



Maternal affective and stress-related factors during pregnancy affect the occurrence of childhood allergic diseases: A Shanghai MCPC study

Yu-yang Shi^a, Qian Wei^a, Xuemei Ma^b, Yunhui Zhang^c, Ling Wang^{d,*}, Hui-jing Shi^{a,*}

^a Department of Maternal, Child and Adolescent Health, School of Public Health, Fudan University, Shanghai 200032, China

^b Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London SE5 8AF, United Kingdom

^c Department of Environment Health, School of Public Health, Fudan University, Shanghai 200032, China

^d Shanghai Medical College of Fudan University, Shanghai 200032, China

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ABSTRACT

Objective: To investigate the association between exposures to maternal affective and stress-related factors during pregnancy and allergies in children from birth to 2 years of age.

Methods: We enrolled a total of 4178 children from the Shanghai Maternal-Child Pairs Cohort and measured maternal stress, anxiety, and depression during pregnancy by applying the Life Events Scale for Pregnant Women, Self-Rating Anxiety Scale, and the Center for Epidemiologic Studies–Depression Scale, respectively. Children's allergies were assessed by community physicians at 2, 6, 12, and 24 months, respectively; these included eczema, atopic dermatitis, food allergy, wheezing, asthma, and atopic rhinitis. We applied a latent class analysis (LCA) to these factors and analyzed the impacts of maternal affective and stress-related factors on childhood allergies by exploiting multivariate logistic regression.

Results: Three distinct classes of children were revealed by LCA: healthy (79.8%), transient allergy (15.2%), and persistent allergy (4.9%). High maternal stress in both early and late pregnancy was associated with an increased risk of infant eczema at 2 months (aOR = 1.30, 95% CI = 1.01–1.67; aOR = 1.64, 95% CI = 1.14–2.36). Moreover, high maternal stress in late pregnancy was also associated with food allergy at 6 months, rhinitis at 2 years of age, and persistent allergy (aOR = 3.22, 95% CI = 1.27–8.12; aOR = 1.78, 95% CI = 1.01–3.15; and aOR = 1.93, 95% CI = 1.10–3.40).

Conclusions: The associations of maternal affective and stress-related factors during pregnancy with childhood allergies may vary by type and disease onset. We postulate that maternal stress in late pregnancy may exert a sustained negative effect on early childhood allergic diseases.

1. Introduction

Allergic diseases and manifestations such as eczema, atopic dermatitis (AD), food allergy, asthma, and atopic rhinitis are common chronic diseases among children [1–3]; in recent years, researchers have noted an increasing prevalence of childhood allergies that parallels the growth in maternal affective and stress-related factors during pregnancy [4–6]. This suggests a potential etiologic role for such factors in the onset of allergic diseases in children [7,8]. For example, investigators have previously demonstrated that children whose mothers experienced adverse life events during the second half of pregnancy were considerably more likely to develop asthma and eczema at age 14 [9].

Furthermore, Brew et al. [10] ascertained that the effect of maternal emotional disorders on childhood asthma could best be explained by cumulative exposure to maternal depression or anxiety during pre-conception, pregnancy, the postnatal period, and even subsequent periods. Furthermore, it was reported that severe stress in the first trimester was particularly associated with an increased risk of schizophrenia [11]. Maternal stress varies throughout pregnancy [12], and it now appears that the timing and type of exposure affect the consequences of maternal stress-related factor involvement. However, previous studies have largely taken the duration of pregnancy in its entirety, and entailed the evaluation of single measures or a limited number of measures of psychosocial stress-related factors such as maternal negative life events

* Correspondence to: Hui-jing Shi, Department of Maternal, Child and Adolescent Health, School of Public Health, Fudan University, Shanghai 200032, China.

** Correspondence to: Ling Wang, Shanghai Medical College of Fudan University, Shanghai 200032, China.

E-mail addresses: lingwang@fudan.edu.cn (L. Wang), hjshi@fudan.edu.cn (H.-j. Shi).

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[8,13–17], perceived stress [8,18,19], depression [8,10,20,21], and anxiety [10,20,21]. Therefore, enhancing our understanding of the long-term effects of multiple, common prenatal stressors on allergic diseases in children as well as the impacts of prenatal timing is urgently needed.

