ORIGINAL RESEARCH

Association of Parasomnia Symptoms with Risk of Childhood Asthma and the Role of Preterm Birth

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Purpose: To examine whether parasomnia symptoms are associated with increased odds of childhood asthma and wheeze, and the role of preterm birth.

Patients and Methods: The Shanghai Children's Allergy Study was cross-sectionally conducted in 31 kindergartens and 17 primary schools in Shanghai, China. After excluding the missing data of gestational week and child's age, this study included a total of 16,487 individuals with a mean age of 7.74 years and 52.4% of males. The association between parasomnia symptoms and wheeze/asthma was assessed by univariate and multivariate analyses. The interaction effects of parasomnias and preterm birth were primarily evaluated by P for multiplicative interaction, and the relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP), and synergy index (SI) were also measured.

Results: Parasomnias, especially rapid eye movement (REM) parasomnia symptoms, were associated with an increased risk of childhood wheeze/asthma, and the interaction between parasomnia and preterm birth exhibited an excess risk of current wheeze (RERI, 1.43; 95% CI, 0.41–2.45) and ever asthma (RERI, 0.75; 95% CI, 0.01–1.50). In the stratification analyses, the combination of parasomnia symptoms and preterm birth had higher odds of wheeze/asthma. And the odds of current wheeze (OR, 4.55; 95% CI, 1.69–12.25; *p*=0.003) and ever asthma (OR, 6.17; 95% CI, 2.36–16.11; *p*<0.001) were much higher in cumulative parasomnia symptoms plus very preterm birth. And sensitive analyses were further conducted in populations without sleep disordered breathing (SDB), and an allergen test subgroup, yielding similar results.

Conclusion: Parasomnia symptoms are associated with increased odds of childhood wheeze/asthma, and the odds were even higher in premature population. The findings suggest that parasomnia symptoms, as a developmental sleep disorder, are supposed to be closely watched among children who have asthma or are at risk for asthma, and that preterm children deserve more attention.

Keywords: sleep, sleep disorders, premature, respiratory allergies

Introduction

Parasomnias, characterized by abnormal movement or partial arousals while sleeping, are one of the most common developmental disorders in children.[1] The development and establishment of sleep structures occur during the undifferentiated, spontaneous fetal activity in the womb, known as "pre-sleep".[1] According to its occurrence at different sleep periods, parasomnias are mainly divided into rapid eye movement (REM) and non-REM (NREM) parasomnias.[1–3] The pathophysiology of parasomnias has not been elucidated, detrimental perinatal factors might have an impact on the maturity

of some neural circuits, resulting in parasomnia symptoms.[4] Up to 50% of children reported experiencing at least one parasomnia episode, which is prevalent before the age of five, and with the maturation of the nervous system, it tends to ease by about ten.[1,5] Research on the health effects of parasomnia symptoms is scarce. Although evidence indicates that they might cause potential health injuries, there is controversial clinical advice on whether or not to intervene.

As a leading chronic disease in children, asthma usually onsets by the age of four.[6] Wheezing usually be an early symptom of later asthma, and about 3–5% of childhood asthma persists to adulthood, and more than 10% of childhood asthma relapses in adulthood, often with a worse prognosis.[6] Since genetic influences are insufficient to explain the alarming increase in asthma prevalence, many underestimated factors have been proposed to be involved in the pathogenesis of asthma.[7] From both the biomedical and public health perspective, increased asthma risks have been linked to preterm birth, and data on more readily modifiable factors of asthma among preterm newborns are relatively scarce.[7]

Generally, previous studies have established a relationship between poor sleep characteristics, including sleep-wake habits, sleep duration, and sleep disordered breathing (SDB), with an increased risk of wheeze/asthma.[8–10] Parasomnia is modulated by several neural circuits, including γ-aminobutyric acid (GABA) and serotonin circuits.[2,3] In neuroimmune pathophysiology in asthma, inflammatory mediators and neurotransmitters seem to facilitate the crosstalk and positive feedback loops between immune cells and nervous systems.[11,12] However, regarding neuro-immune crosstalk, epidemiologic data on the association between parasomnia and asthma are quite sparse. To our knowledge, 15 studies have looked at a certain kind of parasomnia symptom with conflicting results. Restless leg syndrome,[13,14] bruxism,[15–18] and sleep terror[19,20] were found to have supportive correlations, whereas enuresis had inconsistent results, with 5 positive relationships[21–25] and 2 non-significant associations.[26,27] Others, like sleep talking, sleepwalking, sleep terror, and nightmares, have rarely been touched by previous studies.

Our aim was, therefore, to estimate the association of both specific and holistic parasomnia symptoms with childhood wheeze/asthma. Given the importance of fetal maturation in the development of parasomnia,[1] the interaction role of preterm and parasomnia with the association of wheeze/asthma would be given a point evaluation. Considering SDB is potentially a key confounder in the association between parasomnia and asthma, sensitivity analyses were performed on children without SDB. It is hoped that our study would be conducive to calling for clinical concerns about the health effects of parasomnia symptoms, as well as paying special attention to children with special sleep traits, and strengthening the emphasis on the long-term health of premature children.

Material and Methods

Study Design and Population

This cross-sectional study used data from the Shanghai Children's Allergy Study, which took place in Shanghai, China, from April 12 to June 1, 2019.[28] A multistage cluster sampling strategy was adopted. Among a total of 9 urban areas and 8 suburban/rural areas in Shanghai, 31 kindergartens and 17 primary schools in 7 urban areas (Xuhui, Huangpu, Hongkou, Putuo, Changning, Yangpu, and Pudong New Area) and 6 suburban/rural areas (Minhang, Jinshan, Qingpu, Songjiang, Baoshan, and Chongming) were randomly sampled. After permission was obtained from these schools, the children and their caregivers were told of the study's purposes and were advised that participation was voluntary. Informed consent form and the questionnaire were provided to the eligible population. Of all the 16,936 children included, a total of 16,487 children aged 3–12 years met the criteria after removing the missing data on gestational age and child age (Figure 1). Ethical approval was obtained from the ethics committee of Shanghai Jiao Tong University School of Medicine (Ethics Approval Number: SJUPN-201717) in accordance with the Declaration of Helsinki. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cross-sectional studies was followed.

