Associations of sleep problems with asthma and allergic rhinitis among Chinese preschoolers

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The aim of this study was to examine the associations of sleep problems with asthma and allergic rhinitis among Chinese preschoolers. This cross-sectional survey was conducted in Guangzhou, China. Children aged 3–6 years were recruited from 32 kindergartens in 7 administrative districts. Asthma, allergic rhinitis and sleep problems were evaluated using a valid questionnaire. Binary logistic regression models were employed to estimate the odds ratios (OR) and 95% confidence intervals (CI) for the associations of asthma and allergic rhinitis with short sleep duration, late bedtime and frequent nocturnal awakening. We included 4876 preschool children in the current analysis. Of these, 182 (3.7%) diagnosed as asthma, and 511 (10.5%) diagnosed as allergic rhinitis. Frequent nocturnal awakening was associated with asthma and allergic rhinitis, with adjusted OR were 1.49 (95% CI 1.05–2.13) and 1.59 (95% CI 1.27–1.99), respectively. Subgroup analysis showed the OR for frequent nocturnal awakening with asthma was higher in girls (1.68; 95% CI 1.02–2.78) than in boys (1.35; 95% CI 0.81–2.24), but the OR for frequent nocturnal awakening with allergic rhinitis were similar in girls (1.73; 95% CI 1.15–2.30) and boys (1.57; 95% CI 1.17–2.12). No significant associations of short sleep duration and late bedtime with asthma or allergic rhinitis were identified. Our data suggested that frequent nocturnal awakening was associated with asthma and allergic rhinitis among preschoolers, and the association of frequent nocturnal awakening with asthma differed by gender. Further studies are warranted to address the causal relationship between nocturnal awakening and asthma and allergic rhinitis.

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

Allergic respiratory diseases (ARDs), primarily asthma and allergic rhinitis, are attracting important clinical and public concerns all over the world. Globally, asthma and allergic rhinitis affect 4–10% and 10–30% of the whole population1, respectively. Among children, the prevalence of ARDs is disparate across regions and countries, but the overall prevalence increases year by year2–4. ARDs not only increase health and care costs, but also reduce the life quality of sufferers5,6, calling for more preventive measures to minimize its detriment fundamentally.

ARDs are associated with a broad range of environmental factors and lifestyles other than genetic factors7, which are not fully understood. Recently, associations between sleep problems and ARDs have gained increasing attentions. Sleep problems, such as difficulty in settling to sleep, nocturnal awakening, irregular sleep patterns and short sleep duration are common in children. Approximately 25% of children experienced some forms of sleep problems during childhood8. To date, several studies have examined the associations between sleep problems and ARDs. However, few studies have been conducted among pre-school age children9,10. Previous studies have suggested that residency in urban areas, prenatal smoking and passive smoking are associated with an increased risk of wheezing and asthma11–13, but most available studies on sleep problems and ARDs have not adjusted for such confounders. Therefore, the associations of sleep problems with asthma and allergic rhinitis among preschoolers, and the association of frequent nocturnal awakening with asthma differed by gender. Further studies are warranted to address the causal relationship between nocturnal awakening and asthma and allergic rhinitis.

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among pre-school aged children remains unclear. It is of substantial importance to identify the associations among pre-school age children, as this is a critical period for developing the physique and immune system and forming a healthy lifestyle, including developing good sleep habits10,24.

We hypothesized that sleep problems, including frequent nocturnal awakening, short sleep duration and late bedtime are associated with ARDs even after controlling for potential confounders.

Methods

Study design and participants. This study was a part of the National Survey on Physical Growth and Development of Children in nine cities of China (NSPGDC), which used the identical methodology to collect data to monitor growth and development of children aged 0–6 years15. The study design, organization, and implementation of the NSPGDC have been published previously16. 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 sub-group) for both urban and rural areas was employed to produce a random sample17. 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, serious diseases (such as serious congenital cardiopathy, serious hepatopathy and nephrosis, neurological disease), and malnourished and physically handicapped.

We conducted the NSPGDC in Guangzhou between July and October in 2015. Because we aimed to explore the associations of sleep problems with asthma and allergic rhinitis among preschool children, a subgroup of children aged between 3 and 6 years who participated in the NSPGDC of Guangzhou were included in the analysis. Using a random cluster sampling, we recruited 5102 children aged 3 to 6 years from 16 kindergartens in urban administrative districts (Yuexiu, Liwan and Haizhu), and 16 kindergartens in rural administrative districts (Conghua, Huadu, Panyu and Baiyun) of Guangzhou. There were 18 children declined to participate in this survey and 217 children submitted an incomplete questionnaire with missing data of >15%. Therefore, the remaining 4867 children aged 3 to 6 years old were included for analysis. The response rate was 95.4% (4867/5102). Data were collected by local trained physicians using a structured questionnaire, which included participants’ demographic characteristics, mother’s health conditions during pregnancy, delivery mode, feeding patterns in the first 6 months, sleep problems and ARDs of the participants. Body weight and height were also measured by calibrated instruments and standard specifications, and body mass index (BMI) was calculated by dividing the weight in kilogram (kg) by the square of length in meters (m). Age and sex specific BMI z-score was calculated according to the Chinese standard18.

