12560(98.4)
	Others	216(1.6)	5(1.3)	211(1.6)	10(1.6)	206(1.6)
Mother's educational level*	College or above	6859(51.3)	224(60.4)	6635(51.0)	421(69.0)	6438(50.4)
	Senior high school	3468(25.9)	82(22.1)	3386(26.0)	111(18.2)	3357(26.3)
	Junior high school or below	3049(22.8)	65(17.5)	2984(22.9)	78(12.6)	2971(23.3)
Mother's occupation*	Famers	425(3.2)	2(0.5)	423(3.3)	8(1.3)	417(3.3)
	Workers	3067(22.9)	101(27.2)	2966(22.8)	166(27.2)	2901(22.7)
	Servicer	2443(18.3)	66(17.8)	2377(18.3)	131(21.5)	2312(18.1)
	Others	7441(55.6)	202(54.4)	7239(55.7)	305(50.0)	7136(55.9)
Family annual income (RMB)*	<50000	3381(25.3)	68(18.3)	3313(25.5)	84(13.8)	3297(25.8)
	~100000	4133(30.9)	108(29.1)	4025(30.9)	162(26.6)	3971(31.1)
	~300000	4596(34.4)	149(40.2)	4447(34.2)	292(47.9)	4304(33.7)
	>300000	1266(9.5)	46(12.4)	1220 (9.4)	72(11.8)	1194(9.4)
Delivery methods	Vaginal delivery	8156(61.0)	213(57.4)	7943(61.1)	318(52.1) *	7838(61.4)
	Caesarean delivery	5220(39.0)	158(42.6)	5062(38.9)	292(47.9)	4928(38.6)
Preterm birth*	Yes	265(2.0)	14(3.8)	251(1.9)	20(3.3)	245(1.9)
	No	13111(98.0)	357(96.2)	12754(98.1)	590(96.7)	12521(98.1)
Birth weight (g)	<2500	176(1.3)	9(2.4) *	167(1.3)	9(1.5)	167(1.3)
	2500-3999	12752(95.3)	355(95.7)	12397(95.3)	585(95.9)	12167(95.4)
	≥4000	448(3.3)	7(1.9)	441(3.4)	16(2.6)	432(3.4)
Feeding patterns in the first 6 months*	Breastfeeding	5252(39.3)	113(30.5)	5139(39.5)	174(28.5)	5078(39.8)
	Artificial feeding	1709(12.8)	51(13.7)	1658(12.7)	110(18.0)	1599(12.5)
	Mixed feeding	6415(48.0)	207(55.8)	6208 (47.7)	326(53.4)	6089(47.7)
Maternal smoking during pregnancy	Yes	40(0.3)	0(0)	40(0.3)	2(0.3)	38(0.3)
	No	13336(99.7)	371(100.0)	12965(99.7)	608(99.7)	12728(99.7)

* $P<0.05$

Characteristics		Total	Asthma/Wheeze		Allergic rhinitis	
		(n=13376)	Yes(n=371)	No(n=13005)	Yes(n=610)	No(n=12766)
Alcohol consumption during pregnancy	Yes	54(0.4)	1(0.3)	53(0.4)	3(0.5)	51(0.4)
	No	13303(99.5)	370(99.7)	12952(99.6)	607(99.5)	12696(99.5)
Passive smoking of Children	Yes	6167(46.1)	189(50.9)	5978(46.0)	266(43.6)	5901(46.2)
	No	7209(53.9)	182(49.1)	7027(54.0)	344(56.4)	6865(53.8)
Children's BMI (Continuous data)		15.89±1.69	15.86±1.70	15.89±1.69	15.30±1.63*	15.91±1.69
* P<0.05						

Overall, 371 (2.8%) of the participants were diagnosed as asthma/wheeze. Compared with the participants without asthma/wheeze, participants with asthma/wheeze were more likely to be living in urban areas, boys and premature. There were 610 (4.6%) participants diagnosed as allergic rhinitis. Compared with participants without allergic rhinitis, those with allergic rhinitis were likely to be living in urban areas, boys, premature and cesarean delivery (see Table 1).