Allergic Outcomes

The current study used the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire to assess childhood allergic diseases.[29] In brief, information on ever-diagnosed asthma and current wheeze, as well as children's allergen tests, was asked (details are described in the Supplement Figure 1). The Cronbach's alpha coefficient of the ISAAC questionnaire in the sampled children was 0.94. The validity determined by the Kaiser-Meyer-Olkin method was 0.94.
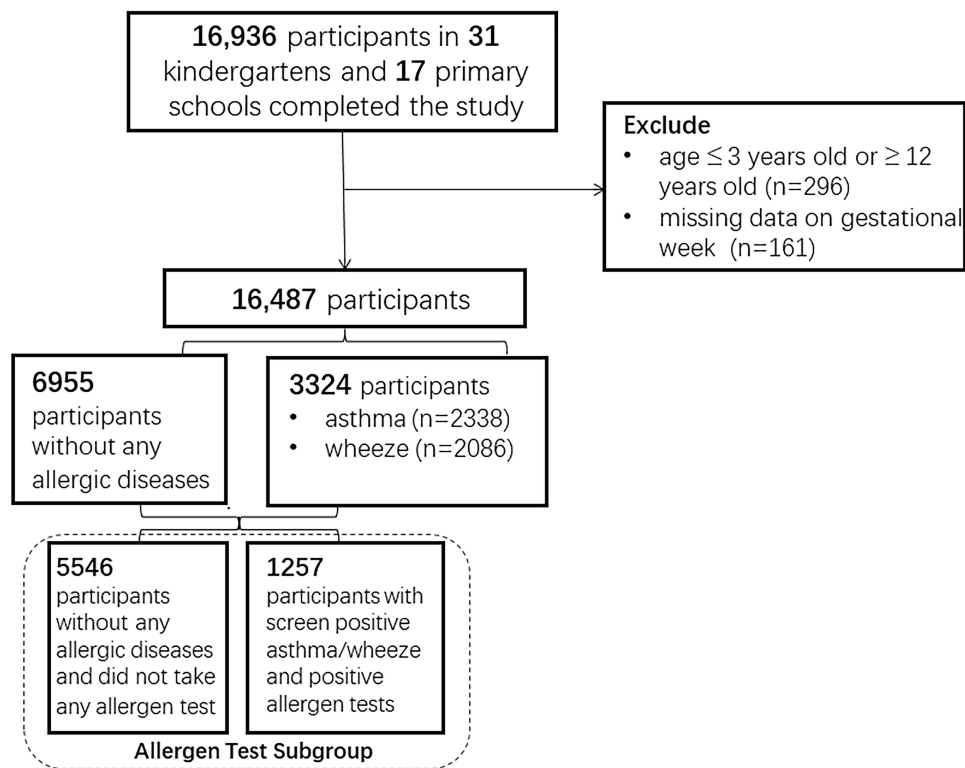
Figure 1 Flow chart of this study. For this study, a total of 16,963 students were recruited from 36 kindergartens and 17 primary schools. 296 children were ruled out because they were not between the ages of 3 and 12, and 161 were ruled out owing to missing data on gestational week, leaving 16,487 children in the final analysis. In the analysis process, 6955 children without any allergic diseases (asthma, wheeze, allergic rhinitis, eczema, food allergy, and drug allergy) were regarded as the control group, and 2086 being screened for current wheeze and 2338 being screened for ever asthma. In the allergen test subgroup, 1257 children who had a positive response to both current wheeze/ever asthma and the allergen test were included, while 5546 children who did not have any of the stated allergic diseases and did not take the allergen test were regarded as reference group.

Exposure

Sleep characteristics were assessed by the Children's Sleep Habits Questionnaire (CSHQ), which was widely adopted to evaluate sleep characteristics from eight domains for children aged 2–12 years.[30,31] In the CSHQ, the parasomnias subscale has seven items, including NREM parasomnias (sleep walking, sleep terror), REM parasomnias (sleep talking, sleep restless, and nightmares), and other symptoms (bruxism, enuresis); and the SDB subscale has three items, including loud snoring, stopped breathing, and snorts and gasps. Each question had three options, 1 = rarely (0–1 time/week), 2 = sometimes (2–4 times/week), and 3 = usually (5–7 times/week).[30,31] Suffering from a specific parasomnia symptom was defined as answering "sometimes" or "usually" to the related question;[32] and SDB was defined as at least two SDB-related symptoms occurring two or more times per week.[33] Of the parasomnia and SDB subscales, the test–retest reliability (ICCs) was 0.46 and 0.43, and the internal consistency (Cronbach's alpha) was 0.83 and 0.77, respectively, which were similar to previous studies.[34,35]

In terms of gestational weeks, a gestational age of less than 36 weeks is defined as a preterm birth. Further, moderate preterm and very preterm were classified as gestational age at 33–36 weeks and less than 32 weeks, respectively.

Additional Covariates

Information was collected on child age, gender, child overweight/obesity (defined as over 85% of standard age and sex-specific percentile[36]), parent's educational level, family income, family structure, family allergic history, family sleep disorder history, maternal age at delivery, maternal pre-pregnancy overweight (body mass index ≥25),[37] smoking, drinking, and negative life events in the mother's life during pregnancy, cesarean delivery, low birth weight

(birth weight <2500g),[38] multiple pregnancies, breastfeeding <6 months, passive smoking, and pet-keeping at home in the first year of child's life. All these variables were recognized as potential confounders.

Statistical Analysis

The Chi-square test and *t*-test were adopted to compare the group differences where appropriate. Both crude and adjusted logistic regressions were conducted to explore the association of parasomnias with childhood wheeze/asthma. For the dependent variable, "1" indicates children with ever asthma, or with current wheeze, and "0" indicates the absence of any of the following allergy symptoms, including asthma, wheeze, allergic rhinitis, eczema, food allergy, and drug allergy (the determination of allergic rhinitis, eczema, food allergy, and drug allergy was illustrated in the Supplement Figure 1). In adjusted models, we first controlled for the demographic factors, then for the maternal and perinatal factors.

The following analyses were conducted to assess the association between parasomnias and wheeze/asthma while considering the possible role of preterm birth. First, both the multiplicative and additive interactions were performed to evaluate the possible interaction effects between preterm birth and parasomnias on the odds of childhood wheeze/asthma. When the combined OR was greater than the sum of parasomnias and preterm birth, there was an interaction on the additive scale. The three main indexes are calculated with the following equations, and computations were made for the 95% CIs with the Hosmer–Lemeshow delta method: the relative excess risk due to interaction (RERI) = $RR_{11} - RR_{10} - RR_{01} + 1$; the proportion attributable to interaction (AP) = $RERI/RR_{11}$; the synergy index (SI) = $(RR_{11} - 1)/([RR_{10} - 1] + [RR_{01} - 1])$. RERI or AP of 0, or synergy index of 1 suggests no interaction.[39] Second, each single parasomnia symptom was enrolled to analyze their association with ever asthma and current wheeze, stratified by gestational age (full-term vs preterm birth). Multiple testing corrections were implemented using the Benjamini and Hochberg false discovery rate methods.[40] Finally, the association of cumulative parasomnia symptoms with wheeze/asthma was investigated, with preterm birth being further stratified (full-term vs moderately preterm (33–36 weeks) vs very preterm birth (≤32 weeks)).

Sensitivity analyses were performed on the SDB excluded population (n = 15,884) and the allergen testing subgroup (n = 6803). In the allergen test subgroup, "1" was coded for those with positive screens for wheeze/asthma and allergen tests, "0" was for those without any screened allergic symptoms and did not take the allergen test.

All analyses were performed using SPSS, version 23.0 (IBM-SPSS Statistics Inc) and R, version 3.5.3 (The R Foundation for Statistical Computer, www.r-project.org). A 2-sided *p* value <0.05 was recognized to be statistically significant.