Measurement. Asthma and allergic rhinitis were defined as having current symptoms and physician diagnosis19. Current symptoms of asthma and allergic rhinitis were assessed by the questions derived from 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?”)20. Information on diagnosis of asthma and allergic rhinitis were obtained by the questions of “Has your baby had ever been diagnosed with asthma by the doctor?” and “Has your baby had ever been diagnosed with allergic rhinitis by the doctor?”.

We assessed sleep duration, usual bedtime and nocturnal awakening frequency in 2 weeks preceding to the survey, using the questions derived from the Chinese version of the Children’s Sleep Habits Questionnaire (CSHQ)20. Sleep duration was assessed based on the following question “What is your child’s usual amount of sleep each day (combining nighttime sleep and naps)”. According to the National Sleep Foundation’s recommendation, preschoolers (3–6 years) who slept for less than 10 h were defined as short sleep duration21. Bedtime was assessed by the question “What is your child’s usual bedtime?”. As the 75 percentiles of bedtime among 3 to 6 aged children was 22:00, the bedtime was classified into 2 groups: at or before 22:00 and after 22:00, and bedtime later than 22:00 was considered as late bedtime. The nocturnal awakening frequency was assessed by the question “What is your child’s number of wake-up times during the night?”, and classified into 2 groups: none or seldom, and once or more per night. According to the previous study by the National Sleep Foundation22, children who wakened once or more per night among preschoolers (3–6 years) were defined as frequent nocturnal awakening.

Previous studies suggested a broad range of demographic characteristics and environmental factors that were associated with asthma and allergic rhinitis9,10,23,24. Therefore, we adjusted for these potential confounders, which was distributed differently according to the allergic disease in our analysis, including resident area, age, gender, mother’s education, BMI z-score of children, delivery mode, birth weight, maternal tobacco exposure during pregnancy, and feeding patterns in the first 6 months.

Ethics declarations. The study was approved by the Ethical Committee for Biomedical Research in Guangzhou Women and Children’s Medical Center, and was conducted in accordance with Helsinki Declaration and Ethical Guidelines for Research Involving Human Participants. A written informed consent was obtained from all the participants’ parents before starting of the survey.

Statistical analysis. Mean and standard deviation were reported for continuous variables. Frequencies and percentages 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 the associations of asthma and allergic rhinitis with short sleep duration, late bedtime and frequent nocturnal awakening, respectively. In each logistic regression model, three models were fitted.
In model 1, we estimated the crude ORs. In model 2, we adjusted for demographic characteristics, included region (urban/rural), gender (boys/girls), age, mother’s educational level (college or above/senior high school/junior high school or below) and BMI z-score (continuous data). In model 3, we additionally adjusted for delivery mode (vaginal delivery/cesarean delivery), birth weight (< 2500 g/2500–3900 g/≥ 4000 g), maternal tobacco exposure (smoking or passive smoking) during pregnancy, feeding patterns in the first 6 months of the children (breastfeeding/artificial feeding/mixed feeding), passive smoking (yes/no).

We further conducted subgroup analysis to examine the gender influence on the associations of asthma/allergic rhinitis with frequent nocturnal awakening where significant associations were found. In subgroup analysis, we adjusted for the covariates as we did in model 3. Missing data of continuous covariates was inputted based on means and categorical covariates was inputted by the median. Significance level was set at $P < 0.05$.

To reduce the potential type I error due to multiple comparisons in subgroup analyses, significance level was adjusted using the Bonferroni method, and all tests were 2-sided. Statistical analyses were conducted using SPSS Statistics, version 25.0 (IBM Corp).

**Results**

**Participants’ characteristics.** We included 4867 children in the current analysis. Of them, 2518 (51.7%) were boys and 2383 (49.0%) were from the urban areas. The mean age of the participants was 4.28 ± 1.05 years. Other characteristics of the participants were summarized in Table 1. Overall, 182 (3.7%) participants were diag-