Current evidence on the effects of maternal stress during pregnancy on childhood AD is inconsistent. Although Braig et al. [22] demonstrated a link between maternal prenatal stress and atopic dermatitis symptoms, this association with AD diagnoses remains limited. In addition, studies have revealed that maternal stress and distress during pregnancy were associated with an increased risk of childhood eczema [18,20]. Moreover, a few studies have shown an association between maternal affective and stress-related factors and childhood food allergies, their results remain controversial. According to a previous study, food-allergic children were shown to have been exposed to more stressful events during the in-utero period compared to siblings [17]. By contrast, Smejda et al. [23] did not uncover a significant association between maternal stress and childhood food allergy during the first year of life. Regarding wheezing and asthma, Magnus et al. [24] discerned that maternal anxiety/depression and negative life events were associated with offspring asthma.

In summary, these allergic diseases are related and share many

common risk factors, and there is growing evidence that early skin contact with allergens leads to food allergy [25–27]; whereas early oral exposure may result in tolerance (known as the “dual-allergen exposure hypothesis”) [28]. For example, Caffarelli et al. [29] found that early food sensitization predicted the onset of asthma, and other authors showed that wheezing episodes in young children marked the onset of asthma and lung function deficits [30]. Epidemiologic data as well as numerous loci linked to both AD and asthma have also suggested shared underlying pathways [31].

Thus, there is a critical need for prospective cohort studies that entail the impact of maternal psychological stress on childhood allergic diseases in offspring. We herein therefore assessed the impact of maternal affective and stress-related factors during pregnancy (i.e., high stress, anxiety, and depression) on the occurrence of eczema, AD, food allergy, wheezing, asthma, and allergic rhinitis in offspring during their first 2 years of life.