Results

Our analysis comprised 16,487 children (8641 males [52.4%]) with a mean (SD) age of 7.74 (2.33) years after excluding the missing data on gestational age (n = 161) and child age (n = 296). A total of 2086 (12.7%) children were screened as having current wheeze, 2338 (14.2%) as having ever-diagnosed asthma, and 6955 were not screened with any allergic symptoms (Figure 1). In the allergen test subgroup, 1257 children were in the case group, and 5546 were in the control group (Figure 1).

Children with wheeze/asthma were more likely to be younger, overweight/obesity, male, and have higher education of parents, higher family income, extended family life, family histories of allergies and sleep disorders, mothers of higher delivery age and experiencing negative life events during pregnancy, born by cesarean, preterm birth, breastfed for a shorter period of time, with more passive smoke exposure and keeping pet during first year of life (Table 1). The prevalence of current wheeze, ever-diagnosed asthma, and parasomnias was shown to be decreased with age (Figure 2). The parasomnias were more likely to be occurred in children born preterm, particularly in the very preterm population (Table 2). Meanwhile, children with current wheeze and ever asthma were more likely to have parasomnia symptoms, with the exception of sleep walking (Table 2).

Interaction Effects of Parasomnia and Preterm Birth on Childhood Current Wheeze and Ever Asthma

As reported in Table 3, after adjusting for all confounders, the multiplicative interaction between parasomnia and preterm birth was only significant in current wheeze (OR, 1.48; 95% CI, 1.01–2.19; *p*=0.049), while their interaction effects on the additive scale were presented to be both significant in current wheeze (RERI, 1.43; 95% CI, 0.41–2.45) and ever

Table 1 Sample Characteristics

Variable	Total (N = 16,487)	No Symptom (N = 6955)	Current Wheeze (N = 2086)		Ever Asthma (N = 2338)	
	N (%)	N (%)	N (%)	χ^2/t (p-value)	N (%)	χ^2/t (p-value)
Demographic factors						
Age (yr)[#] (mean (sd))	7.74 (2.33)	7.95 (2.33)	7.35 (2.31)	**10.493 (<.001)**	7.67 (2.32)	**5.125 (<.001)**
Overweight/obesity	4940 (30.0)	2062 (29.6)	679 (32.6)	**6.400 (0.011)**	760 (32.5)	**6.762 (0.009)**
Gender				**101.577 (<.001)**		**83.383 (<.001)**
Male	8641 (52.4)	3400 (48.9)	1282 (61.5)		1498 (59.8)	
Female	7846 (47.6)	3555 (51.1)	804 (38.5)		940 (40.2)	
Mother's educational level				**342.299 (<.001)**		**290.657 (<.001)**
Secondary education and below	5255 (31.9)	3044 (43.8)	444 (21.3)		559 (23.9)	
College and above	11,232 (68.1)	3911 (56.2)	1642 (78.7)		1779 (76.1)	
Father's educational level				**246.237 (<.001)**		**222.849 (<.001)**
Secondary education and below	5211 (31.6)	2909 (41.8)	477 (22.9)		574 (24.6)	
College and above	11,276 (68.4)	4046 (58.2)	1609 (77.1)		1764 (75.4)	
Family income* ≥ 6000RMB	10,963 (66.5)	4131 (59.4)	1510 (72.4)	**115.423 (<.001)**	1644 (70.3)	**88.701 (<.001)**
Family structure				**17.598 (<.001)**		**7.702 (0.021)**
Single parent	554 (3.4)	246 (3.5)	82 (3.9)		90 (3.8)	
Nuclear family	9746 (59.1)	4277 (61.5)	1176 (56.4)		1362 (58.3)	
Extended family	6187 (37.5)	2432 (35.0)	828 (39.7)		886 (37.9)	
Family allergic history	4088 (24.8)	632 (9.1)	984 (47.2)	**1585.585 (<.001)**	1024 (43.8)	**1439.634 (<.001)**
Family sleep disorder history	3779 (22.9)	1045 (15.0)	685 (32.8)	**329.056 (<.001)**	730 (31.2)	**297.116 (<.001)**
Prenatal and perinatal factors						
Maternal age at delivery (yr)				**97.336 (<.001)**		**51.967 (<.001)**
≤ 24	3247 (19.7)	1657 (24.7)	288 (14.4)		392 (17.4)	
25–29	7468 (45.3)	2895 (43.1)	1022 (51.1)		1092 (48.4)	
≥ 30	5220 (31.7)	2163 (32.2)	691 (34.5)		770 (34.2)	
Maternal pre-pregnancy overweight	828 (5.0)	379 (5.5)	123 (6.0)	0.609 (0.435)	136 (5.9)	0.429 (0.512)
Maternal smoking during pregnancy	310 (1.9)	164 (2.4)	38 (1.8)	2.113 (0.146)	36 (1.5)	**5.563 (0.018)**
Maternal drinking during pregnancy	362 (2.2)	162 (2.3)	50 (2.4)	0.032 (0.858)	43 (1.8)	1.948 (0.163)
Negative event during pregnancy	571 (3.5)	185 (2.7)	110 (4.7)	**23.806 (<.001)**	109 (5.2)	**33.567 (<.001)**
Cesarean delivery	9291 (56.4)	3773 (54.2)	1237 (59.3)	**16.573 (<.001)**	1432 (61.2)	**34.800 (<.001)**
Gestational ages				**27.847 (<.001)**		**17.227 (<.001)**
Full-term	15,099 (91.6)	6403 (92.1)	1848 (88.6)		2094 (89.6)	
Moderately preterm, 33–36wk	962 (5.8)	374 (5.4)	176 (8.4)		180 (7.7)	
Very preterm, ≤ 32 wk	426 (2.6)	178 (2.6)	62 (3.0)		64 (2.7)	
Low birthweight	509 (3.1)	228 (3.4)	86 (4.3)	2.850 (0.091)	76 (3.3)	0.059 (0.807)
Multiple pregnancy	779 (4.7)	397 (5.7)	107 (5.1)	1.021 (0.312)	109 (4.7)	3.719 (0.054)
Breastfeeding < 6 months	7873 (47.8)	3124 (44.9)	1061 (50.9)	**22.816 (<.001)**	1201 (51.4)	**29.271 (<.001)**
Passive smoking	9238 (56.0)	3762 (54.1)	1244 (59.6)	**19.967 (<.001)**	1389 (59.4)	**20.039 (<.001)**
Pet keeping during first year of life	2002 (12.1)	769 (11.1)	318 (13.6)	**10.969 (0.001)**	288 (13.8)	**11.750 (0.001)**

Notes: [#]Continuous variables were presented by mean (sd); *Family income is calculated as RMB/person/month, RMB is China's currency (yuan). Statistically significant results (p < 0.05) are in bold.
Abbreviations: yr, year; sd, standard deviation; wk, week.