Association between sleep problems and asthma/wheeze

Of the 13376 children included, 1220 (9.1%) had a short sleep duration. Among the children who diagnosed as asthma/wheeze, 26 (7.0%) had a short sleep duration; while among the children without asthma/wheeze, 1194 (9.2%) had a short sleep duration. No significant association between short sleep duration and asthma/wheeze was found (Table 2). There were 655 (4.9%) participants go to sleep after 11 PM, namely had late bedtime. Among the children who diagnosed as asthma/wheeze or not, 13 (3.5%) and 643 (4.9%) had late bedtime, respectively. There was also no significant association between late bedtime and asthma/wheeze (Table 2). There were 3651 (27.3 %) participants had frequent nocturnal awakenings, 121 (32.6%) participants diagnosed as asthma/wheeze and 3530 (27.1%) participants without asthma/wheeze had frequent nocturnal awakenings, significant association between frequent nocturnal awakenings and asthma/wheeze was found (Table 2).

Table 2
Frequency and proportion of sleep problems by asthma/wheeze and allergic rhinitis

Sleep problems	Total(N=13376)	Asthma/Wheeze(n/%)		χ^2	<i>P</i>	Allergic rhinitis(n/%)		χ^2	<i>P</i>
		Yes(N=371)	No(N=13005)			Yes(N=610)	No(N=12766)		
Short Sleep duration									
No	12156(90.9)	345(93.0)	11811(90.8)	2.06	0.173	563(92.3)	11593(90.8)	1.55	0.250
Yes	1220(9.1)	26(7.0)	1194(9.2)			47(7.7)	1173(9.2)		
Late Bedtime									
No	12156(95.1)	358(95.6)	12363(95.1)	1.59	0.276	600(98.4)	12121(94.9)	14.56	<0.001
Yes	655(4.9)	13(3.5)	642(4.9)			10(1.6)	645(5.1)		
Frequent Nocturnal awaking									
No	9725(72.7)	250(67.4)	9475(72.9)	5.44	0.020	465(76.2)	9260(72.5)	4.00	0.047
Yes	3651(27.3)	121(32.6)	3530(27.1)			145(23.8)	3506(27.5)		

The unadjusted and adjusted ORs for asthma/wheeze for sleep problems were showed in Table 3. From model 1 to model 4, the ORs were not change substantially. In the fully adjusted models, significant association was only found between frequent nocturnal awakenings and asthma/wheeze, the OR was 1.53 (95% CI: 1.20~1.94). Further subgroup analysis showed that significant

association between frequent nocturnal awakenings and asthma/wheeze was found among children aged 1-6 years but not among children aged 0-12months (Table 4).

Table 3
Association of sleep problems with asthma/wheeze or allergic rhinitis among children aged 0- 6 years

	Model 1 ^a	<i>P</i>	Model 2 ^b	<i>P</i>	Model 3 ^c	<i>P</i>	Model 4 ^d	<i>P</i>
	OR (95%CI)		OR (95%CI)		OR (95%CI)		OR (95%CI)	
Sleep problems and asthma/wheeze								
Short Sleep duration								
No	1(Ref)		1(Ref)		1(Ref)		1(Ref)	
Yes	0.75(0.50-1.12)	0.182	0.79(0.52-1.18)	0.242	0.79(0.52-1.18)	0.245	0.76(0.50-1.15)	0.194
Late Bedtime								
No	1(Ref)		1(Ref)		1(Ref)		1(Ref)	
Yes	0.70(0.40-1.22)	0.210	0.87(0.49-1.54)	0.632	0.87(0.49-1.54)	0.640	0.85(0.48-1.51)	0.578
Frequent Nocturnal awaking								
No	1(Ref)		1(Ref)		1(Ref)		1(Ref)	
Yes	1.30(1.04-1.62)	0.016	1.50(1.18-1.91)	0.001	1.50(1.18-1.91)	0.001	1.53(1.20-1.94)	<0.001
Sleep problems and allergic rhinitis								
Short Sleep duration								
No	1(Ref)		1(Ref)		1(Ref)		1(Ref)	
Yes	0.83(0.61-1.12)	0.214	1.15(0.84-1.58)	0.386	1.14(0.83-1.56)	0.414	1.12(0.81-1.53)	0.497
Late Bedtime								
No	1(Ref)		1(Ref)		1(Ref)		1(Ref)	
Yes	0.31(0.17-0.59)	<0.001	0.99(0.52-1.90)	0.979	0.99(0.52-1.91)	0.986	0.98(0.51-1.89)	0.954
Frequent Nocturnal awaking								
No	1(Ref)		1(Ref)		1(Ref)		1(Ref)	
Yes	0.82(0.68-1.00)	0.046	1.39(1.13-1.70)	0.001	1.39(1.13-1.70)	0.002	1.39(1.14-1.71)	0.001
a Model 1: Unadjusted;								
b Model 2: Adjusted for demographic characteristics: region, gender, age, family income, mother's educational level and occupation.								
c Model 3: Additionally adjusted for factors related to pregnancy, including delivery model, preterm birth, birth weight, maternal alcohol consumption and smoking during the pregnancy.								
d Model 4: Adjusted for feeding pattern before 6 months, BMI and passive smoking of children, in additional to the covariates in Model 3.								