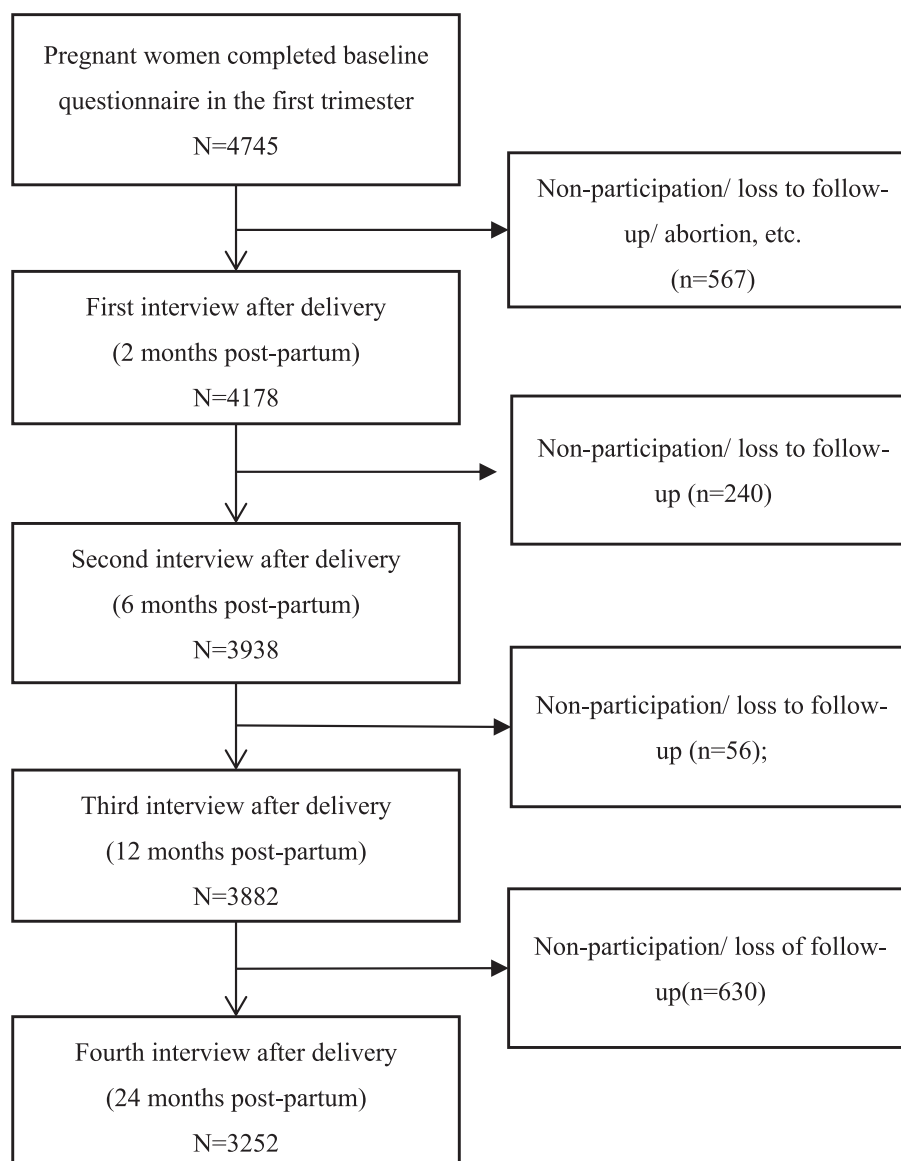


Fig. 1. Flowchart describing the selection process of pregnant women and the follow-up of their children.

2. Methods

2.1. Study design

Participants in this study were enrolled from the Shanghai Maternal-Child Pairs Cohort (Shanghai MCPC), which was the first prospective birth cohort study in China since the implementation of the comprehensive two-child policy. Pregnant women were recruited at two regional maternity hospitals in the Shanghai Pudong and Songjiang Districts between April 2016 and April 2018. A baseline questionnaire that was completed by pregnant women at 12–16 gestational weeks included sociodemographic characteristics, psychological stress during early pregnancy, living situation, and lifestyle; follow-up questionnaires were then completed by the pregnant women at 32–36 weeks of gestation and at childbirth [12]. Additionally, the health information of children was collected with self-completed questionnaires by a primary caregiver (usually the mother) at 2, 6, 12, and 24 months after childbirth under the supervision of community physicians. A total of 4178 children who were born up to October of 2018 were included in this study; and all requisite data were available for 3938 children at 6 months, 3882 children at 12 months, and 3252 children at 24 months (Fig. 1). The study was approved by the ethics committee of the School of Public Health, Fudan University (IRB number 2016-04-0587, IRB# 2016-04-0587-EX), and written informed consent was obtained from each participating woman after full explanation of the purpose and nature of all procedures used.

2.2. Assessments of maternal affective and stress-related factors

Maternal affective and stress-related factors, including perceived stress, anxiety, and depression, were collected by maternal self-administered questionnaires.

The Life Events Scale for Pregnant Women (LESPW) was applied to assess perceived stress derived from family life, work, study, social relationships, and other aspects during early pregnancy (12–16 weeks) and late pregnancy (32–36 weeks). The LESPW is a comprehensive, reliable, and widely employed self-reporting scale that was designed specifically for pregnant women; the instrument asks women whether they had experienced 53 potentially stressful life events [32,33]. Stressful life events are classified into two types: subjective events (SE) and objective events (OE). SE principally includes subjective perceptions such as dissatisfaction with one's job, fetal developmental concerns, and stress with learning or work. OE is further subdivided into three subscales (OE1, OE2, and OE3) according to objective event stress levels. The LESPW total score is calculated according to the weighted scores for the events, and a higher score indicates a higher level of life-event stress during pregnancy. The demarcation points for total score and subscale scores are 375, 130 (SE), 310 (positive objective events), 235 (generally negative objective events), and 145 (severely negative objective events); these were defined based on the neurobehavioral development of the fetus and how the factors affected neonatal cord plasma ACTH, cortisol, norepinephrine, and epinephrine. [34] High stress was delineated when the total score or one of the subscale scores met or exceeded the cut-off value, while participants with scores below all cut-off values were categorized in the low-stress group. The LESPW has demonstrated good reliability, with a Cronbach's alpha of 0.961 for the total and 0.776, 0.880, 0.892, and 0.902 for the respective subscales [35]. The correlation coefficient of criterion-related validity between the total score on the LESPW and the social readjustment rating scale was 0.727 [36].