asthma (RERI, 0.75; 95% CI, 0.01–1.50). Compared with children who have neither preterm nor parasomnias, those only with preterm were associated with an increased risk of current wheeze (OR, 1.42; 95% CI,1.07–1.90; p=0.017); those only having parasomnias were associated with increased odds of current wheeze (OR, 1.66; 95% CI, 1.46–1.88; p<0.001) and ever asthma (OR, 1.56; 95% CI, 1.38–1.75; p<0.001); and the co-existence of parasomnia and preterm birth showed
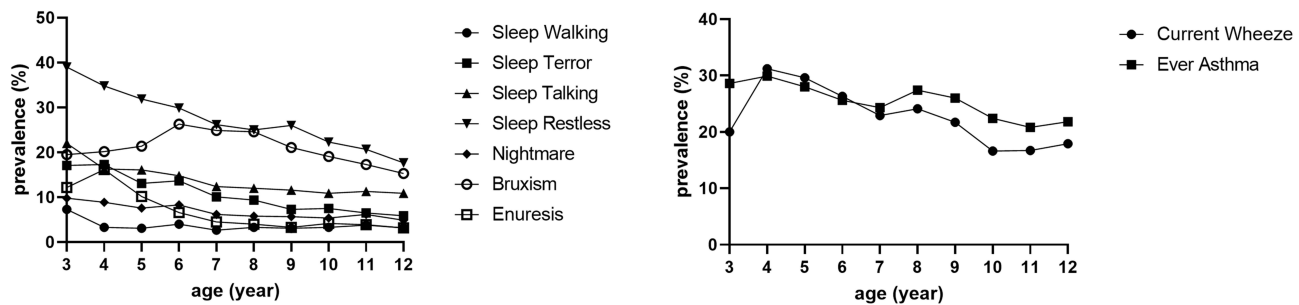
Figure 2 Age specific prevalence of current wheeze/ever asthma and single parasomnia symptoms.

the most pronounced association with both current wheeze (OR, 3.50; 95% CI, 2.61–4.70; $p<0.001$) and ever asthma (OR, 2.60; 95% CI, 1.94–3.47; $p<0.001$).

Association of Single Parasomnia Symptom and Childhood Current Wheeze and Ever Asthma, Stratified by Full-Term vs Preterm Children

Considering the correlation between each parasomnia symptom (Supplement Table 1), we corrected the p values for multiple comparisons. As detailed in Table 4, regarding NREM parasomnias, an absence of association of sleepwalking with wheeze and asthma in the full-term group was reported, while significance was found in ever asthma in the preterm birth group after adjusting for all covariates (OR, 2.37; 95% CI, 1.06–5.34; corrected $p=0.037$). For REM parasomnias, the significant associations with current wheeze an ever asthma were consistently established in both full-term and preterm groups, whereas the strengths were higher in children born preterm. In terms of other parasomnia symptoms, similarly, bruxism was observed to be related to increased odds of current wheeze and ever asthma, and the odds were higher in the preterm group. The significant associations of enuresis with wheeze and asthma were only presented in the preterm children, even after full adjustments (ever asthma: OR, 2.35; 95% CI, 1.21–4.57; corrected $p=0.014$; current wheeze: OR, 2.56; 95% CI, 1.34–4.90; corrected $p=0.009$).

Cumulative Association Between Parasomnias and Childhood Current Wheeze and Ever Asthma, Stratified by Full-Term vs Preterm Children

Further subdivided to create a hierarchy on preterm variables (Table 5), it showed that the more parasomnia symptoms children have, the higher the odds of current wheeze and ever-diagnosed asthma they would have in all three groups. Moreover, the shorter the gestational age, the higher the odds of current wheeze and ever asthma. Two or more parasomnia symptoms with very preterm birth were most strongly associated with both current wheeze (OR, 4.55; 95% CI, 1.69–12.25; $p=0.003$) and ever-diagnosed asthma (OR, 6.17; 95% CI,2.36–16.11; $p<0.001$).

In the sensitivity analyses, either among the population without SDB (Supplement Tables 2–4) or in Allergen Test Subgroup (Figure 3 and Supplement Tables 5–7), similar results were observed in most cases.

Discussion

To the best of our knowledge, this is the largest population-based study to discuss the association between parasomnia symptoms and the risk of childhood wheeze/asthma in its full range, considering the interaction effect of preterm birth. We should highlight two core findings. First, parasomnia symptoms, especially REM parasomnias, were associated with increased odds of current wheeze and ever asthma in children, with the trend being the more parasomnia symptoms, the higher the risks. Second, preterm birth interacts with parasomnia symptoms of an additive magnitude, suggesting that the combination of very preterm birth with multiple parasomnia symptoms has the highest odds of childhood wheeze/asthma. The sensitivity analyses performed in populations without SDB symptoms and with allergen test results yield similar results. Our findings indicate that the sleep health of children, especially in children with wheeze/asthma, requires practical support, and premature children merit more attention.

Table 2 Comparison of Parasomnia Symptoms Between Gestational Age Groups, and of Respiratory Allergic Groups in the Preterm Group

| | Full-Term (n = 15,099) | Preterm | | | No Symptom (N = 6955) | Current Wheeze (N = 2086) | | Ever Asthma (N = 2338) | |
| | | Moderately Preterm 33–36 Wk (n = 962) | Very Preterm ≤ 32 Wk (n = 426) | | | | | | |
	N (%)	N (%)	N (%)	χ^2 (p-value)	N (%)	N (%)	χ^2 (p-value)	N (%)	χ^2 (p-value)
NREM									
Sleep Walking	478 (3.2)	32 (3.3)	35 (8.2)	**33.060 (<.001)**	282 (4.1%)	73 (3.5%)	1.311 (0.252)	75 (3.2%)	3.396(0.065)
Sleep Terror	1508 (10.0)	116 (12.1)	63 (14.8)	**14.106 (0.001)**	602 (8.7%)	319 (15.3%)	**77.255 (<.001)**	333 (14.2%)	**60.365 (<.001)**
REM									
Sleep Talking	1938 (12.8)	126 (13.1)	81 (19.0)	**13.98 (0.001)**	765 (11.0%)	348 (16.7%)	**48.015 (<.001)**	343 (14.7%)	**22.459 (<.001)**
Sleep Restless	3997 (26.5)	260 (27.0)	122 (28.6)	1.111 (0.574)	1459 (21.0%)	773 (37.1%)	**223.131 (<.001)**	763 (32.6%)	**130.692 (<.001)**
Nightmare	968 (6.4)	65 (6.8)	59 (13.8)	**37.098 (<.001)**	444 (6.4%)	182 (8.7%)	**13.645 (<.001)**	194 (8.3%)	**10.023 (0.002)**
Others									
Bruxism	3238 (21.4)	231 (24.0)	115 (27.0)	**10.607 (0.005)**	1277 (18.4%)	596 (28.6%)	**101.857 (<.001)**	612 (26.2%)	**65.992 (<.001)**
Enuresis	910 (6.0)	62 (6.4)	46 (10.8)	**16.409 (001)**	440 (6.3%)	158 (7.6%)	**4.046 (0.044)**	164 (7.0%)	1.364 (0.243)
Parasomnia				**23.615 (<.001)**			**297.778 (<.001)**		**225.979 (<.001)**
0	8652 (56.7)	528 (54.9)	239 (56.1)		4466 (64.2%)	924 (44.3%)		1115 (47.7%)	
1 symptom	3530 (23.1)	215 (22.3)	69 (16.2)		1400 (20.1%)	546 (26.2%)		586 (25.1%)	
≥ 2 symptoms	3071 (20.1)	219 (22.8)	118 (27.7)		1089 (15.7%)	616 (29.5%)		637 (27.2%)	

Notes: Statistically significant results (p < 0.05) are in bold.
Abbreviations: REM, rapid eye movement; NREM, non-rapid eye movement; wk, week.