Table 4
association between frequent nocturnal awaking and asthma/wheeze according to age group

Frequent nocturnal awaking	No. of asthma/wheeze	Mode 1 ^a	<i>P</i>	Model 2 ^b	<i>P</i>
		OR (95%CI)		OR (95%CI)	
< 12months					
No (N=2503)	54(2.2)	1(Ref)		1(Ref)	
Yes (N=2392)	58(2.4)	1.13(0.78-1.64)	0.532	1.08(0.74-1.58)	0.698
1-3 years					
No (N=3167)	56(1.8)	1(Ref)		1(Ref)	
Yes (N=443)	21(4.7)	2.77(1.66-4.61)	<0.001	2.64(1.58-4.42)	<0.001
3-6years					
No (N=4055)	140(3.2)	1(Ref)		1(Ref)	
Yes(N=816)	42(5.1)	1.52(1.07-2.16)	0.020	1.52(1.07-2.19)	0.021
a Model 1: Unadjusted;					
b Model 2: Adjusted for demographic characteristics: region, gender, age, family income, mother's educational level and occupation, delivery mode, preterm birth, birth weight, maternal alcohol consumption and smoking during the pregnancy, feeding patterns in the first 6 months, BMI and passive smoking of children.					

Association between sleep problems and allergic rhinitis

Among participants diagnosed having allergic rhinitis, 47 (7.7%) had short sleep duration, 10 (1.6%) had a late bedtime, and 145 (23.8%) had frequent nocturnal awakenings, respectively; while among participants without allergic rhinitis, 1173 (9.2%) had short sleep duration, 645 (5.1%) had a late bedtime, and 3506 (27.5%) had frequent nocturnal awakenings, respectively. Significant associations of late bedtime and frequent nocturnal awakenings with allergic rhinitis were found (Table 2 and Model 1 in Table 3). However, significant association was only found between frequent nocturnal awakenings and allergic rhinitis after adjusted for potential confounders (Table 3). In the fully adjusted model (Model 4), the adjusted OR for allergic rhinitis for frequent nocturnal awakenings was 1.39(95%CI: 1.14-1.71). However, similar association between frequent nocturnal awakenings and allergic rhinitis was only found among children aged 3-6 years, the adjusted OR was 1.52 (95%CI: 1.11-1.92) (Table 5).

Table 5
association between frequent nocturnal awakening and allergic rhinitis according to age group

Frequent Nocturnal awakening	No. of asthma/wheeze	Mode 1 ^a	<i>P</i>	Model 2 ^b	<i>P</i>
		OR (95%CI)		OR (95%CI)	
< 12months					
No (N=2503)	26(1.0)	1(Ref)		1(Ref)	
Yes (N=2392)	25(1.0)	1.10(0.68-1.75)	0.982	1.13(0.65-1.99)	0.664
1-3 years					
No (N=3167)	42(1.3)	1(Ref)		1(Ref)	
Yes (N=443)	4(0.9)	0.68(0.24-1.90)	532	0.62(0.22-1.76)	0.372
3-6years					
No (N=4055)	397(9.8)	1(Ref)		1(Ref)	
Yes(N=816)	116(14.2)	1.53(1.22-1.91)	<0.001	1.53(1.22-1.92)	<0.001
a Model 1: Unadjusted;					
b Model 2: Adjusted for demographic characteristics: region, gender, age, family income, mother's educational level and occupation, delivery mode, preterm birth, birth weight, maternal alcohol consumption and smoking during the pregnancy, feeding patterns in the first 6 months, BMI and passive smoking of children.					