| Characteristics | Total (n = 4867) | Asthma (n = 182) | No (n = 4685) | Allergic rhinitis (n = 511) | No (n = 4356) |
|-----------------|-----------------|-----------------|---------------|-----------------|-------------|
| Region          | Urban           | 2383 (49.0)     | 103 (56.6)*   | 2280 (48.7)     | 283 (55.4)* | 2100 (48.2) |
|                 | Rural           | 2484 (51.0)     | 79 (43.4)     | 2405 (51.3)     | 228 (44.6)  | 2256 (51.8) |
| Gender          | Boys            | 2518 (51.7)     | 93 (51.1)     | 2425 (51.8)     | 300 (58.7)* | 2218 (50.9) |
|                 | Girls           | 2349 (48.3)     | 89 (48.9)     | 2260 (48.2)     | 211 (41.3)  | 2138 (49.1) |
| Age             | 3 years         | 1448 (29.8)     | 58 (31.9)     | 1390 (29.7)     | 124 (24.3)* | 1324 (30.4) |
|                 | 4 years         | 1381 (28.4)     | 56 (30.8)     | 1325 (28.3)     | 144 (28.2)  | 1237 (28.4) |
|                 | 5 years         | 1273 (26.2)     | 49 (26.9)     | 1224 (26.1)     | 161 (31.5)  | 1112 (25.5) |
|                 | 6 years         | 765 (15.7)      | 19 (10.4)     | 746 (15.9)      | 82 (16.0)   | 683 (15.7)  |
| Ethnicity       | Han             | 4767 (97.9)     | 178 (97.8)    | 4589 (98.0)     | 503 (98.4)  | 4264 (97.9) |
|                 | Others          | 100 (2.1)       | 4 (2.2)       | 96 (2.0)        | 8 (1.6)     | 92 (2.1)    |
| Mother’s educational level | College or above | 3205 (65.9) | 133 (73.1) | 3072 (65.6) | 374 (73.2)* | 2831 (65.0) |
|                 | Senior high school | 1063 (21.8) | 29 (15.9) | 1034 (22.1) | 83 (16.2) | 980 (22.5) |
|                 | Junior high school or below | 599 (12.3) | 20 (11.0) | 579 (12.4) | 54 (10.6) | 545 (12.5) |
| Mother’s occupation | Farmers | 36 (0.7)  | 0 (0)   | 36 (0.8)  | 6 (1.2)  | 30 (0.7)  |
|                 | Workers         | 1467 (30.1)     | 65 (35.7)     | 1402 (29.9)     | 151 (29.5)  | 1316 (30.2) |
|                 | Servicer        | 977 (20.1)      | 33 (18.1)     | 944 (20.1)      | 106 (20.7)  | 871 (20.0)  |
|                 | Others          | 2387 (49.0)     | 84 (46.2)     | 2303 (49.2)     | 248 (48.5)  | 2139 (49.1) |
| Family annual income (RMB) | < 50,000 | 567 (11.6) | 15 (8.2) | 5523 (11.8) | 58 (11.4) | 509 (11.7) |
|                 | ~ 100,000       | 1262 (25.9)     | 46 (25.3)     | 1216 (26.0)     | 125 (24.5)  | 1137 (26.1) |
|                 | ~ 300,000       | 2292 (47.1)     | 89 (48.9)     | 2203 (47.0)     | 263 (51.5)  | 2029 (46.6) |
|                 | > 300,000       | 746 (15.3)      | 32 (17.6)     | 714 (15.2)      | 65 (12.7)   | 681 (15.6)  |
| Delivery methods | Vaginal delivery | 2587 (53.2) | 94 (51.6) | 2493 (53.2) | 249 (48.7)* | 2338 (53.7) |
|                 | Caesarean delivery | 2280 (46.8) | 88 (48.4) | 2192 (46.8) | 262 (51.3) | 2018 (46.3) |
| Preterm birth   | Yes             | 134 (2.8)       | 9 (4.9)       | 125 (2.7)       | 19 (3.7)    | 115 (2.6)  |
|                 | No              | 4733 (97.2)     | 173 (95.1)    | 4560 (97.3)     | 492 (96.3)  | 4241 (97.4) |
| Birth weight (g) | < 2500 | 74 (1.5) | 5 (2.7)* | 69 (1.5) | 9 (1.8) | 65 (1.5) |
|                 | 2500–3999       | 4610 (94.7)     | 173 (95.1)    | 4437 (94.7)     | 489 (95.7)  | 4121 (94.6) |
|                 | ≥ 4000          | 183 (3.8)       | 4 (2.2)       | 179 (3.8)       | 13 (2.5)    | 170 (3.9)  |
| Feeding patterns in the first 6 months | Breastfeeding | 1585 (32.6) | 45 (24.7) | 1540 (32.9) | 37 (26.8)* | 1448 (33.2) |
|                 | Artificial feeding | 873 (17.9) | 33 (18.17) | 840 (17.9) | 101 (19.8) | 772 (17.7) |
|                 | Mixed feeding   | 2409 (49.5)     | 104 (57.1)    | 2305 (49.2)     | 273 (53.4)  | 2136 (49.0) |
| Maternal tobacco exposure during pregnancy | Yes | 1694 (34.8) | 76 (41.8)* | 1618 (34.5) | 194 (38.0) | 1500 (34.4) |
|                 | No              | 3173 (65.2)     | 106 (58.2)    | 3067 (65.5)     | 317 (62.0)  | 2856 (56.6) |
| Passive smoking of children | Yes | 1969 (40.5) | 82 (45.1) | 1887 (46.0) | 215 (42.1) | 1754 (40.3) |
|                 | No              | 2898 (59.5)     | 100 (54.9)    | 2798 (59.7)     | 296 (57.9)  | 2602 (59.7) |
| Children’s BMI z-score | 0.09 ± 0.98 | 0.14 ± 0.97 | 0.09 ± 0.98 | 0.03 ± 0.92 | 0.10 ± 0.99 |
rhinitis was 7.3% Bloom et al.’s research in UK showed the prevalence of preschool wheeze requiring attendance for allergy and sinus symptoms was 3–5% and the prevalence of physician-diagnosed asthma was 4.6%, and 11.8% for the physician-diagnosed allergic rhinitis27. Deng et al.’s research in Changsha in China exhibited the prevalence of ever doctor-diagnosed allergic rhinitis was 10.5% respectively. The findings also suggested that frequent nocturnal awakening but not short sleep duration was significantly associated with asthma and allergic rhinitis. However, these associations of sleep problems with asthma and allergic rhinitis among children aged 3–6 years in Guangzhou were not found (Table 2 and Model 1 in Table 3). However, significant association was only found between frequent nocturnal awakening and allergic rhinitis after adjusted for potential confounders (Table 3). In the fully adjusted models, the significant associations of sleep problems with asthma and allergic rhinitis remained consistent. Of the 4867 children included, 292 (6.0%) had a short sleep duration. Among the children who diagnosed as asthma, 10 (5.5%) had a short sleep duration; while among the children without asthma, 282 (6.0%) had a short sleep duration. No significant association between short sleep duration and asthma was found (Table 2). There were 976 (20.1%) participants went to sleep after 22:00. Among the children with asthma, 41 (22.5%) had late bedtime, while in the group without asthma diagnosis, 935 (20.0%) went to sleep lately. There was also no significant association between late bedtime and asthma (Table 2). There were 816 (16.8%) participants who had frequent nocturnal awakening, of whom 42 (8.0%) had short sleep duration, 120 (23.1%) had late bedtime, and 116 (22.7%) had frequent nocturnal awakening, respectively. Significant associations between short sleep duration, late bedtime, frequent nocturnal awakening and allergic rhinitis were found among boys but not among girls (Table 4).