Table 3 Interactive Associations Between Parasomnia, Preterm Birth and Current Wheeze and Ever Asthma

		Current Wheeze						Ever Asthma					
		Crude Model		Adjusted Model I		Adjusted Model II		Crude Model		Adjusted Model I		Adjusted Model II	
		OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Parasomnia * Preterm		1.31 (0.93–1.85)	0.128	1.47 (1.00–2.17)	0.051	**1.48 (1.01–2.19)**	**0.049**	1.29 (0.91–1.81)	0.148	1.30 (0.89–1.90)	0.174	1.29 (0.89–1.89)	0.183
Parasomnia	Preterm												
No	No	Ref		Ref		Ref		Ref		Ref		Ref	
No	Yes	**1.40 (1.10–1.79)**	**0.007**	**1.44 (1.09–1.89)**	**0.010**	**1.42 (1.07–1.90)**	**0.017**	1.23 (0.97–1.56)	0.084	1.24 (0.96–1.61)	0.100	1.29 (0.98–1.69)	0.069
Yes	No	**2.20 (1.97–2.45)**	**<0.001**	**1.69 (1.49–1.92)**	**<0.001**	**1.66 (1.46–1.88)**	**<0.001**	**1.91 (1.72–2.12)**	**<0.001**	**1.59 (1.41–1.79)**	**<0.001**	**1.56 (1.38–1.75)**	**<0.001**
Yes	Yes	**4.02 (3.14–5.13)**	**<0.001**	**3.59 (2.72–4.74)**	**<0.001**	**3.50 (2.61–4.70)**	**<0.001**	**3.03 (2.36–3.87)**	**<0.001**	**2.57 (1.95–3.39)**	**<0.001**	**2.60 (1.94–3.47)**	**<0.001**
		RERI, 1.43 (0.41–2.45); AP, 0.41 (0.21–0.60); SI, 2.33 (1.36–3.99)						RERI, 0.75 (0.01–1.50); AP, 0.29 (0.06–0.52); SI, 1.90 (1.02–3.52)					

Notes: Statistically significant results (p < 0.05) are in bold. Parasomnia, preterm, and parasomnia *Preterm are mutually adjusted for each other. Model I adjusted for child age, overweight/obesity, gender, mother's educational level, father's educational level, family income, family structure, family allergic history, family sleep disorder history; Model II further adjusted for maternal age at delivery, maternal pre-pregnancy overweight, maternal smoking, maternal drinking, negative life event, cesarean delivery, low birthweight, multiple pregnancy, breastfeeding, passive smoking, pet keeping during first year of life.
Abbreviations: OR, odd ratio; CI, confidence interval; RERI, relative excess risk due to interaction; AP, proportion attributable to interaction; SI, synergy index.

Table 4 Association Between Single Parasomnia Characteristic and Current Wheeze and Ever Asthma

	Current Wheeze									Ever Asthma								
	Crude Model			Adjusted Model I			Adjusted Model II			Crude Model			Adjusted Model I			Adjusted Model II		
	OR (95% CI)	p	p*	OR (95% CI)	p	p*	OR (95% CI)	p	p*	OR (95% CI)	p	p*	OR (95% CI)	p	p*	OR (95% CI)	p	p*
Full-term																		
NREM																		
Sleep Walking	0.82 (0.60–1.12)	0.201	0.201	1.21 (0.86–1.71)	0.280	0.327	1.22 (0.86–1.73)	0.268	0.313	**0.72 (0.53–0.99)**	**0.040**	**0.047**	0.99 (0.71–1.39)	0.963	0.963	1.03 (0.73–1.45)	0.873	0.873
Sleep Terror	**1.91 (1.62–2.25)**	**<0.001**	**<0.001**	**1.81 (1.50–2.18)**	**<0.001**	**<0.001**	**1.76 (1.46–2.14)**	**<0.001**	**<0.001**	**1.69 (1.44–1.98)**	**<0.001**	**<0.001**	**1.67 (1.40–2.01)**	**<0.001**	**<0.001**	**1.66 (1.38–1.99)**	**<0.001**	**<0.001**
REM																		
Sleep Talking	**1.57 (1.35–1.83)**	**<0.001**	**<0.001**	**1.33 (1.11–1.59)**	**0.002**	**0.003**	**1.32 (1.10–1.58)**	**0.003**	**0.004**	**1.36 (1.17–1.59)**	**<0.001**	**<0.001**	**1.21 (1.02–1.43)**	**0.032**	**0.045**	**1.20 (1.01–1.43)**	**0.039**	0.055
Sleep Restless	**2.15 (1.91–2.42)**	**<0.001**	**<0.001**	**1.80 (1.57–2.06)**	**<0.001**	**<0.001**	**1.75 (1.53–2.01)**	**<0.001**	**<0.001**	**1.78 (1.58–1.99)**	**<0.001**	**<0.001**	**1.54 (1.35–1.75)**	**<0.001**	**<0.001**	**1.51 (1.32–1.72)**	**<0.001**	**<0.001**
Nightmare	**1.30 (1.06–1.60)**	**0.014**	**0.020**	**1.47 (1.16–1.87)**	**0.001**	**0.002**	**1.46 (1.15–1.85)**	**0.002**	**0.004**	**1.27 (1.04–1.55)**	**0.020**	**0.028**	**1.44 (1.16–1.80)**	**0.001**	**0.002**	**1.46 (1.17–1.83)**	**0.001**	**0.002**
Others																		
Bruxism	**1.71 (1.51–1.94)**	**<0.001**	**<0.001**	**1.50 (1.30–1.73)**	**<0.001**	**<0.001**	**1.48 (1.28–1.71)**	**<0.001**	**<0.001**	**1.52 (1.35–1.72)**	**<0.001**	**<0.001**	**1.32 (1.15–1.51)**	**<0.001**	**<0.001**	**1.30 (1.14–1.50)**	**<0.001**	**<0.001**
Enuresis	1.20 (0.97–1.49)	0.092	0.107	1.06 (0.82–1.37)	0.649	0.649	1.08 (0.84–1.40)	0.542	0.542	1.08 (0.87–1.33)	0.492	0.492	1.06 (0.83–1.35)	0.637	0.743	1.10 (0.87–1.41)	0.426	0.497
Preterm, ≤ 36 wk																		
NREM																		
Sleep Walking	1.32 (0.63–2.75)	0.459	0.459	1.84 (0.82–4.14)	0.139	0.139	2.13 (0.91–4.98)	0.081	0.081	1.44 (0.71–2.96)	0.316	0.316	**2.21 (1.01–4.88)**	**0.049**	**0.049**	**2.37 (1.06–5.34)**	**0.037**	**0.037**
Sleep Terror	**2.58 (1.63–4.10)**	**<0.001**	**<0.001**	**2.59 (1.52–4.41)**	**<0.001**	**<0.001**	**2.91 (1.66–5.11)**	**<0.001**	**<0.001**	**2.52 (1.59–4.01)**	**<0.001**	**<0.001**	**3.57 (2.11–6.05)**	**<0.001**	**<0.001**	**3.74 (2.17–6.46)**	**<0.001**	**<0.001**
REM																		
Sleep Talking	**2.38 (1.55–3.68)**	**<0.001**	**<0.001**	**2.40 (1.47–3.94)**	**0.001**	**0.002**	**2.55 (1.53–4.24)**	**<0.001**	**<0.001**	**2.03 (1.30–3.17)**	**0.002**	**0.004**	**1.92 (1.15–3.21)**	**0.013**	**0.015**	**1.94 (1.14–3.28)**	**0.014**	**0.020**
Sleep Restless	**2.74 (1.92–3.91)**	**<0.001**	**<0.001**	**2.59 (1.72–3.90)**	**<0.001**	**<0.001**	**2.58 (1.70–3.93)**	**<0.001**	**<0.001**	**2.56 (1.79–3.65)**	**<0.001**	**<0.001**	**2.44 (1.60–3.70)**	**<0.001**	**<0.001**	**2.34 (1.53–3.58)**	**<0.001**	**0.002**
Nightmare	**2.25 (1.29–3.91)**	**0.004**	**0.006**	**2.23 (1.22–4.27)**	**0.010**	**0.014**	**2.39 (1.24–4.59)**	**0.009**	**0.013**	**1.98 (1.12–3.49)**	**0.019**	**0.022**	**2.27 (1.19–4.34)**	**0.013**	**0.015**	**2.24 (1.15–4.37)**	**0.018**	**0.021**
Others																		
Bruxism	**2.20 (1.52–3.17)**	**<0.001**	**<0.001**	**1.96 (1.29–2.98)**	**0.002**	**0.004**	**2.05 (1.33–3.16)**	**0.002**	**0.004**	**2.12 (1.47–3.07)**	**<0.001**	**<0.001**	**2.05 (1.35–3.13)**	**0.001**	**0.002**	**2.12 (1.37–3.27)**	**0.001**	**0.002**
Enuresis	**1.76 (1.01–3.08)**	**0.047**	0.055	**1.96 (1.05–3.68)**	**0.036**	**0.042**	**2.35 (1.21–4.57)**	**0.012**	**0.014**	**1.94 (1.12–3.35)**	**0.018**	**0.022**	**2.30 (1.23–4.29)**	**0.009**	**0.015**	**2.56 (1.34–4.90)**	**0.005**	**0.009**

