Effect of Maternal Sleep, Physical Activity and Screen Time during Pregnancy on the Risk of Childhood Respiratory Allergies: a Gender-specific Study

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Research

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Abstract

Background: Early life exposure in the uterus had long-term effect on children's health. As the prevalence of allergies is increasing with a remarkable gender difference, very few studies have traced back to their early origins. We sought to investigate if maternal behavioral exposure, herein sleep, physical activity and screen time during pregnancy, is associated childhood respiratory allergies. The gender difference would be examined.

Methods: 6236 mother-child pairs from Shanghai Children Allergy Study (SCAS) were enrolled. The International Study of Asthma and Allergies in Childhood questionnaire was adopted to evaluate respiratory allergic diseases.

Results: 14.6%, 16.2% and 21.0% of children had asthma, wheeze, and allergic rhinitis, respectively. Maternal short sleep duration, lack of physical activity and too much screen exposure during pregnancy could increase the risk of childhood respiratory allergies. Moreover, a dose-response trend was clearly shown. However, the significance was found only in boys, any two of the three combined could increase the risk (OR,1.915; 95%CI,1.212-3.024), and the coexistence of all three further amplified the risk (OR,2.406; 95%CI,1.485-3.900). The findings can be verified in allergen test subgroup and single type of respiratory allergies in most cases. And gender difference was identified, all above associations were mainly observed in boys.

Conclusions: Maternal unhealthy behaviors during pregnancy could increase the risk of childhood respiratory allergies with a dose-response pattern. Boys were more susceptible to the association. The identification of modifiable maternal risk behaviors lies in the emphasis of intervention in early life to face up increasing childhood allergies.

1. Introduction

The prevalence of childhood allergic diseases continues to rise with the development of the world economy and urbanization.[1,2] China is a country with the largest population in the world. With the acceleration of urbanization, quantities of rural people flooded into cities.[3] Shanghai is one of the fastest urbanizing cities in China. It was reported that the prevalence of childhood asthma in Shanghai increased almost fivefold from 1990 to 2011.[3] Data from a national survey covering 10 cities across China demonstrated that childhood allergic diseases, except for wheezing, was the highest prevalent in Shanghai.[4] Although numerous potential environmental risk factors have been proposed, it is still far away to explain the rapid rise.[2] It has been a general recognition that early life *in utero* is a special period for imprinting, programming and the establishment of epigenome.[5] Accumulating studies were providing evidence that early life exposure has not only short term effects on fetal growth but also long-term impacts on individual’s health and disease susceptibility in later life.[5]

To date there is a number of evidence suggesting that early life exposure during pregnancy may be implicated in the development of the immune system.[1] Rodent model has long shown that air pollution exposure during pregnancy increased the susceptibility of neonates to allergic asthma.[6] A meta-analysis on epidemiology evidence similarly suggested that prenatal exposures to NO_2, SO_2, and PM_{10} increased the risk of wheezing and asthma in childhood.[7] In addition, the association between prenatal nutritional exposures and childhood allergies were also proposed in the last two decades.[8] Meanwhile, a few studies reported that maternal behavior choice was involved in childhood allergies.[8,9] Early in 1998, Boston conducted a prospective birth cohort study in 505 mother-infant pairs, revealing that maternal smoking during pregnancy could increase the risk of childhood wheezing in the first year of life.[9] A newly published cross-sectional study also reported that maternal smoking was associated with a higher risk of asthma in their offspring.[10] However, data on maternal life style such as sleeping and physical activity are largely lacking. With rapid modernization, sleep duration, physical activity and screen using are indeed lifestyle choices people face every day. It has been a growing concern that unhealthy and sedentary lifestyle, including chronic sleep loss, inactivity, and excessive screen exposure, is quite common.[11] A national school-based health survey in Greek revealed that physical activity during pregnancy was significantly associated with childhood obesity.[12] A prospective study found that sleep difficulties during pregnancy affected social development of their offspring when they were 1 year old.[13] However, none of studies have investigated whether maternal lifestyle factors during pregnancy had an impact on childhood allergies.

Gender dimorphism has long been known to childhood allergies,[3,14] but the gender difference by the same risk exposure has rarely been studied. Genetic background has considered to be a risk factor for allergies.[15] Therefore, attention to gender differences, taking familial heredity into account, would help us deeply understand the childhood allergy, which should be the basis of personalized allergy intervention.

A citywide study was conducted in Shanghai to explore the association of maternal lifestyle factors, including sleep duration, daily physical activity, and screen exposure, with the risk of respiratory allergies in their offspring. Specifically, gender differences will be a focus.

2. Methods

2.1 Study participants and ethics statement

Shanghai Children Allergy Study (SCAS) explores the epidemic characteristics of childhood allergies, and provides a basis for formulating the intervention strategy for children allergy in Shanghai. The study was sponsored by Shanghai Education Commission. We collaborated with Shanghai Children's Medical Center to carry out the project research. This cross-sectional baseline study was conducted during April-June 2019, using a multi-stage and multi-strata sampling approach. Among the total 9 urban areas and 8 suburban/rural areas in Shanghai, 4 urban areas (Xuhui, Putuo, Yangpu, and Pudong New area) and 4 suburban/rural areas (Minhang, Jinshan, Qingpu, and Chongming) were randomly sampled. In all sampled areas, 31 kindergartens were randomly selected. The investigation purpose was explained ahead

to the principals and teachers. To obtain parental permission, the purpose was conveyed to parents through parents' meetings, in which voluntary and anonymous participation was stressed. Informed consent form was then obtained from parents. Each child's mother completed the questionnaire on behalf of herself and her child.