At 32–36 gestational weeks, anxiety was measured using the four-point Self-Rating Anxiety Scale (SAS) [37]. Twenty-item scores were summed and standardized according to the formula standardized score = integer $(1.25 \times \text{raw score})$; the standardized score was then used as an index of anxiety, with a cut-off value of 50 [37]. The SAS displays excellent psychometric properties in both clinical and epidemiologic studies for the detection of anxiety, with a Cronbach's alpha of 0.897

and acceptable reliability in previous studies [38].

The Chinese version of the Center for Epidemiologic Studies–Depression Scale (CES–D) was used to measure the levels of depressive symptoms over the previous week at 32–36 weeks of gestation [35]. The CES-D has been widely used as a primary screening tool in research and clinical practice and contains 20 items with a total score ranging from 0 to 60. A score of 16 or above indicates a depressive mood, and a higher score indicates severe depressive symptoms. Cronbach's alpha for the scale was 0.86, with 100% sensitivity (95% CI, 44% to 100%) and 76% specificity (95% CI, 69% to 82%) for a cut-off score of 16 [39].

2.3. Assessments of allergic disease in children

The childhood allergies (including eczema, AD, food allergy, wheezing, asthma, and allergic rhinitis) were defined based on questions that were adapted from the International Study of Asthma and Allergies in Childhood (ISAAC) core questionnaires as follows [40].

“Has your child had eczema in last 2 weeks?” (At 2 and 12 months);

“Has your child exhibited atopic dermatitis in the last 2 weeks?” (At 6 months);

“Has your child had food allergy in the last 2 weeks?” (At 6, 12, and 24 months);

“Has your child had wheezing symptoms in the last 4 weeks?” (At 24 months); and “Has your child had allergic rhinitis in the last 4 weeks?” (At 24 months).

Eczema is defined as having an itchy rash on one or more areas of the skin (e.g., at the folds of the elbows or behind the knees, around the ears or eyes, or at the front of the ankles) [41,42]. We defined atopic dermatitis as intense itching and recurrent eczematous lesions associated with individual specific or non-specific causes [43]. Those individuals who responded “yes” were then asked to answer a few more questions concerning symptoms, medication use, and healthcare utilization. Individuals who reported allergic diseases could be identified as control subjects by a negative response to multiple survey questions on allergy symptoms, medication use, and healthcare utilization [44]. For example, if a child ever had wheezing symptoms, the primary caregiver would answer if the child had ever been diagnosed with asthma—either showing current symptoms or having taken asthma medication in the past 4 weeks. For each type of medication, examples were provided (including short-acting β_2 -agonists, inhaled corticosteroids, leukotriene antagonists, and oral glucocorticoids) to assist respondents in better understanding the queries. Respondents were further asked whether the child had manifested allergic symptoms toward certain foods. The duration of allergic rhinitis, medical treatments, and hospitalizations was also collected, allowing us to identify children with allergic rhinitis within a minimal false-positive inclusion [24]. A family history of allergic diseases (food allergy, asthma, and allergic rhinitis) was also noted. A child was considered to possess definite allergies if a clinical diagnosis had been made by a healthcare professional.

2.4. Covariates

Maternal variables were included as covariates based on the previous literature and obtained by questionnaires at enrollment (i.e., at 12–16 gestational weeks), including age at delivery, educational level, household income, maternal and paternal occupational status, parity, and personal and family history (parents and siblings) of asthma (self-reported for asthma as “ever”) [10]. Socioeconomic status (SES) was derived from family income and the educational level and occupational status of mothers and their partners. In our study educational level was a six-response categorical variable that ranged from no schooling to completion of a postgraduate degree, and then converted to years of