Notes: p *p corrected for multiple comparison. Statistically significant results (p < 0.05) are in bold. Model I adjusted for child age, overweight/obesity, gender, mother's educational level, father's educational level, family income, family structure, family allergic history, family sleep disorder history; Model II further adjusted for maternal age at delivery, maternal pre-pregnancy overweight, maternal smoking, maternal drinking, negative life event, cesarean delivery, low birthweight, multiple pregnancy, breastfeeding, passive smoking, pet keeping during first year of life.
Abbreviations: REM, rapid eye movement; NREM, non-rapid eye movement; OR, odd ratio; CI, confidence interval; wks, week.

Table 5 Association Between Parasomnia Symptoms and Current Wheeze and Ever Asthma, Stratified by Gestational Age

	Current Wheeze						Ever Asthma					
	Crude Model		Adjusted Model I		Adjusted Model II		Crude Model		Adjusted Model I		Adjusted Model II	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Full-term												
Parasomnia												
0	Ref		Ref		Ref		Ref		Ref		Ref	
1 symptom	**1.90 (1.67–2.17)**	**<0.001**	**1.51 (1.30–1.76)**	**<0.001**	**1.48 (1.27–1.72)**	**<0.001**	**1.68 (1.48–1.91)**	**<0.001**	**1.43 (1.24–1.64)**	**<0.001**	**1.40 (1.22–1.61)**	**<0.001**
≥ 2 symptoms	**2.59 (2.26–2.96)**	**<0.001**	**1.95 (1.67–2.28)**	**<0.001**	**1.90 (1.63–2.23)**	**<0.001**	**2.22 (1.95–2.52)**	**<0.001**	**1.81 (1.57–2.10)**	**<0.001**	**1.77 (1.53–2.05)**	**<0.001**
Preterm, ≤ 36 wk												
0												
1 symptom	**1.88 (1.23–2.86)**	**0.004**	**1.76 (1.10–2.84)**	**0.020**	**1.76 (1.09–2.86)**	**0.021**	**1.58 (1.03–2.42)**	**0.037**	1.24 (0.75–2.04)	0.397	1.24 (0.75–2.05)	0.401
≥ 2 symptoms	**4.10 (2.77–6.08)**	**<0.001**	**3.47 (2.22–5.43)**	**0.002**	**3.71 (2.33–5.91)**	**<0.001**	**3.55 (2.40–5.25)**	**<0.001**	**3.22 (2.05–5.05)**	**<0.001**	**3.26 (2.05–5.18)**	**<0.001**
Moderately preterm, 33–36 wk												
Parasomnia												
0	Ref		Ref		Ref		Ref		Ref		Ref	
1 symptom	**1.99 (1.23–3.23)**	**0.005**	**1.98 (1.15–3.39)**	**0.013**	**2.05 (1.18–3.55)**	**0.011**	1.49 (0.91–2.43)	0.110	1.21 (0.69–2.14)	0.499	1.19 (0.67–2.12)	0.550
≥ 2 symptoms	**3.65 (2.29–5.80)**	**<0.001**	**3.13 (1.84–5.31)**	**<0.001**	**3.55 (2.03–6.19)**	**<0.001**	**2.70 (1.69–4.30)**	**<0.001**	**2.35 (1.37–4.04)**	**0.002**	**2.37 (1.35–4.14)**	**0.003**
Very preterm birth, ≤ 32 wk												
Parasomnia												
0	Ref		Ref		Ref		Ref		Ref		Ref	
1 symptom	1.39 (0.56–3.45)	0.482	1.06 (0.35–3.22)	0.918	1.23 (0.37–4.10)	0.731	1.77 (0.73–4.33)	0.209	1.28 (0.43–3.84)	0.662	1.33 (0.42–4.23)	0.631
≥ 2 symptoms	**5.47 (2.61–11.46)**	**<0.001**	**4.95 (2.02–12.13)**	**<0.001**	**4.55 (1.69–12.25)**	**0.003**	**6.97 (3.32–14.63)**	**<0.001**	**7.44 (3.10–17.88)**	**<0.001**	**6.17 (2.36–16.11)**	**<0.001**