Overall, 6389 children were recruited to participate in this baseline survey. Among them, 6237 (97.62%) completed the questionnaires. After the exclusion of 1 missing data on allergic diseases, the valid sample of this study consisted of 6236 mother-children pairs (defined as All Population Group).

The ethical application and the consent procedure of this study were approved by the Ethics Committee of Shanghai Jiao Tong University School of Medicine.

2.2 Maternal behavioral variables

A brief Maternal Life-style Questionnaire (MLQ) was utilized to evaluate maternal life styles during pregnancy based on the literature reviewed.[16–18] Daily behavioral choice during pregnancy included the duration of sleep per day, the frequency of physical activity (never/occasionally, 1-3hrs./week, 3-6hrs./week, ≥1hrs./day), and the frequency of phone/computer/television exposure (< 2hrs./day, 2-4hrs./day, 4-8hrs./day, ≥8hrs./day) on average. The optimal duration of sleep for pregnant woman is not yet known, the cutoff for short sleep duration was defined as less than 8 hours/day in this study with the reference of most studies.[18,19] Meanwhile, 8 hours/day was close to the 25th percentile of the distribution of total sleep duration during pregnancy in our dataset. The answers for daily physical activity were classified into two groups: <1hr./day vs. ≥1hrs./day; and screen exposure were classified into two groups: ≥2hrs./day vs. <2hrs./day.

2.3 Ascertainment of allergic diseases

The International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire was applied to detect respiratory allergies.[20,21] The Cronbach's alpha coefficient of the ISAAC allergic questionnaire in our sampled children was 0.91. The intra-class correlation coefficient of retest reliability at intervals of 2 weeks was 0.94. Validity presented by Kaiser-Meyer-Olkin (KMO) was 0.94 and the high validity among preschool children has been confirmed.[22] All questions were answered by yes or no. For the assessment of asthma, the question was asked: "Has your child ever been diagnosed with asthma?". We further assessed the current wheezing by questions: "Has your child had any wheezing, or breathing difficulties in the last 12 months?" or "Has your child ever experienced wheezing or whistling in the chest in the last 12 months?". Two questions were utilized for allergic rhinitis diagnosis: "Has your child ever been diagnosed with allergic rhinitis?" and "Has your child ever sneezing, runny nose, stuffy, itchy or itchy eyes in the last 12 months not due to having a cold or flu?". Children were screened out one of above three types of respiratory allergies were considered to be Screened Positive (SP).

In addition to using the ISAAC questionnaire to screen respiratory allergies, we further collected information on allergen tests. 4438 participants in total ever took allergen test, including skin prick test (SPT), immunoglobulin E (IgE) and the others (defined as Allergen Test Subgroup). We further asked the

children who had been tested for allergens: “Did the allergen test is positive, if so, which of the following allergens?” Common allergens were listed, including dust mite, mold, milk/dairy products, eggs, fish and shrimp, peanut, nuts other than peanuts, wheat, beans or soy products, fruit, vegetables, pollen, mugwort, ragweed, cat/dog hair, and so forth. Among children with screened respiratory allergies positive, those who tested positive for any of allergens were further regarded as Screened and Test Positive (STP).

2.4 Confounding variables

2.4.1 Demographic characteristics

Demographic characteristics included age and childhood overweight/obesity (yes/no), child’s sleep duration on weekdays (< 10hrs./day, ≥ 10hrs./day), child’s sleep duration on weekends (< 10hrs./day, ≥ 10hrs./day), child’s exercise frequency (< 1hr./day, ≥1hrs./day), child’s screen exposure frequency (< 5 times./week, ≥ 5 times./week). BMI (body mass index) for age and sex-specific percentile over 85% was implemented to define the overweight/obesity.[23] Family background contained household incomes (< 4000, 4000–8000, > 8000), family structures (single parent family, nuclear family, extended family), both mother and father’s educational levels (primary education, secondary education, college and above), and first-degree relative with allergies (yes/no).

2.4.2 Obstetric characteristics and health status of parents

Obstetric characteristics included gestational weeks (premature delivery, post-delivery and term delivery), delivery modes (cesarean delivery, vaginal delivery/midwifery), and full breastfeeding over 6 months (yes/no). Health status of parents contained maternal smoking exposure status (yes/no), maternal drinking habits (yes/no), gestational hypertension (yes/no), gestational diabetes (yes/no), gestational anemia (yes/no), mother's age at delivery (≥ 30, 25–29, ≤ 24).

2.5 Statistical analysis

Statistical descriptions were made utilizing the percentage for categorical variables. The univariate logistic regression was applied to compare differences between groups.

Univariate logistic regression was implemented to calculate the unadjusted odds ratios (OR) and 95% confidence intervals (CI), thus evaluating the relationship between maternal behavioral characteristics and allergic diseases. In All Population Group, '1' for children with screened allergies positive and '0' for children screened allergies negative. In Allergen Test Subgroup, children with both positive in allergen test and screened respiratory allergies were defined as '1', and who had neither been screened with any allergy nor found any allergen were defined as '0'. Adjustments of confounding factors were made by the multivariate regression models followed by a two-step procedure: Model I only adjusted for demographic characteristics; in Model II, obstetric characteristics and health status of parents were further adjusted.

All other analyses were performed with the Statistical Package for the Social Sciences (SPSS) (IBM-SPSS Statistics version 23.0, Inc., Chicago, IL). Statistical significance level was set at p value < .05 (two sided).