Discussion

In this study, we used a large-scale survey data, which was part of the NSPGDC, to investigate the association of sleep problems with asthma/wheeze and allergic rhinitis among children aged 0-6 years in Guangzhou. The results revealed the prevalence of asthma/wheeze and allergic rhinitis among children aged 0-6 years was 2.8%, and 4.6% respectively. The findings also suggested that frequent nocturnal awakenings but not short sleep duration and late bedtime, was significant associated with asthma/wheeze and allergic rhinitis. However, these associations differed by children' age.

Comparison with other studies

In the present study, we found that the prevalence of asthma/wheeze and allergic rhinitis were lower than previous studies conducted both in China and western countries. For example, a study conducted in six representative cities in China, found that the prevalence of asthma and allergic rhinitis were 8.0% and 16.6%, respectively [26]. A population-based birth cohort study conducted in Sweden reported that the prevalence of wheeze episodes before 2 years of age was 25% [27]. A nationwide study conducted in Portugal reported that the prevalence of current rhinitis was 43.4% among child aged 3-5 years [28]. The discrepancies might be related to different characteristics of study participants, apart from the different measurements for asthma/wheeze and allergic rhinitis. However, our findings were similar to a study conducted in Shanghai, which reported that the prevalence of wheeze and allergic rhinitis were 3.7% and 2.5%, respectively [9].

Our findings suggest that frequent nocturnal awakening was associated with asthma/wheeze (OR=1.53, 1.20-1.94) and allergic rhinitis (OR=1.39, 1.14-1.71), which were similar to previous studies that investigated the association of sleep problems with allergic diseases among children under 6 years [9, 10]. Wang *et al* conducted a study to examine the associations of sleep disorders with the risk of wheeze and allergic rhinitis among 566 Chinese toddlers and found that having more than 2 times of nocturnal awakening per night was associated with a higher risk of wheeze (OR=6.16, 1.28~29.74) [9]. Kozyrskyj *et al* analyzed the conditions of 2398 children from on a community-based birth cohort in Australia and found that persistent nocturnal awakening before 3 years of age was associated with an increased risk of nonatopic asthma at age 6 (OR=1.87, 1.08~3.25), after adjusting for other risk factors of asthma, including co-sleeping, wheeze and family stress [10]. In this study, we also found that the associations of frequent nocturnal awakening with asthma/wheeze and allergic rhinitis were differed by age, which was not reported in previous studies [9, 10]. This age differences may be due to age difference prevalence rate of asthma/wheeze and allergic rhinitis, which had low diagnosis rate among children aged 0-3 years. To reduce the harmful of asthma/wheeze and allergic rhinitis to the child, parent need detect the

early symptoms of the disease as early as possible [29], although age difference on association of frequent nocturnal awakening with asthma/wheeze and allergic rhinitis need to be verified in different population.

Possible explanations of the association of frequent nocturnal awaking with asthma/wheeze and allergic rhinitis

The association between frequent nocturnal awaking and asthma/wheeze and allergic rhinitis could be explained by several plausible biological mechanisms. Firstly, frequent nocturnal awakening may increase the levels of pro-inflammatory cytokines and decrease the immunologic tolerance to allergen [9, 10], shifting the balance between Th1 and Th2 cytokines towards an allergy related (Th2) pattern [30], which are known factors contributing to allergic diseases such as asthma/wheeze and allergic rhinitis. Secondly, frequent nocturnal awakening could disrupt the regulation of the hypothalamic–pituitary–adrenal (HPA) axis [31, 32] and the circadian rhythms of melatonin [33, 34]. Children with impaired HPA-axis regulation showed a blunted cortisol awakening response and lower cortisol levels [31, 32], which lacks suppression of airway inflammation that could increase the risk of asthma and rhinitis [35, 36]. Additionally, melatonin may also play a very important role in anti-inflammatory and immunomodulatory functions [35, 37], thus a decline in the level of melatonin could reduce the suppression of inflammation and airway hyper-responsiveness, which in turn could trigger asthma and allergic rhinitis [38, 39].

Strengths and limitations

The major strength of this study is the sample size. For this large-scale cross-sectional study, we recruited 13376 representative participants from rural and urban Guangzhou by using a well-designed protocol, which makes our results more generalized. The other major strength of this study is that we have adjusted for several important confounders, such as region and maternal smoking and children's passive smoking, which was not adjusted in previous studies, making our results more robust. Additionally, this is the first investigation on the association of sleep problems with asthma/wheeze and allergic rhinitis among Chinese child aged 0-6 years, which also filled in the age gap in this area of research.