Notes: Statistically significant results (p < 0.05) are in bold. Model I adjusted for child age, overweight/obesity, gender, mother's educational level, father's educational level, family income, family structure, family allergic history, family sleep disorder history; Model II further adjusted for maternal age at delivery, maternal pre-pregnancy overweight, maternal smoking, maternal drinking, negative life event, cesarean delivery, low birthweight, multiple pregnancy, breastfeeding, passive smoking, pet keeping during first year of life.
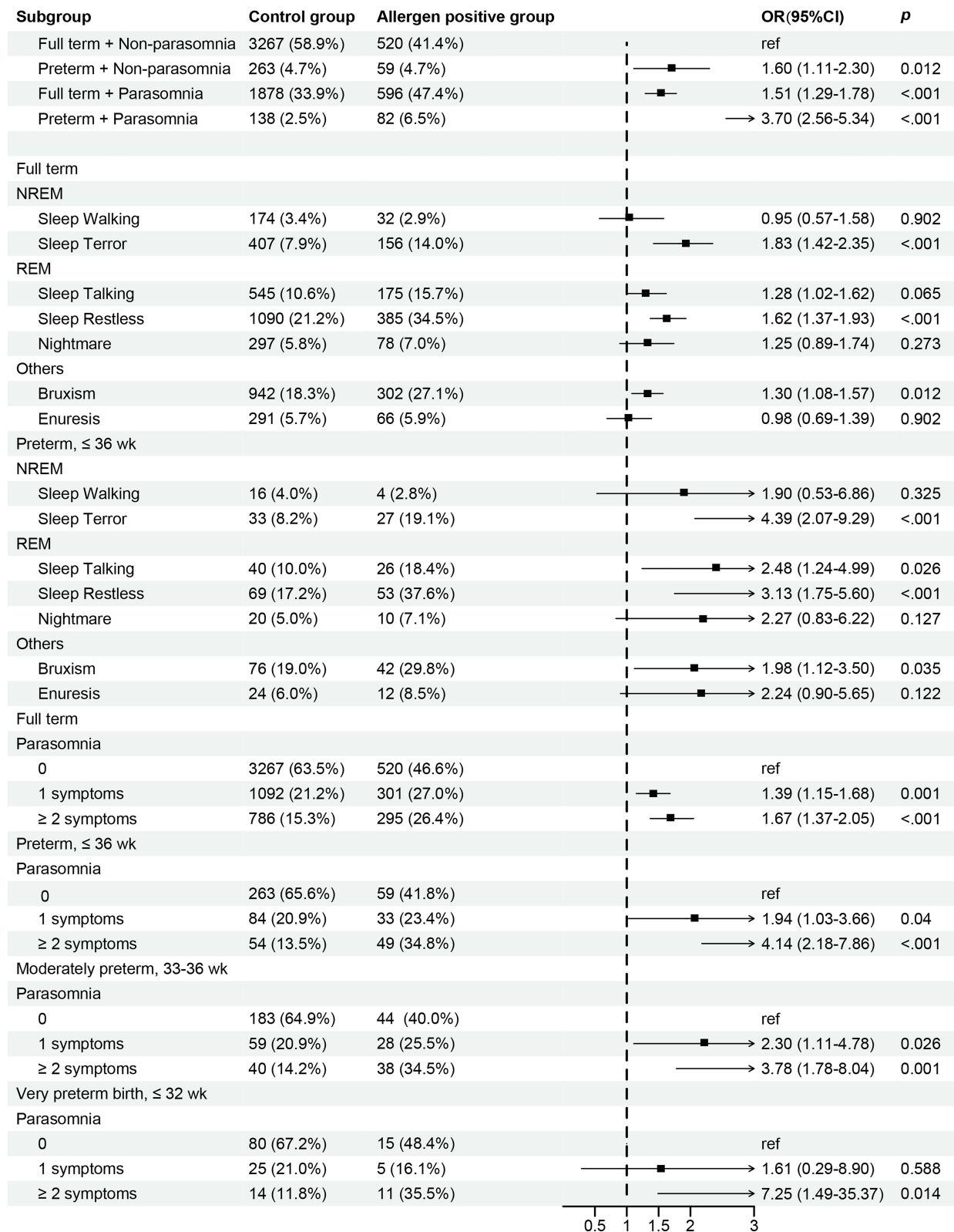**Abbreviations**: OR, odd ratio; CI, confidence interval; wk, week.

Subgroup	Control group	Allergen positive group		OR(95%CI)	p
Full term + Non-parasomnia	3267 (58.9%)	520 (41.4%)		ref	
Preterm + Non-parasomnia	263 (4.7%)	59 (4.7%)		1.60 (1.11-2.30)	0.012
Full term + Parasomnia	1878 (33.9%)	596 (47.4%)		1.51 (1.29-1.78)	<.001
Preterm + Parasomnia	138 (2.5%)	82 (6.5%)		3.70 (2.56-5.34)	<.001
Full term					
NREM					
Sleep Walking	174 (3.4%)	32 (2.9%)		0.95 (0.57-1.58)	0.902
Sleep Terror	407 (7.9%)	156 (14.0%)		1.83 (1.42-2.35)	<.001
REM					
Sleep Talking	545 (10.6%)	175 (15.7%)		1.28 (1.02-1.62)	0.065
Sleep Restless	1090 (21.2%)	385 (34.5%)		1.62 (1.37-1.93)	<.001
Nightmare	297 (5.8%)	78 (7.0%)		1.25 (0.89-1.74)	0.273
Others					
Bruxism	942 (18.3%)	302 (27.1%)		1.30 (1.08-1.57)	0.012
Enuresis	291 (5.7%)	66 (5.9%)		0.98 (0.69-1.39)	0.902
Preterm, ≤ 36 wk					
NREM					
Sleep Walking	16 (4.0%)	4 (2.8%)		1.90 (0.53-6.86)	0.325
Sleep Terror	33 (8.2%)	27 (19.1%)		4.39 (2.07-9.29)	<.001
REM					
Sleep Talking	40 (10.0%)	26 (18.4%)		2.48 (1.24-4.99)	0.026
Sleep Restless	69 (17.2%)	53 (37.6%)		3.13 (1.75-5.60)	<.001
Nightmare	20 (5.0%)	10 (7.1%)		2.27 (0.83-6.22)	0.127
Others					
Bruxism	76 (19.0%)	42 (29.8%)		1.98 (1.12-3.50)	0.035
Enuresis	24 (6.0%)	12 (8.5%)		2.24 (0.90-5.65)	0.122
Full term					
Parasomnia					
0	3267 (63.5%)	520 (46.6%)		ref	
1 symptoms	1092 (21.2%)	301 (27.0%)		1.39 (1.15-1.68)	0.001
≥ 2 symptoms	786 (15.3%)	295 (26.4%)		1.67 (1.37-2.05)	<.001
Preterm, ≤ 36 wk					
Parasomnia					
0	263 (65.6%)	59 (41.8%)		ref	
1 symptoms	84 (20.9%)	33 (23.4%)		1.94 (1.03-3.66)	0.04
≥ 2 symptoms	54 (13.5%)	49 (34.8%)		4.14 (2.18-7.86)	<.001
Moderately preterm, 33-36 wk					
Parasomnia					
0	183 (64.9%)	44 (40.0%)		ref	
1 symptoms	59 (20.9%)	28 (25.5%)		2.30 (1.11-4.78)	0.026
≥ 2 symptoms	40 (14.2%)	38 (34.5%)		3.78 (1.78-8.04)	0.001
Very preterm birth, ≤ 32 wk					
Parasomnia					
0	80 (67.2%)	15 (48.4%)		ref	
1 symptoms	25 (21.0%)	5 (16.1%)		1.61 (0.29-8.90)	0.588
≥ 2 symptoms	14 (11.8%)	11 (35.5%)		7.25 (1.49-35.37)	0.014

0.5   1   1.5   2   3

Figure 3 Forest plot for allergen test subgroup. Model adjusted for child age, overweight/obesity, gender, mother's educational level, father's educational level, family income, family structure, family allergic history, family sleep disorder history, maternal age at delivery, maternal pre-pregnancy overweight, maternal smoking, maternal drinking, negative life event, cesarean delivery, preterm birth, low birthweight, multiple pregnancy, breastfeeding, passive smoking, pet keeping during first year of life.
Abbreviation: OR, odds ratio; CI, confidence interval; wk, week.