3. Results

3.1 Descriptive analysis

The study sample included 6236 children (3289 boys vs. 2947 girls), aged 5.66 years (SD=0.95). 14.6%, 16.2%, and 21.0% of children had asthma, wheeze, and allergic rhinitis, respectively. 4438 participants who took allergen test had demographic characteristics similar to those of the 6236 population (**Table 1**). Among allergic children, there is no gender difference in maternal exposure to unhealthy behaviors (**Table 2**). **Figure 1** plots the prevalence of asthma, wheeze, and allergic rhinitis with increasing age by different gender. It can be seen that**,** compared to girls, boys are more susceptible to all three of respiratory allergies.

	All Population Group			Allergen Test Subgroup		
	Boy (n=3289)	Girl (n=2947)	c^2/t	Boy (n=2292)	Girl (n=2146)	c^2/t
	n (%)	n (%)		n (%)	n (%)	
Demographic characteristics						
Age (years); mean (SD)	5.66 (0.94)	5.66 (0.95)	1.167	5.65 (0.94)	5.66 (0.96)	.071
Childhood overweight/ obesity	666 (20.3%)	469 (16.0%)	**19.768*** **	465 (20.4%)	337 (15.8%)	**15.880*** **
Child's sleep duration on weekdays (≥10 hrs./day)	557 (16.9%)	496 (16.8%)	0.013	386 (16.8%)	359 (16.7%)	.010
Child's sleep duration on weekends (≥10 hrs./day)	960 (29.3%)	980 (33.3%)	**12.001*** **	690 (30.2%)	705 (33.0%)	**3.905* **
Child's screen exposure frequency (≥5 times./week)	436 (13.3%)	400 (13.6%)	0.134	290 (12.7%)	286 (13.3%)	0.446
Child's exercise frequency (≥1 hr./day)	1450 (44.1%)	1225 (41.6%)	**4.025* **	1058 (46.2%)	916 (42.7%)	**5.424* **
Family income #			0.265			0.383
> 8000RMB	1705 (51.8%)	1519 (51.5%)		1201 (52.4%)	1087(50.7%)	
4000- 8000RMB	1228 (37.3%)	1117 (37.9%)		833 (36.3%)	823 (38.4%)	
< 4000RMB	356 (10.8%)	311 (10.6%)		258 (11.3%)	236 (11.0%)	
Family structure			0.587			0.256
Single parent	89 (2.7%)	81 (2.7%)		63 (2.7%)	60 (2.8%)	
Nuclear family	1864 (56.7%)	1697 (57.6%)		1317 (57.5%)	1248 (58.2%)	
Extended family	1336 (40.6%)	1169 (39.7%)		912 (39.8%)	838 (39.0%)	
Mother's education level			**6.026* **			4.017
College and above	2442 (74.2%)	2243 (76.1%)		1685 (73.5%)	1624 (75.7%)	
Secondary education	509 (15.5%)	454 (15.4%)		366 (16.0%)	332 (15.5%)	
Primary education	338 (10.3%)	250 (8.5%)		241 (10.5%)	190 (8.9%)	
Father's education level			2.524			2.015
College and above	2439 (74.2%)	2234 (75.8%)		1681 (73.3%)	1613 (75.2%)	
Secondary education	564 (17.1%)	482 (16.4%)		404 (17.6%)	357 (16.6%)	
Primary education	286 (8.7%)	231 (7.8%)		207 (9.0%)	176 (8.2%)	
First-degree relative with allergies	897	767	1.234	548 (23.9%)	482 (22.5%)	1.305

	(27.3%)	(26.0%)				
Obstetric and parental health condition						
Gestational weeks			2.022			1.577
Premature delivery	248 (7.6%)	202 (6.9%)		166 (7.3%)	146 (6.9%)	
Post-term delivery	128 (3.9%)	130 (4.5%)		84 (3.7%)	93 (4.4%)	
Term delivery	2890 (88.5%)	2589 (88.6%)		2029 (89.0%)	1887 (88.8%)	
Delivery mode			**6.525***			**8.304****
Cesarean delivery	1717 (52.2%)	1443 (49.0%)		1195 (52.1%)	1026 (47.8%)	
Vaginal delivery/ midwifery	1572 (47.8%)	1504 (51.0%)		1097 (47.9%)	1120 (52.2%)	
Mother's age at delivery			0.612			1.745
≥ 30	1286 (39.6%)	1139 (39.2%)		868 (38.4%)	817 (38.7%)	
25-29	1458 (44.9%)	1332 (45.9%)		1025 (45.4%)	982 (46.5%)	
≤ 24	500 (15.4%)	433 (14.9%)		367 (16.2%)	313 (14.8%)	
Full breastfeeding ≥ 6 month	1885 (57.3%)	1754 (59.5%)	3.112	1332 (58.1%)	1264 (58.9%)	0.281
Gestational smoking exposure	71 (2.2%)	63 (2.1%)	0.003	46 (2.0%)	46 (2.1%)	0.102
Gestational drinking	84 (2.6%)	2878 (97.7%)	0.294	54 (2.4%)	52 (2.4%)	0.021
Gestational hypertension	60 (1.8%)	85 (2.9%)	**7.690****	41 (1.8%)	52 (2.4%)	2.173
Gestational diabetes	149 (4.5%)	142 (4.8%)	0.290	101 (4.4%)	98 (4.6%)	0.066
Gestational anemia	189 (5.7%)	200 (6.8%)	2.875	126 (5.5%)	138 (6.4%)	1.725
Respiratory allergic disease						
Asthma	533 (16.2%) [a]	380 (12.9%) [a]	**13.635*****	202 (8.8%) [b]	122 (5.7%) [b]	**16.026*****
Wheeze	586 (17.8%) [a]	427 (14.5%) [a]	**12.650*****	226 (9.9%) [b]	138 (6.4%) [b]	**17.316*****
Allergic rhinitis	802 (24.4%) [a]	509 (17.3%) [a]	**47.357*****	325 (14.2%) [b]	183 (8.5%) [b]	**34.932*****