Association between sleep problems and asthma. Of the 4867 children included, 292 (6.0%) had a short sleep duration. Among the children who diagnosed as asthma, 10 (5.5%) had a short sleep duration; while among the children without asthma, 282 (6.0%) had a short sleep duration. No significant association between short sleep duration and asthma was found (Table 2). There were 976 (20.1%) participants went to sleep after 22:00. Among the children with asthma, 41 (22.5%) had late bedtime, while in the group without asthma diagnosis, 935 (20.0%) went to sleep lately. There was also no significant association between late bedtime and asthma (Table 2). There were 816 (16.8%) participants who had frequent nocturnal awakening, of whom 42 (8.0%) had short sleep duration, 120 (23.1%) had late bedtime, and 116 (22.7%) had frequent nocturnal awakening, respectively. Significant associations between short sleep duration, late bedtime, frequent nocturnal awakening and allergic rhinitis were found among boys but not among girls (Table 4).

Association between sleep problems and allergic rhinitis. Among participants diagnosed with allergic rhinitis, 41 (8.0%) had short sleep duration, 120 (23.1%) had late bedtime, and 116 (22.7%) had frequent nocturnal awakening; while among participants without allergic rhinitis diagnosis, 251 (5.8%) had short sleep duration, 856 (19.7%) had a late bedtime, and 700 (16.1%) had frequent nocturnal awakening, respectively. Significant associations between short sleep duration, late bedtime, frequent nocturnal awakening and allergic rhinitis were found among girls but not among boys (Table 4).

Discussion

In this study, we used a representative citywide survey data, which was part of the NSPGDC, to investigate the associations of sleep problems with asthma and allergic rhinitis among children aged 3–6 years in Guangzhou. The results revealed the prevalence of asthma and allergic rhinitis among preschool children were 3.7%, and 10.5% respectively. The findings also suggested that frequent nocturnal awakening but not short sleep duration and late bedtime, was significantly associated with asthma and allergic rhinitis. However, these associations of frequent nocturnal awakening and asthma differed by gender.

The prevalence of asthma and allergic rhinitis among preschool children was consistent with previous studies. For example, Deng et al.’s research in Beijing among preschool children revealed the prevalence of doctor-diagnosed childhood asthma was 2.8%36. Similarly, Pereira et al. conducted a study in Portuguese children aged 3–5 years and the prevalence of physician-diagnosed asthma was 4.6%, and 11.8% for the physician-diagnosed allergic rhinitis37. Deng et al.’s research in Changsha in China exhibited the prevalence of ever doctor-diagnosed allergic rhinitis was 7.3%38. Bloom et al.’s research in UK showed the prevalence of preschool wheeze requiring attendance to a physician in 2017 was 7.7%, but only one fifth of the preschool children with wheeze received an asthma diagnosis39. However, in six representative cities in China, the average prevalence of asthma and allergic rhinitis among preschool children were higher than ours, with 8.0% for asthma and 16.6% for allergic rhinitis, respectively40. Previously, regional difference in the prevalence of asthma and allergic rhinitis were found40, and