Concurring with previous evidence from clinic populations that implemented objective measures of parasomnia, the current study verifies the positive relationship between parasomnia symptoms (enuresis, sleep restlessness, sleep terror, and bruxism) and wheeze/asthma.[13–25] Moreover, our finding extends preliminary work with novel evidence for the relationship of the other parasomnia symptoms (sleep talking, sleepwalking, and nightmares) with childhood wheeze/asthma. Two other studies of enuresis in the early 1970s yielded inconsistent results.[26,27] One involving 234 Caucasians from the upper-middle-class compared the persistent enuresis conditions in children who were treated for respiratory allergies and health controls,[26] and the other, involving a sample size of 55, used serum IgE as an indicator of allergy.[27] Both reported no association. The limited sample sizes may decrease statistical power and increase the probability of false negatives,[26,27] and the diagnostic criteria for allergy only with IgE may include asymptomatic people or those with other allergic symptoms.[27] Back to the results of our study, the significant association between enuresis and wheeze/asthma was only exhibited in children born preterm, suggesting that the physiology early in life may play a pivotal role in that relationship. Broadly, our findings illustrated a comprehensive relationship between both combined and independent parasomnia symptoms and childhood wheeze/asthma, thereby making a prominent contribution to a cursory evidence base.

The underpinning mechanism between parasomnias and asthmatic diseases may be explained by the long-standing neuro-immune interactions. During NREM parasomnias, inactivation of the frontal lobe could produce disinhibition of the basal ganglia and activation of central pattern generator (functional clustering of motor neurons).[2] And NREM parasomnias have been suggested to be linked with anomalies in serotonin metabolism.[2] Serotonin could increase airway resistance, and allergen exposure results in serotonin-positive cells within the airway epithelia.[41] Besides, greater degrees of airway inflammation could be generated, as T cell proliferation and the release of proinflammatory cytokines like interleukin-2 (IL-2) and interferons (IFNs) are both dependent on serotonin-1A receptor activation.[42] As for REM parasomnias, they are indicated to be induced by the hyperpolarization of motor neurons by GABA and glycine during REM sleep, resulting in muscle atonia.[3] GABA has actions in the epithelium that are linked to bronchial remodeling,[11] and the GABA pathway could modulate mucus differentiation and result in increased excitability of vagal preganglionic neurons, elevating cholinergic output to the airways and producing airway hyperresponsiveness and chronic constriction.[43–45] And REM parasomnias are also suggested to be associated with an increase in inflammatory monocytes and mature natural killer cells, which may exert a role in regulating airway inflammation.[46,47] For genetic etiologies, we performed the bidirectional Mendelian randomization, and revealed that genetically predicted insomnia was the risk factor for asthma, whereas asthma was not genetically associated with an increased risk of insomnia.[48] Conversely, shortness of breath, airway hyperresponsiveness, and the psychological stress caused by asthmatic symptoms, may be triggers for the occurrence of parasomnia.[49] And asthma-induced stress may also be a trigger for parasomnia.[1] As an airway obstruction condition, SDB was suggested to be a comorbidity of parasomnias and asthma.[21,23,25] However, due to a lack of or limited sample of SDB data in prior studies, this hypothesis has not been further investigated.[21,25] In our analyses, the results of subgroup without SDB were consistent with our primary findings, implying that the link between parasomnias and childhood asthma/wheezing could be independent of SDB.

It is also the first time that our study found that the additive interaction effects of preterm birth with parasomnias could amplify the risk of childhood wheeze/asthma. Existing evidence has reported links between preterm birth and both wheeze/asthma[7,50] and parasomnias,[51] but no one has ever examined the role of preterm in the association between parasomnias and asthma. Since sleep develops during fetal life, prematurity is linked to poor sleep quality and later bedtimes in school-aged children, according to a systematic evaluation of nine qualitative cohort studies.[52] Our findings further support the "Developmental Origins of Health and Disease (DOHaD)" paradigm,[53] linking premature birth with the later impaired nervous system and lung development. Given the foregoing, it is recommended that future research focuses more on the impact of disrupted sleep, particularly in vulnerable infants born preterm, in order to optimize the chances of reducing asthma burden in these children.

Several limitations of this study should be noted. First, the assessment of parasomnias and asthmatic symptoms was done by parent-reported questionnaires. However, the CSHQ and ISAAC questionnaires we adopted were universally used, and their reliability and validity have been verified.[35] Parasomnia symptoms are comparatively obvious and easily detectable, and the questionnaire allowed us to assess a wide range of parasomnia symptoms in a large epidemiological

study. The ascertainment of asthmatic symptoms was based on the questions asked about the doctor-diagnosed situations, and the allergen test subgroup was further applied to verify the result. And the age-specific prevalence trends we found were consistent with the previous literature.[1,4] Second, although we extensively adjusted for prenatal and perinatal factors, there could be other unadjusted confounders. This may limit our results due to our inability to adequately distinguish between confounding and mediation in a cross-sectional setting. Third, the pathological link between each of the different symptoms, comorbid symptoms and wheeze/asthma may be divergent and have not been clarified. Generally, multiple parasomnia symptoms can coexist.[1–3,54,55] It is not known whether treatment of one or more of the major parasomnia symptoms will be accompanied by relief or elimination of other symptoms, thereby providing the maximum health benefit. Or alternatively, remission of asthma might help with any parasomnia symptoms. As the cross-sectional study is incapable of determining the temporal relationship, further prospective and mechanistic studies are warranted to prove the in-depth relationship.

Conclusion

Our study demonstrates the association of comprehensive parasomnia symptoms with childhood wheeze/asthma, while also considering the role of prematurity. In particular, multiple parasomnia symptoms combined with extreme prematurity are most strongly associated with increased odds of wheezing/asthma in children. The finding provides further insight into the pathophysiologic mechanism of wheeze/asthma from the perspective of sleep and even neuro-immune interactions, where parasomnia symptoms, as developmental sleep disorders, merit heeding in children with wheeze/asthma. Furthermore, as a vulnerable population, both late and very preterm babies need more prompt attention.

Abbreviations

REM, rapid eye movement; SDB, sleep disordered breathing; GABA, γ-aminobutyric acid; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; ISAAC, International Study of Asthma and Allergies in Childhood; CSHQ, Children's Sleep Habits Questionnaire; RERI, relative excess risk due to interaction; AP, attributable proportion due to interaction; SI, synergy index; IL-2, interleukin-2; IFNs, interferons; DOHaD, Developmental Origins of Health and Disease.

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Disclosure

The authors report no conflicts of interest in this work.

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