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; [#]Family income is calculated as RMB/person/month, RMB is China's currency (yuan)

[as] Children only with screened respiratory allergies. [b] Children with both screened respiratory allergies and allergen test positive.

Table 1

Sample characteristics, stratified by gender

Table 2

Maternal behavioral characteristics among children with respiratory allergies, stratified by gender

	SP (n = 1904)		χ^2/t	STP (n = 665)		χ^2/t
	boy	**girl**		**boy**	**girl**	
Individual factor						
Sleep duration			2.093			.046
< 8hrs./day	340 (30.4%)	213 (27.3%)		117 (28.1%)	67 (27.3%)	
≥ 8hrs./day	778 (69.6%)	566 (72.7%)		299 (71.9%)	178 (72.7%)	
Physical activity			.095			.430
< 1hr./day	936 (83.6%)	651 (83.0%)		349 (83.9%)	204 (81.9%)	
≥ 1hrs./day	184 (16.4%)	133 (17.0%)		67 (16.1%)	45 (18.1%)	
Screen exposure			1.376			2.441
≥ 2hrs./day	887 (79.2%)	638 (81.4%)		325 (78.1%)	207 (83.1%)	
< 2hrs./day	233 (20.8%)	146 (18.6%)		91 (21.9%)	42 (16.9%)	
Combined factor index						
0	30 (2.7%)	22 (2.8%)	.857	10 (2.4%)	5 (2.0%)	.646
1	249 (22.3%)	170 (21.8%)		100 (24.0%)	60 (24.5%)	
2	607 (54.3%)	437 (56.1%)		227 (54.6%)	128 (52.2%)	

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

SP, screened respiratory allergies positive; STP, both screened respiratory allergies positive and allergen test positive.

Maternal behavioral factors included sleep less than 8 hours/day, exercise less than 1 hour/day, screen time more than 2 hours/day.

“0” demonstrated that none of three risk factors were occurred; “1” demonstrated that one of these three risk factors was occurred; “2” demonstrated that two of these three risk factors were occurred.; “3” demonstrated that these three risk factors were all occurred.

	SP (n = 1904)		χ^2/t	STP (n = 665)		χ^2/t
	boy	girl		boy	girl	
3	232 (20.8%)	150 (19.3%)		79 (19.0%)	52 (21.2%)	
* p < 0.05, **p < 0.01, ***p < 0.001.						
SP, screened respiratory allergies positive; STP, both screened respiratory allergies positive and allergen test positive.						
Maternal behavioral factors included sleep less than 8 hours/day, exercise less than 1 hour/day, screen time more than 2 hours/day.						
“0” demonstrated that none of three risk factors were occurred; “1” demonstrated that one of these three risk factors was occurred; “2” demonstrated that two of these three risk factors were occurred.; “3” demonstrated that these three risk factors were all occurred.						

3.2 Maternal behavioral exposure during pregnancy and childhood allergic diseases

3.2.1 Individual associations

In Table 3, we applied a gender stratified analysis and found that maternal short sleep duration, lack of physical activity and too much screen exposure during pregnancy were associated with an increased risk of childhood respiratory allergies. When the analyses were repeated in Allergen Test Subgroup, very similar results were obtained. However, a significant gender difference was identified, all above associations were mainly observed in boys. Through two-step adjustment for possible confounding factors, the results were generally kept in most cases. In the final adjusted model (Model II), maternal short sleep duration (OR,1.322; 95%CI:1.106–1.579) and lack of physical activity (OR,1.287; 95%CI:1.046–1.584) were found to be an independent predictor for childhood allergies, however, only in the All Population Group; Among girls, by contrast to boys, only sleep duration and screen exposure were shown to be associated with childhood respiratory allergies. However, after accounting for confounding factors, the associations were not shown any more.

Table 3

Association of maternal behavioral factors during pregnancy with childhood respiratory allergies

	All Population Group			Allergen Test Subgroup		
	OR (95% CI)			OR (95% CI)		
	Crude Model	Adjusted Model I	Adjusted Model II	Crude Model	Adjusted Model I	Adjusted Model II
Boy						
Sleep duration						
< 8 vs. ≥8hrs./day	**1.485 (1.260–1.750) *****	**1.336 (1.120–1.593) *****	**1.322 (1.106–1.579) ****	**1.376 (1.079–1.755) ****	1.215 (0.930–1.587)	1.174 (0.896–1.539)
Physical activity						
< 1 vs. ≥1hrs./day	**1.530 (1.264–1.853) ****	**1.318 (1.073–1.618)****	**1.287 (1.046–1.584) ***	**1.622(1.211–2.171) ****	**1.379 (1.006–1.890) ***	1.323 (0.960–1.824)
Screen exposure						
≥ 2 vs. <2hrs./day	**1.473 (1.236–1.756) *****	1.158(0.955–1.405)	1.170 (0.963–1.422)	**1.297 (1.001–1.681) ***	0.940 (0.701–1.259)	0.924 (0.685–1.245)
Girl						
Sleep duration						

OR, odds ratios; CI, confidence interval

* $p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Model I adjusted for child's age, childhood overweight/obesity, child's sleep duration on weekdays, child's sleep duration on weekends, child's exercise frequency, children's screen exposure frequency, family income, family structure, mother's education, father's education, family history of allergic diseases.