There were several limitations in our study. First, asthma/wheeze and allergic rhinitis were not determined by objective measures, but rather parent reported ISAACQ, which although was highly recognized for its reliability and validity and was used in previous studies [30, 17]. Second, sleep problems were assessed through questionnaires based on the parents' reports, instead of objective measurement, thus recall bias may exist. On balance, previous studies have demonstrated that information regarding sleep garnered from parents is likely to be reliable [40]. Third, although we have adjusted for various potential confounders, we did not adjust for family allergy history of the parents or mother's stress during pregnancy, which are risk factors for allergenic diseases [10]. Fourth, this study is a cross-sectional study, which deduces a weak association in the exploration of the causal relationship of sleep problems and asthma/wheeze and allergic rhinitis. Future prospective research studies are needed to validate these findings, since asthma/wheeze and allergic rhinitis are significant clinical and public concerns.

Sleep problems including shortened sleep duration, late bedtime and frequent nocturnal awaking are common among children aged 0-6 years, which have a broad impact on children's development and physical health. In the present study, we used data from the NSPGDC to investigate the association of sleep problems with asthma/wheeze and allergic rhinitis among Chinese children 0-6 years and found that frequent nocturnal awakening was associated with asthma/wheeze and allergic rhinitis. Although this is a cross-sectional study and the association of frequent nocturnal awakening with asthma/wheeze and allergic rhinitis differed by age, the results suggests that pediatricians should consider evaluating sleep problems when evaluating the risk factors for asthma/wheeze and allergic rhinitis, and that parents should help their children develop good sleeping habits to reduce the risk of asthma/wheeze and allergic rhinitis.

Conclusions

Findings from this large-scale cross-sectional study suggested that frequent nocturnal awakening was associated with asthma/wheeze and allergic rhinitis, but this association differed by age. Further studies are warranted to confirm whether nocturnal awaking has an impact on asthma/wheeze and allergic rhinitis and to understand the underlying mechanisms.

Abbreviations

ARDs: Allergic respiratory diseases

BMI: Body mass index

CI: Confidence intervals

NSPGDC: National Survey on Physical Growth and Development of Children in nine cities of China

OR: Odds ratio

Declarations

Ethics approval and Consent to participate

The study was approved by the Ethical Committee for Biomedical Research in Guangzhou Women and Children's Medical Center (reference number : 2018052407). A written informed consent was obtained from all the participants' parents.

Consent for publication

Not applicable.

Availability of data and material

Data and material of this study could be available through contacting with the corresponding authors. Data of NSPGDC can't be available because its' intellectual property belongs to Guangzhou Health and Family Planning Commission.

Competing interests

The authors declare that they have no competing interests.

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Authors' contribution

YM participated in the conceptualization of this study, acquisition of data, statistical analyses and drafted the main manuscript. JT participated in the statistical analyses and interpretation analyses and review the manuscript. YQW: participated in the statistical analyses and interpretation analyses and revised the manuscript. YH: participated in the acquisition of data and statistical analyses. JJL participated in data clean and interpretation analyses. LJ and YFX participated in investigation, entering data and review the manuscript. SFL and YYS participated in the acquisition of data.

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References

1. Valero A, Quirce S, Dávila I, Delgado J, Domínguez-Ortega J. Allergic respiratory disease: different allergens, different symptoms. *Allergy*. 2017; 72(9):1306–1316.
2. Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK, Williams H, The ISAAC Phase Three Study Group. 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*. 2006; 368(9537):733–43.
3. Korea Centers for Disease Control and Prevention. The Statistics of the 8th Korea Youth Risk Behavior Web-based Survey (KYRBWS) in 2012. 2012. Available from: <http://yhs.cdc.go.kr/>. Accessed 07 March 2021.