**Table 2. Frequency and proportion of sleep problems by asthma and allergic rhinitis.**

| Sleep problems | Total (N = 4867) | Asthma (n/%) | Allergic rhinitis (n/%) |
|----------------|-----------------|--------------|------------------------|
|                | Yes (N = 182)   | No (N = 4685)| Yes (N = 511)          | No (N = 4356) |
| Short sleep duration | 4575 (94.0) | 172 (94.5) | 4403 (94.0) | 0.09 | 0.77 | 470 (92.0) | 4105 (94.2) | 4.15 | 0.04 |
| Yes | 292 (6.0) | 10 (5.5) | 282 (6.0) | 41 (8.0) | 251 (5.8) |
| Late bedtime | 3891 (19.9) | 141 (77.5) | 3750 (80.0) | 0.72 | 0.40 | 391 (76.5) | 3500 (80.3) | 4.19 | 0.04 |
| Yes | 976 (20.1) | 41 (22.5) | 935 (20.0) | 120 (23.5) | 856 (19.7) |
| Frequent nocturnal awakening | 4051 (83.2) | 140 (76.9) | 3911 (83.5) | 5.40 | 0.02 | 395 (77.3) | 3656 (83.9) | 14.41 | < 0.001 |
| Yes | 816 (16.8) | 42 (23.1) | 774 (16.5) | 116 (22.7) | 700 (16.1) |
### Table 3. Association of sleep problems with asthma or allergic rhinitis among per-school children. *Model 1: Unadjusted. *Model 2: Adjusted for region, gender, age, mother’s educational level, and BMI z-score. *Model 3: Additionally adjusted for delivery mode, birth weight, and maternal tobacco exposure during pregnancy, feeding pattern before 6 months.

| Sleep problems and asthma |  |  |  |
|---------------------------|---|---|---|
| Short sleep duration      |  |  |  |
| No                        | 1 (Ref) | 1 (Ref) | 1 (Ref) |
| Yes                       | 0.91 (0.47–1.74) | 0.770 | 0.940 | 0.95 (0.49–1.84) | 0.867 |
| Late bedtime              |  |  |  |
| No                        | 1 (Ref) | 1 (Ref) | 1 (Ref) |
| Yes                       | 1.17 (0.82–1.66) | 0.396 | 1.12 (0.78–1.60) | 0.535 | 1.11 (0.78–1.58) | 0.574 |
| Frequent nocturnal awakening |  |  |  |
| No                        | 1 (Ref) | 1 (Ref) | 1 (Ref) |
| Yes                       | 1.52 (1.07–2.16) | 0.021 | 1.50 (1.05–2.13) | 0.026 | 1.49 (1.05–2.13) | 0.028 |

| Sleep problems and allergic rhinitis |  |  |  |
|--------------------------------------|---|---|---|
| Short sleep duration                 |  |  |  |
| No                                   | 1 (Ref) | 1 (Ref) | 1 (Ref) |
| Yes                                  | 1.43 (1.01–2.01) | 0.043 | 1.26 (0.89–1.80) | 0.197 | 1.23 (0.86–1.76) | 0.247 |
| Late bedtime                         |  |  |  |
| No                                   | 1 (Ref) | 1 (Ref) | 1 (Ref) |
| Yes                                  | 1.26 (1.01–1.56) | 0.041 | 1.25 (1.01–1.56) | 0.045 | 1.24 (0.99–1.54) | 0.056 |
| Frequent nocturnal awakening         |  |  |  |
| No                                   | 1 (Ref) | 1 (Ref) | 1 (Ref) |
| Yes                                  | 1.53 (1.23–1.91) | <0.001 | 1.59 (1.27–1.99) | <0.001 | 1.59 (1.27–1.99) | <0.001 |

### Table 4. Association between frequent nocturnal awakening and asthma according to gender. Model a: Unadjusted. Model b: Adjusted for region, age, mother’s educational level, BMI z-score, delivery mode, birth weight, maternal tobacco exposure during pregnancy, feeding pattern before 6 months.

| Frequent nocturnal awakening | No. of asthma | Model a |  | Model b |  |
|-----------------------------|---------------|---------|---|---------|---|
|                             |               | OR (95% CI) | P | OR (95% CI) | P |
| Boy                         |               |         |   |         |   |
| No (N = 2086)               | 73 (3.5)      | 1 (Ref) | 0.259 | 1.35 (0.81–2.24) | 0.253 |
| Yes (N = 432)               | 20 (4.6)      | 1.34 (0.81–2.22) |  | 1.35 (0.81–2.24) | 0.253 |
| Girl                        |               |         |   |         |   |
| No (N = 1965)               | 67 (3.4)      | 1 (Ref) | 0.031 | 1.68 (1.02–2.78) | 0.042 |
| Yes (N = 384)               | 22 (5.7)      | 1.72 (1.05–2.82) |  | 1.68 (1.02–2.78) | 0.042 |