Model II further adjusted for gestational weeks, delivery mode, full breastfeeding, maternal smoking exposure, maternal drinking, gestational hypertension, gestational diabetes, gestational anemia, mother's age at delivery.

	All Population Group			Allergen Test Subgroup		
	OR (95% CI)			OR (95% CI)		
	Crude Model	Adjusted Model I	Adjusted Model II	Crude Model	Adjusted Model I	Adjusted Model II
< 8 vs. ≥8hrs./day	**1.246 (1.031–1.505) ***	1.102 (0.904–1.345)	1.089 (0.891–1.330)	1.281(0.945–1.738)	1.120(0.812–1.546)	1.103 (0.795–1.530)
Physical activity						
< 1 vs. ≥1hrs./day	1.153 (0.927–1.434)	1.016(0.809–1.277)	0.989 (0.785–1.245)	1.053 (0.744–1.491)	0.869 (0.600-1.257)	0.866 (0.595–1.260)
Screen exposure						
≥ 2 vs. <2hrs./day	**1.426 (1.156–1.760) ****	1.149 (0.917–1.440)	1.173 (0.933–1.475)	**1.622(1.128–2.332) ****	1.289 (0.874–1.901)	1.323 (0.893–1.961)

OR, odds ratios; CI, confidence interval

* $p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Model I adjusted for child's age, childhood overweight/obesity, child's sleep duration on weekdays, child's sleep duration on weekends, child's exercise frequency, children's screen exposure frequency, family income, family structure, mother's education, father's education, family history of allergic diseases.

Model II further adjusted for gestational weeks, delivery mode, full breastfeeding, maternal smoking exposure, maternal drinking, gestational hypertension, gestational diabetes, gestational anemia, mother's age at delivery.

The analysis was also repeated in the single type of respiratory allergic disease, and the similar results were obtained (**Table S1**). After further considering family history in first-degree relative, the results were generally repeatable in most cases, however, it seemed that the associations were stronger in those children without allergic family history (**Table S2**).

3.2.2 Combined associations

Table 4 demonstrated the combined associations of three maternal behavioral factors with childhood respiratory allergies with gender as stratified factor. Children's risk of respiratory allergies increased with an increase in unhealthy maternal lifestyles during pregnancy. Very similar results were found when the analysis replicated in the Allergen Test Subgroup. Similar to the individual association, the gender difference of the combination association was significant. After two-step adjustment, the risk remained

mostly in boys. In the final adjusted model (Model II), one of the three factors occurred can result in higher risk of childhood respiratory allergies only in All Population Group (OR,1.649; 95%CI:1.031–2.639); when two of these life styles were involved, the significant results were found in All Population Group (OR,1.915; 95%CI:1.212–3.024); as referring to the combination of three unhealthy behavioral factors, the risk further amplified in both All Population Group (OR,2.406; 95%CI:1.485-3.900) and Allergen Test Subgroup (OR,2.187; 95%CI:1.000-4.785). When it came to girls, the risk of allergies increased only when two or more of the maternal unhealthy lifestyles concentrated together. However, after controlling for confounding factors, no association was revealed. Figure 2 demonstrates the combined association of maternal lifestyle with asthma, wheeze and allergic rhinitis, respectively.

Table 4

Combined association of maternal behavioral factors during pregnancy with childhood respiratory allergies

	All Population Group				Allergen Test Subgroup			
	N (%)	OR (95% CI)			N (%)	OR (95% CI)		
Crude Model	Adjusted Model I	Adjusted Model II	Crude Model	Adjusted Model I	Adjusted Model II			
Boy								
0	30 (2.7%)	Ref	Ref	Ref	10 (2.4%)	Ref	Ref	Ref
1 vs. 0	249 (22.3%)	**1.758 (1.129–2.737) ***	**1.672 (1.048–2.668)***	**1.649 (1.031–2.639) ***	100 (24.0%)	**2.119 (1.037–4.329) ***	2.008 (0.942–4.278)	1.966 (0.914–4.226)
2 vs. 0	607 (54.3%)	**2.516 (1.638–3.863) *****	**1.966 (1.248–3.097)****	**1.915 (1.212–3.024) ****	227 (54.6%)	**2.787 (1.389–5.592) ****	**2.151 (1.027–4.505) ***	2.043 (0.967–4.318)
3 vs. 0	232 (20.8%)	**3.520 (2.240–5.531) *****	**2.466 (1.526–3.985)*****	**2.406 (1.485-3.900) *****	79 (19.0%)	**3.586 (1.735–7.412) *****	**2.325 (1.072–5.042) ***	**2.187 (1.000-4.785) ***
Girl								
0	22 (2.8%)	Ref	Ref	Ref	5 (2.0%)	Ref	Ref	Ref

OR, odds ratios; CI, confidence interval; Ref, reference.

** $p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Maternal risk behavioral factors included sleep duration less than 8 hours, physical activity less than 1 hour/day, screen exposure more than 2 hours/day; “0” demonstrated that none of three risk factors were occurred. “1” demonstrated that one of these three risk factors was occurred; “2” demonstrated that two of these three risk factors were occurred; and “3” demonstrated that these three risk factors were all occurred.