4. Huang C, Liu W, Hu Y, Zou Z, Zhao Z, Shen L, Shen L, Weschler LB. Updated prevalences of asthma, allergy, and airway symptoms, and a systematic review of trends over time for childhood asthma in Shanghai, China. *PLoS One*. 2015; 10: e0121577.
5. Linneberg A, Dam Petersen K, Hahn-Pedersen J, Hammerby E, Serup-Hansen N, Boxall N. Burden of allergic respiratory disease: a systematic review. *Clin Mol Allergy*. 2016;14: 12.
6. Wang XD, Zheng M, Lou HF, Wang CS, Zhang Y, Bo MY, Ge SQ, Zhang N, Zhang L, Bachert C. An increased prevalence of self-reported allergic rhinitis in major Chinese cities from 2005 to 2011. *Allergy*. 2016; 71(8):1170–1180.
7. Gilles S, Akdis C, Lauener R, Schmid-Grendelmeier P, Bieber T, Schäppi G, Traidl-Hoffmann C. The role of environmental factors in allergy: A critical reappraisal. *Exp Dermatol*. 2018; 27(11):1193–1200.
8. Owens J. Classification and epidemiology of childhood sleep disorders. *Prim Care*. 2008; 35(3):533–46.
9. Wang X, Gao X, Yang Q, Wang X, Li S, Jiang F, Zhang J, Ouyang F. Sleep disorders and allergic diseases in Chinese toddlers. *Sleep Med*. 2017; 37:174–179.
10. Kozyrskyj AL, Kendall GE, Zubrick SR, Newnham JP, Sly PD. Frequent nocturnal awakening in early life is associated with nonatopic asthma in children. *Eur Respir J*. 2009; 34(6):1288–95.
11. Nilsson L, Castor O, Löfman O, Magnusson A, Kjellman NI. Allergic disease in teenagers in relation to urban or rural residence at various stages of childhood. *Allergy*. 1999; 54(7): 716–21.
12. Vardavas CI, Hohmann C, Patelarou E, Martinez D, Henderson AJ, Granell R, Sunyer J, Torrent M, Fantini MP, Gori D, et al. The independent role of prenatal and postnatal exposure to active and passive smoking on the development of early wheeze in children. *Eur Respir J*. 2016; 48(1):115–24.
13. Hill DL, Carr EJ, Rutishauser T, Moncunill G, Campo JJ, Innocentin S, Mpina M, Nhabomba A, Tumbo A, Jairoce C, et al. Immune system development varies according to age, location, and anemia in African children. *Sci Transl Med*. 2020; 12(529): eaaw9522.
14. Capital Institute of Pediatrics, The Coordinating Study Group of Nine Cities on the Physical Growth and Development of Children. A national survey on physical growth and development of children under seven years of age in nine cities of China in 2015. *Zhonghua Er Ke Za Zhi*. 2018; 56(3):192–199.
15. Zong XN, Li H, Zhu ZH. Secular Trends in Height and Weight for Healthy Han Children Aged 0-7 Years in China, 1975–2005. *Am J Hum Biol*. 2011; 23(2):209–15.
16. Ye W. Cluster random sampling in population survey. *Renkou Yanjiu*. 1983; 29(6): 51.
17. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhino conjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. *Lancet*. 1998; 351(9111):1225–32.
18. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989; 28(2): 193–213.
19. Hirshkowitz M, Whiton K, Albert SM, Alessi C, Bruni O, DonCarlos L, Hazen N, Herman J, Hillard PJA, Katz ES, et al. National Sleep Foundation's updated sleep duration recommendations: final report. *Sleep Health*. 2015; 1(4):233–243.
20. Kohyama J, Shiiki T, Hasegawa T. Sleep duration of young children is affected by nocturnal sleep onset time. *Pediatr Int*. 2000; 42(5):589–91.
21. Liu S, Zhang J, Ma J, Shang Y, Ma Y, Zhang X, Wang S, Yuan Y, Deng X, Niu W, et al. Synergistic interaction between bedtime and eating speed in predicting overweight and obesity in Chinese preschool-aged children. *Aging (Albany NY)*. 2019; 11(7):2127–2137.
22. National Sleep Foundation. Sleep in America Poll 2004. Available from: <https://www.sleepfoundation.org/professionals/sleep-america-polls/2004-children-and-sleep>.
23. Yao TC, Ou LS, Yeh KW, Lee WI, Chen LC, Huang JL, PATCH Study Group. Associations of age, gender, and BMI with prevalence of allergic diseases in children: PATCH study. *J Asthma*. 2011; 48(5):503–10.
24. Bisanti L, Russo A, Migliore E, Galassi C, Caranci N, Mirabelli D, Agabiti N, Dell'Orco V, Armenio L, Gruppo Collaborativo SIDRIA-2. Respiratory and allergic disorders in children: differences in socio-economic status. *Epidemiol Prev*. 2005; 29,32–5.