### Table 5. Association between frequent nocturnal awakening and allergic rhinitis according to gender. Model a: Unadjusted. Model b: Adjusted for region, age, mother’s educational level, BMI z-score, delivery mode, birth weight, maternal tobacco exposure during pregnancy, feeding pattern before 6 months.

| Frequent nocturnal awakening | No. of allergic rhinitis | Model a |  | Model b |  |
|------------------------------|--------------------------|---------|---|---------|---|
|                             |                          | OR (95% CI) | P | OR (95% CI) | P |
| Boy                         |                          |         |   |         |   |
| No (N = 2086)               | 232 (11.1)               | 1 (Ref) | 0.007 | 1.57 (1.17–2.12) | 0.003 |
| Yes (N = 432)               | 68 (15.7)                | 1.49 (1.11–2.00) |  | 1.57 (1.17–2.12) | 0.003 |
| Girl                        |                          |         |   |         |   |
| No (N = 1965)               | 163 (8.3)                | 1 (Ref) | 0.009 | 1.73 (1.15–2.30) | 0.006 |
| Yes (N = 384)               | 48 (12.5)                | 1.58 (1.12–2.22) |  | 1.73 (1.15–2.30) | 0.006 |
our result was consisted with the Urumqi’s prevalence, showing prevalence of 3.5% for asthma and 10.9% for allergic rhinitis. The discrepancies might be related to different characteristics of study participants (residence, ethnicity), apart from the different measurements for asthma and allergic rhinitis. Besides, the under-diagnosis of asthma among Chinese children, which is commonly not adjusted in previous studies, making our results more robust. Additionally, there were few studies that explored the associations of sleep problems with asthma and allergic rhinitis among Chinese preschool children in a large sample size, and there were no studies that explored the gender difference of the associations in community population.

There were several limitations in our study. First, asthma and allergic rhinitis were not determined by objective measures, rather than parents’ reported symptom from ISAAC and previous diagnosis. However, although weak, the objective measurement is highly recognized for its reliability and validity and was used in previous studies. 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. Third, although we have adjusted for various potential confounders, we did not adjust for family allergy history of the parents or mother’s stress, which may be driven by hormonal effect in school-age children. However, it is noticed that the sex difference of sex may be explained from two aspects. On one hand, the nocturnal awakening may be consequence of asthma or allergic rhinitis, as the airway inflammation and congestion or the nasal obstruction, may cause them to wake up frequently. There is evidence showing high prevalence of nocturnal awakening caused by asthma or allergic rhinitis among children. On the other hand, the frequent nocturnal awakening may increase risk of asthma or allergic rhinitis, which was demonstrated in a longitudinal study. The possible biological mechanism was as follow: first, frequent nocturnal awakening may increase the levels of pro-inflammatory cytokines and decrease the immunologic tolerance to allergen, shifting the balance between Th1 and Th2 towards an allergy related (Th2) pattern, which are known factors contributing to allergic diseases such as asthma and allergic rhinitis. Second, frequent nocturnal awakening could disrupt the regulation of the hypothalamic–pituitary–adrenal (HPA) axis and the circadian rhythms of melatonin, which showed blunted cortisol awakening response and lower cortisol levels and a decline in the level of melatonin, and increase the risk of asthma and rhinitis.

In summary, the association between frequent nocturnal awakening and asthma/allergic rhinitis might work in both directions. However, as our study was a cross-sectional study, we cannot ascribe causality of the association of frequent nocturnal awakening and asthma/allergic rhinitis further research to address the causal relationship between sleep problems and allergic diseases seems warranted.

In this study, we also found that the associations of frequent nocturnal awakening with asthma differed by gender, showing only associations in girls. Few studies have detected the gender difference of association between sleep problems and allergic disease among preschooler in community population, and our finding was consistent with the studies conducted in asthma patients. For example, Strunk et al. showed that night awakening caused by asthma was marginally less for males than females. Goldstein et al. also found that the association of asthma with sleep-disordered breathing was only significant in girls but not in boys. The gender differences may be driven by hormonal effect on school-age children. However, it is noticed that the sex difference of sex hormonal will not be significant, until the onset of puberty. Therefore, whether the explanation can be applied to preschoolers need further studies to verify.

Strengths and limitations. For this citywide cross-sectional study, we recruited 4867 representative participants from rural and urban in Guangzhou by using a well-designed protocol, which makes our results more generalized. In the analysis we have adjusted for several important confounders, such as region and maternal tobacco exposure during pregnancy, which were not adjusted in previous studies. Our findings suggested that frequent nocturnal awakening was associated with asthma and allergic rhinitis among Chinese preschool children and found that frequent nocturnal awakening was associated with asthma and allergic rhinitis, and the association of frequent nocturnal awakening with asthma differed by gender. The results suggested that pediatricians should consider evaluating sleep problems when appraising the consequence or modifiable factors of asthma and allergic rhinitis and developing good sleep habits may be beneficial for asthma and allergic rhinitis.
Conclusions
Findings from this well representative study suggested that frequent nocturnal awakening was associated with asthma and allergic rhinitis, and the association of frequent nocturnal awakening with asthma differed by gender. Further studies are warranted to address the causal relationship between nocturnal awakening and asthma and allergic rhinitis.