Model I adjusted for child's age, childhood overweight/ obesity, child’s sleep duration on weekdays, child’s sleep duration on weekends, child’s exercise frequency, children’s screen exposure frequency, family income, family structure, mother’s education, father’s education, family history of allergic diseases.

Model II further adjusted for gestational weeks, delivery mode, full breastfeeding, maternal smoking exposure, maternal drinking, gestational hypertension, gestational diabetes, gestational anemia, mother's age at delivery.

	All Population Group				Allergen Test Subgroup			
	N (%)	OR (95% CI)			N (%)	OR (95% CI)		
1 vs. 0	170 (21.8%)	1.223 (0.744–2.010)	1.074 (0.645–1.789)	1.021 (0.610–1.709)	60 (24.5%)	1.902 (0.740–4.892)	1.640 (0.623–4.318)	1.595 (0.602–4.229)
2 vs. 0	437 (56.1%)	1.576 (0.977–2.542)	1.145 (0.696–1.882)	1.086 (0.657–1.794)	128 (52.2%)	2.060 (0.819–5.180)	1.374 (0.530–3.564)	1.310 (0.502–3.418)
3 vs. 0	150 (19.3%)	**1.886 (1.139–3.122)** *	1.271 (0.751–2.152)	1.209 (0.711–2.056)	52 (21.2%)	**2.909 (1.125–7.525)** *	1.801 (0.672–4.828)	1.760 (0.652–4.753)

OR, odds ratios; CI, confidence interval; Ref, reference.

*** $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Maternal risk behavioral factors included sleep duration less than 8 hours, physical activity less than 1 hour/day, screen exposure more than 2 hours/day; “0” demonstrated that none of three risk factors were occurred. “1” demonstrated that one of these three risk factors was occurred; “2” demonstrated that two of these three risk factors were occurred; and “3” demonstrated that these three risk factors were all occurred.

Model I adjusted for child's age, childhood overweight/ obesity, child’s sleep duration on weekdays, child’s sleep duration on weekends, child’s exercise frequency, children’s screen exposure frequency, family income, family structure, mother’s education, father’s education, family history of allergic diseases.

Model II further adjusted for gestational weeks, delivery mode, full breastfeeding, maternal smoking exposure, maternal drinking, gestational hypertension, gestational diabetes, gestational anemia, mother's age at delivery.

The similar results were observed when the analysis was repeated in the single type of respiratory allergic disease (**Table S3**).

4. Discussion

This is the first study exploring the associations of maternal lifestyle choice during pregnancy with the risk of childhood respiratory allergic diseases. Our findings demonstrated that all of the three unhealthy maternal lifestyles, including short sleep duration, lack of physical activity and too much screen exposure, were independent risk predictors. Also of concern was significant dose-response trend, the more concentrations of maternal unhealthy lifestyles during pregnancy, the greater risk of respiratory allergies in their children. Moreover, significant gender difference was identified that boys were more susceptible to the adverse effects. The results, in most cases, can be verified in the Allergen Test Subgroup and the single type of disease, which further enforced the evidence. The present study extended our attention on the association of maternal behavior exposure with immune development and allergic disease susceptibility in their offspring, in which gender difference should be taken into consideration.

The rapid increase in childhood allergic disease may be correlated to rapid economic growth or modernization.[3] In developed countries, the prevalence of childhood allergic respiratory symptoms appears to have peaked and stabilized.[24] China, as a developing country, is rapidly urbanizing and the prevalence of childhood respiratory allergies is now on the rise, especially in fast-growing cities such as Shanghai.[3] Urbanization is accompanied by a modern style of life, electronic screen exposure is more frequent, sedentary time is increasing while sleeping time is decreasing,[11] and there has been proved that pregnant women spend at least half their time on sedentary behaviors.[25]

Our results provided new evidence to the hypothesis that mother's lifestyle during pregnancy affects offspring's long-term health, herein childhood respiratory allergies. Previous studies exploring the effect of lifestyle during pregnancy on the long-term health of children largely focused on the neurological and behavioral development.[26–29] A rodent model found that lacking of sleeping in the third trimester can impair autonomic responses in male offspring with a long-term effect.[26] Cohorts data from 83,884 mother-child pairs from five countries revealed that maternal cellphone use during pregnancy increased the risk of hyperactivity in their offspring.[27] Another two prospective studies found that adequate physical activity during pregnancy could promote language development in children.[28,29] This study, for the first time, focused on maternal lifestyle choice and the susceptibility of childhood allergic disease. In addition, most of previous studies only assessed one aspect of maternal life styles, and their combined effects have never been studied. In our study, a clear dose-response relationship was established, the more exposures to maternal unhealthy lifestyles during pregnancy, the higher risk of childhood respiratory allergies.

Early life exposure *in utero* can affect fetal airway and lung development, as well as immune function.[30] As suggested by previous studies, maternal smoking, unqualified diet, vitamin D deficiency and exposure to air pollution has been found to be possible potential risk factors.[7,31–34] A retrospective follow-up study was conducted among 1201 Los Angeles women between 3 and 6 months after delivery, where it was shown that children whose mothers ate more fast food during pregnancy had a relative increased risk of asthma.[31] Although there existed different conclusions,[32,33] a more recent meta-analysis revealed that maternal prenatal vitamin D supplementation was associated with a lower risk of allergic diseases in children.[34] Compared to these studies, we focused on daily lifestyle choices, including sleep duration, physical activity and screen using, and established the relationship between them and the risk of childhood respiratory allergies with a dose-response pattern. As far as we know, to date this is the only one population-based study to explore the associations. To test the association, analysis was further applied in subgroup whose allergen test was positive, and the similar results further enforced the evidence that maternal daily lifestyle choices is involved in childhood susceptibility to respiratory allergic diseases.