25. The National Bureau of Statistics of China. Basic Condition of urban households by Income _Percentile. Available from: <http://data.stats.gov.cn/english/easyquery.htm?cn=C01>.
26. Chen F, Lin Z, Chen R, Norback D, Liu C, Kan H, Deng Q, Huang C, Hu Y, Zou Z, et al. The effects of PM_{2.5} on asthmatic and allergic diseases or symptoms in preschool children of six Chinese cities, based on China, Children, Homes and Health (CCHH) project. *Environ Pollut*. 2018; 232: 329–337.
27. Neuman A, Bergström A, Gustafsson P, Thunqvist P, Andersson N, Nordvall L, Kull I, Wickman M. Infant wheeze, comorbidities and school age asthma. *Pediatr Allergy Immunol*. 2014; 25(4): 380–6.
28. Morais-Almeida M, Santos N, Pereira AM, Branco-Ferreira M, Nunes C, Bousquet J, Fonseca JA. Prevalence and classification of rhinitis in preschool children in Portugal: a nationwide study. *Allergy*. 2013; 68(10):1278–88.
29. Miller Ek, Avila PC, Kan YW, Word CR, Pelz BJ, Papadopoulos NG, Peebles RS, Heymann PW, Microbes, Allergy, and Asthma Committee. Wheezing exacerbations in early childhood: evaluation, treatment, and recent advances relevant to the genesis of asthma. *J Allergy Clin Immunol Pract*. 2014; 2(5): 537–43.
30. Jernelöv S, Lekander M, Almqvist C, Axelsson J, Larsson H. Development of atopic disease and disturbed sleep in childhood and adolescence—a longitudinal population-based study. *Clin Exp Allergy*. 2013; 43(5):552–9.
31. Tsai JC, Chou KR, Tsai HT, Yen YC, Niu SF. Effects of Nocturnal Sleep Quality on Diurnal Cortisol Profiles and Attention in Nurses: A Cross-Sectional Study. *Biol Res Nurs*. 2019; 21(5): 510–518.
32. Vargas I, Lopez-Duran N. The cortisol awakening response after sleep deprivation: Is the cortisol awakening response a “response” to awakening or a circadian process? *J Health Psychol*. 2020; 25(7):900–912.
33. Kohyama J. Late nocturnal sleep onset impairs a melatonin shower in young children. *Neuro Endocrinol Lett*. 2002; 23(5-6): 385–6.
34. Huang CT, Chiang RP, Chen CL, Tsai YJ. Sleep deprivation aggravates median nerve injury-induced neuropathic pain and enhances microglial activation by suppressing melatonin secretion. *Sleep*. 2014; 37(9):1513–23.
35. Fidan V, Alp HH, Gozeler M, Karaaslan O, Binay O, Cingi C. Variance of melatonin and cortisol rhythm in patients with allergic rhinitis. *Am J Otolaryngol*. 2013; 34(5): 416–9.
36. Kroll JL, Brown ES, Ritz T. Cortisol awakening response and fractional exhaled nitric oxide in asthma. *Clin Exp Allergy*. 2019; 49(8):1150–1153.
37. Shin IS, Park JW, Shin NR, Jeon CM, Kwon OK, Kim JS, Kim JC, Oh SR, Ahn KS. Melatonin reduces airway inflammation in ovalbumin-induced asthma. *Immunobiology*. 2014; 219(12): 901–8.
38. Lebold KM, Jacoby DB, Drake MG. Inflammatory mechanisms linking maternal and childhood asthma. *J Leukoc Biol*. 2020; 108(1): 113–121.
39. Tufvesson E, Aronsson D, Ankerst J, George SC, Bjerner L. Peripheral nitric oxide is increased in rhinitic patients with asthma compared to bronchial hyperresponsiveness. *Respir Med*. 2007; 101(11): 2321–6.
40. Hestetun I, Svendsen MV, Oellingrath IM. Sleep problems and mental health among young Norwegian adolescents. *Nord J Psychiatry*. 2018; 72(8):578–585.