Data availability
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.

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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 72(9), 1306–1316 (2017).
2. Asher, M. I. et al. 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 368(9537), 733–743 (2006).
3. Korea Centers for Disease Control and Prevention. The Statistics of the 8th Korea Youth Risk Behavior Web-Based Survey (KYRBWS) in 2012 (Korea Centers for Disease Control and Prevention, 2012).
4. Huang, C. et al. Updated prevalence of asthma, allergy, and airway symptoms, and a systematic review of trends over time for childhood asthma in Shanghai, China. PLoS ONE 10(4), e0121577. https://doi.org/10.1371/journal.pone.0121577 (2015).
5. Linneberg, A. et al. Burden of allergic respiratory disease: A systematic review. Clin. Mol. Allergy 14, 12 (2016).
6. Wang, X. D. et al. An increased prevalence of self-reported allergic rhinitis in major Chinese cities from 2005 to 2011. Allergy 71(8), 1170–1180 (2016).
7. Gilles, S. et al. The role of environmental factors in allergy: A critical reappraisal. Exp. Dermatol. 27(11), 1193–1200 (2018).
8. Owens, J. Classification and epidemiology of childhood sleep disorders. Prim. Care 35(3), 533–546 (2008).
9. Wang, X. et al. Sleep disorders and allergic diseases in Chinese toddlers. Sleep Med. 37, 174–179 (2017).
10. Kozyrskyj, A. L., Kendall, G. E., Zubrick, S. R., Newnham, J. P. & Sly, P. D. Frequent nocturnal awakening in early life is associated with nonatopic asthma in children. Eur. Respir. J. 34(6), 1288–1295 (2009).
11. Nilsson, L., Castor, O., Löfman, O., Magnusson, A. & Kjellman, N. I. Allergic disease in teenagers in relation to urban or rural residence at various stages of childhood. Allergy 54(7), 716–721 (1999).
12. Vardavas, C. I. 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. 48(1), 115–124 (2016).
13. Zhou, Y. et al. Maternal tobacco exposure during pregnancy and allergic rhinitis in offspring: A systematic review and meta-analysis. Medicine (Baltimore) 100(34), e26986 (2021).
14. Hill, D. L. et al. Immune system development varies according to age, location, and anemia in African children. Sci. Transl. Med. 12(529), 9322 (2020).
15. 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 56(3), 192–199 (2018).
16. Zong, X. N., Li, H. & Zhu, Z. H. Secular trends in height and weight for healthy han children aged 0–7 years in China, 1975–2005. Am. J. Hum. Biol. 23(2), 209–215 (2011).
17. Ye, W. Cluster random sampling in population survey. Renhou Yanyu 29(6), 51 (1983).
18. Li, H. et al. Body mass index cut-offs for overweight and obesity in Chinese children and adolescents aged 2–18 years. Chin. J. Epidemiol. 31(6), 616–620 (2013).
19. Brøms, K., Norback, D., Sundelin, C., Eriksson, M. & Svärdsudd, K. A nationwide study of asthma incidence rate and its determinants in Swedish pre-school children. Eur. J. Epidemiol. 27(9), 695–703 (2012).
20. Li, S. H. et al. Development and psychometric properties of the Chinese version of children’s sleep habits questionnaire. Chin. J. Pediatr. 45(3), 176–180 (2007).
21. Hirshkowitz, M. et al. National Sleep Foundation’s updated sleep duration recommendations: Final report. Sleep Health 1(4), 233–243 (2015).
22. National Sleep Foundation. Sleep in America Poll 2004. Accessed 10 May 2022. https://www.thensf.org/wp-content/uploads/2021/03/2004-SIA-Findings.pdf.
23. Yao, T. C. et al. Associations of age, gender, and BMI with prevalence of allergic diseases in children: PATCH study. J. Asthma 48(3), 503–510 (2011).
24. Bisanti, L. et al. Respiratory and allergic disorders in children: Differences in socio-economic status. Epidemiol. Prev. 29, 32–35 (2005).
25. Bland, J. M. & Altman, D. G. Multiple significance tests: The Bonferroni method. BMJ 310(6973), 170 (1995).
26. Deng, X. et al. Factors associated with childhood asthma and wheeze in Chinese preschool-aged children. Front. Med. (Lausanne) 8, 742581 (2021).
27. Pereira, A. M. et al. Severity of rhinitis and wheezing is strongly associated in preschoolers: A population-based study. Pediatr. Allergy Immunol. 26(7), 618–627 (2015).
28. Deng, Q. et al. Early life exposure to traffic-related air pollution and allergic rhinitis in preschool children. Respir. Med. 121, 67–73 (2016).