Although this is the first epidemiological study to explore the relationship between maternal lifestyle choice and offspring allergies, several potential explanations were in biological mechanism to support the relationship. A number of studies have demonstrated that early life adverse exposure *in utero* can block the production of the immune response of fetal cytokines to Th1 type and affect the programming of fetal

immune function.[30,35,36] In addition, an increased stress and inflammatory response were put forward to explain the pathway. Sleep deprivation may lead to oxidative stress and inflammation, thus affecting early embryonic development;[37] while regular exercise can effectively buffer stress and prevent inflammation-related diseases through the mother-fetus connection.[38] Moreover, prenatal unhealthy behavioral exposure may also affect microbiota of pregnant women, thereby transferring maternal bacteria to the fetus.[39] The imbalance of intestinal flora in infancy may lead to the deviation of immune function and allergic reactions.[40]

It was impressed that respiratory allergies were mainly prevalent in boys when their mothers were exposed to adverse lifestyle behaviors during pregnancy. In a rat model, maternal high-fat diet during pregnancy was associated with neonatal cardiac dysfunction, reduced respiratory capacity and oxidative stress only in male offspring, indicating that adverse prenatal exposures impaired dynamism with sex-divergent characteristic.[35] It has been recognized that male and female possessed different immune responses, especially in T-helper cells.[36] On referring to genetics, most of respiratory genes are located on sex chromosomes or are involved in the production of sex hormones. Estrogen, the primary female sex hormone, has been regarded as immune-stimulating factor.[15] While testosterone, as male sex hormones, tends to have immunosuppressive effects.[15] Taken together, the current progress in research indicated gender difference existed in immune response, it seemed that female offspring tended to have protective immune response under the function of estrogen.

This study has several limitations. First, information on maternal behavioral exposure was obtained from questionnaires, and thus the recall bias was inevitable. However, due to pregnancy was a special period, and the China's one-child policy in the past decades, the recall bias can lower to a small level. Second, cross-sectional study was poor in determining causal links. However, the dependent variables and the outcome variables we analyzed were mothers' lifestyles during pregnancy and their children's respiratory allergies respectively, which had a time sequence, thus revealing a certain causal relationship. Third, allergic diseases were not diagnosed by professionals. However, the international standard ISAAC questionnaire was applied worldwide with quite good reliability and validity.[22] In addition, children with positive allergen test were analyzed as a subgroup, which further verified our findings. Finally, even though many confounding factors were taken into account, residual confounding may remain. However, given that the results were broadly consistent across all the respiratory allergies in this study, the evidence for link between maternal behavioral exposure and childhood allergic disease appeared to be robust.

Conclusion

This study is the first to emphasize the association between maternal behaviors such as lack of sleep, physical inactivity, and prolonged use of electronic devices during pregnancy and the risk of childhood allergies in a gender-specific manner. In particular, there appeared to have a clear dose-response relationship, the more unhealthy maternal behaviors, the greater risk of childhood respiratory allergies.

However, the risk mainly affects boys. Our findings should be of interventional significance in the early life since maternal lifestyle behaviors are modifiable.

Abbreviations

SCAS: Shanghai Children Allergy Study; MLQ: Maternal Life-style Questionnaire; ISAAC: International Study of Asthma and Allergies in Childhood; KMO: Kaiser-Meyer-Olkin; SP: Screened Positive; SPT: Skin prick test; IgE: Immunoglobulin E; STP: Screened and Test Positive; OR: Odds Ratios; CI: Confidence Intervals; SPSS: Statistical Package for the Social Sciences

Declarations

Ethics approval and consent to participate

The ethical application and the consent procedure of this study were approved by the Ethics Committee of Shanghai Jiao Tong University School of Medicine.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

JZ, ST, YY, and JQ was involved with study design and participants recruitment. YC and JL drafted the manuscript. YC, JL and YX participated in the design of the study and performed the statistical analysis. SL conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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Figures

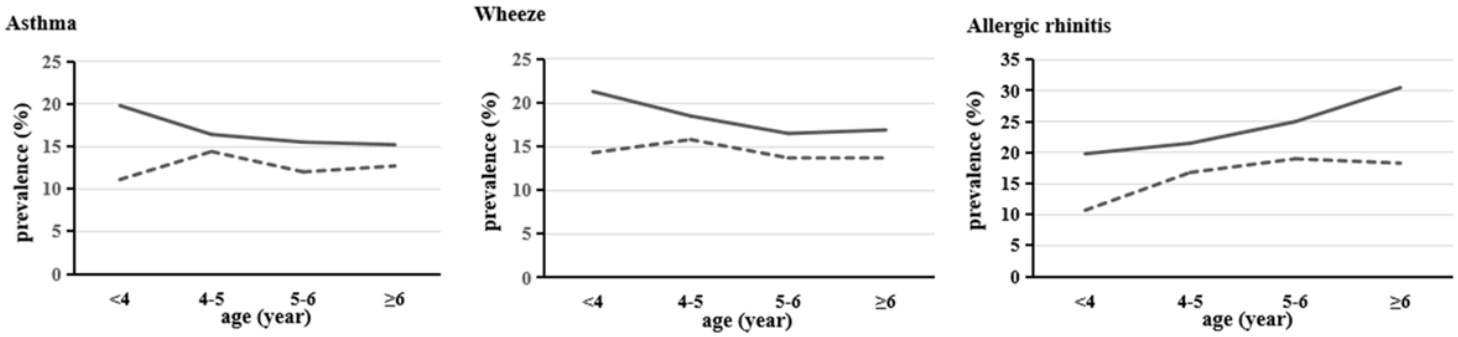

Figure 1

Age and gender-specific prevalence of childhood respiratory allergies. Solid lines represent boys, dotted lines represent girls.

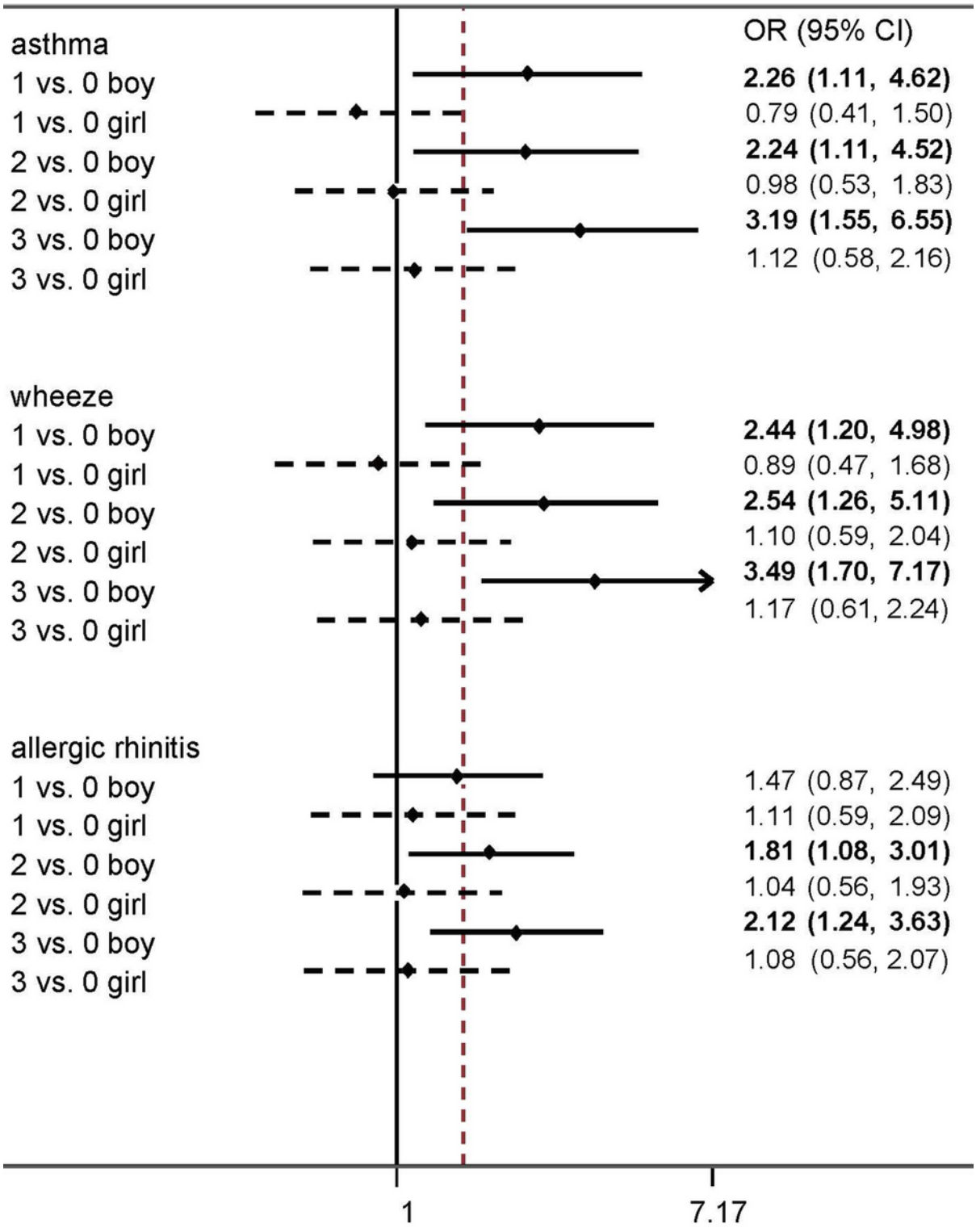

Figure 2

Combined association of maternal behavioral factors and childhood respiratory allergies Solid lines represent boys, dotted lines represent girls. Maternal behavioral factors including sleep less than 8 hours/day, physical activity less than 1 hour/day, screen time more than 2 hours/day. “0” demonstrated that none of three risk factors were occurred. “1” demonstrated that one of these three risk factors were occurred. “2” demonstrated that two of these three risk factors were occurred. “3” demonstrated that these

three risk factors were all occurred. Controlled for child's age, childhood overweight/obesity, child’s sleep duration on weekdays, child’s sleep duration on weekends, child’s exercise frequency, children’s screen exposure frequency, family income, family structure, mother’s education, father’s education, family history of allergic diseases, gestational weeks, delivery mode, full breastfeeding, maternal smoking exposure, maternal drinking, gestational hypertension, gestational diabetes, gestational anemia, mother's age at delivery.

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