29. Bloom, C. I., Franklin, C., Bush, A., Saglani, S. & Quint, J. K. Burden of preschool wheeze and progression to asthma in the UK: Population-based cohort 2007 to 2017. J. Allergy Clin. Immunol. 147(5), 1949–1958 (2021).
30. Chen, J. et al. The effects of PM2.5 on asthmatic and allergic diseases or symptoms in preschool children and the effects in six Chinese cities, based on China, Children, Homes and Health (CCHH) project. Environ. Pollut. 232, 329–337 (2018).
31. Jernelöv, S., Lekander, M., Almqvist, C., Axelsson, J. & Larsson, H. Development of atopic disease and disturbed sleep in childhood—A longitudinal population-based study. Clin. Exp. Allergy 43(5), 552–559 (2013).
32. Strunk, R. C., Sternberg, A. L., Bacharier, L. B. & Szefler, S. J. Nocturnal awakening caused by asthma in children with mild-to-moderate asthma in the childhood asthma management program. J. Allergy Clin. Immunol. 110(3), 395–403 (2002).
33. de Jong, C. C. M. et al. Diagnosis of asthma in children: The contribution of a detailed history and test results. Eur. Respir. J. 54(6), 1901326 (2019).
34. Leger, D., Bonnefoy, B., Pigereias, B., de La Giclais, B. & Chartier, A. Poor sleep is highly associated with house dust mite allergic rhinitis in adults and children. *Allergy Asthma Clin. Immunol.* 13, 36 (2017).
35. Tsai, J. C., Chou, K. R., Tsai, H. T., Yen, Y. C. & Niu, S. F. Effects of nocturnal sleep quality on diurnal cortisol profiles and attention in nurses: A cross-sectional study. *Biol. Res. Nurs.* 21(5), 510–518 (2019).
36. 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.* 25(7), 900–912 (2020).
37. Kobyama, J. Late nocturnal sleep onset impairs a melatonin shower in young children. *Neuro Endocrinol. Lett.* 23(5–6), 385–386 (2002).
38. Huang, C. T., Chiang, R. P., Chen, C. L. & Tsai, Y. J. Sleep deprivation aggravates median nerve injury-induced neuropathic pain and enhances microglial activation by suppressing melatonin secretion. *Sleep* 37(9), 1513–1523 (2014).
39. Fidan, V. et al. Variance of melatonin and cortisol rhythm in patients with allergic rhinitis. *Am. J. Otolaryngol.* 34(5), 416–419 (2013).
40. Kroll, J. L., Brown, E. S. & Ritz, T. Cortisol awakening response and fractional exhaled nitric oxide in asthma. *Clin. Exp. Allergy* 49(8), 1150–1153 (2019).
41. Lebold, K. M., Jacoby, D. B. & Drake, M. G. Inflammatory mechanisms linking maternal and childhood asthma. *J. Leukoc. Biol.* 108(1), 113–121 (2020).
42. Tuftsone, E., Aronsone, D., Ankerst, J., George, S. C. & Bjermer, L. Peripheral nitric oxide is increased in rhinitic patients with asthma compared to bronchial hyperresponsiveness. *Respir. Med.* 101(11), 2321–2326 (2007).
43. Goldstein, N. A. et al. The prevalence of sleep-disordered breathing in children with asthma and its behavioral effects. *Pediatr. Pulmonol.* 50(11), 1128–1136 (2015).
44. Santos, C., Moreira, G., Togete, S. M. & Tufik, S. Gender and asthma-severity differences in sleep disordered breathing in children with asthma. *Pediatr. Pulmonol.* 51(1), 89–90 (2016).
45. Elmlinger, M. W., Kuhnel, W. & Ranke, M. B. Reference ranges for serum concentrations of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E2), prolactin, progesterone, sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS), cortisol and ferritin in neonates, children and young adults. *Clin. Chem. Lab. Med.* 40(11), 1151–1160 (2002).
46. 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* 351(9115), 1225–1232 (1998).
47. Huang, M. M., Qian, Z., Wang, J., Vaughn, M. G. & Lee, Y. L. Validation of the sleep disturbance scale for children and prevalence of parent-reported sleep disorder symptoms in Chinese children. *Sleep Med.* 15(6), 923–928 (2014).

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Author contributions

Y.M. participated in the conceptualization of this study, acquisition of data, statistical analyses and drafted the main manuscript. J.T. participated in the statistical analyses and interpretation analyses and review the manuscript. Y.Q.W.: participated in the statistical analyses and interpretation analyses and revised the manuscript. Y.H.: participated in statistical analyses. Y.J.L. participated in data clean and interpretation analyses. Y.Y.S. participated in the acquisition of data.

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Competing interests

The authors declare no competing interests.

Additional information

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