schooling and treated as a continuous variable (no schooling = 0, primary school = 6, junior high school = 9, senior high school = 12, college = 16, and postgraduate degree = 19) [45]. Occupation was categorized as construction/production, service, or management/professional [46]. Each variable's z-score was computed, which were then summed to create an overall index. Composite scores were subsequently standardized, with a low SES defined as scores below -1 and a high SES defined as scores above $+1$. Maternal exposure to second-hand smoke during pregnancy (at home or work) was self-reported in early and late pregnancy. We also collected data on the child's feeding style (i.e., exclusive breastfeeding; mixed feeding; and formula feeding) at 2, 6, and 12 months. Feeding styles for 2-month-old infants (whether exclusively breastfeeding or not) were included as a covariate in the analysis between maternal stress-related factors during pregnancy and allergic diseases at 2 months of age. As for allergies that occurred after 6 months of age, we adjusted for ever-breastfeeding (whether the mother had never or ever breastfed her children). Child characteristics were obtained by obstetric medical records at birth; these included sex, birth weight and gestational age at birth. Child gestational age was determined by physicians using ultrasonography at the first prenatal visit (i.e., at approximately 18 weeks); we relied on the last menstrual period for the 4.2% of births for which a date of the ultrasonographic evaluation was not available.

2.5. Statistical analysis

We compared demographic characteristics among the groups of mothers and their children at the various time points of 2, 6, 12, and 24 months after childbirth using Chi-squared and *t*-tests. The scores of the LESPW, SAS, and CES-D showed non-normal distributions, and we therefore presented these data as medians and interquartile ranges (IQR, 25–75). To examine the effect sizes of maternal affective and stress-related factors during pregnancy on the risk of childhood allergies, we applied Chi-squared tests and a binary logistic regression model that we adjusted for maternal age at delivery, socioeconomic status, maternal parity, exposure to second-hand smoke during pregnancy (at home or work), a family history of asthma, child's birth weight, gestational age, sex, and ever-breastfeeding. Maternal smoking during pregnancy was not included as a covariate due to its exceedingly low prevalence (0.9%) in our sample. In the logistic regression models, the reference groups were mothers with low stress levels, no anxiety, or no depressive mood. The collinearity among stress, anxiety, and depression were considered individually in a series of regression models. Without a preconceived hypothesis, an exploratory, unsupervised latent class analysis (LCA) was used to discern the overall patterns of allergies in these children. We assessed the following seven factors at 2, 6, 12, and 24 months of age: eczema at 2 months, atopic dermatitis at 6 months, food allergy at 6 months, eczema at 12 months, food allergy at 24 months, wheeze at 24 months, and rhinitis at 24 months. Models encompassing one to five classes were then considered for LCA. We selected the optimal number of classes using the Bayesian information criterion (BIC) and Akaike information criterion (AIC), and the most interpretable model was also taken into consideration [47]. This model then generated a posterior probability of membership in each identified class for each child, and each child was subsequently assigned to the class that yielded the highest posterior probability among all the available classes. We conducted our analyses using SPSS version 20.0 (IBM Corp., College Station), and the "poLCA" package in R3.3.225 was used to perform the LCA [48].

3. Results

3.1. Participant characteristics

Of 4178 pregnant women, 703 (16.8%) and 304 (7.3%) exhibited high stress (i.e., with a total score or one of the subscale scores meeting

or exceeding the cut-off value) during early pregnancy (12–16 weeks) and late pregnancy (32–36 weeks), respectively. A total of 279 (6.7%) and 304 (7.3%) pregnant women manifested anxiety and depressive symptoms in late pregnancy, respectively. The mean age of the pregnant women was 28.90 years ($SD = 4.11$), ranging from 17 to 43 years; and 563 (13.4%) were classified as showing low SES. Half of the pregnant women gave birth for the first time, and 867 (20.8%) were exposed to second-hand smoke during pregnancy. Furthermore, 105 (2.5%) children were born with low birth weight (< 2500 g) and 1852 (44.3%) were breastfed until 6 months of age (with an exclusive breastfeeding rate of 10.7%). The majority of participant characteristics did not differ significantly across different surveys (Table 1).

3.2. Prevalence of allergic diseases in children

The most common allergic disease during the first 2 years of life was skin allergy (eczema), with a prevalence of 19.7% ($n = 821$) at 2 months of age and 41.3% ($n = 1255$) at 12 months of age; while 6.3% ($n = 247$) aged 6 months were defined with AD (Table 2). The prevalence of food allergy increased from 1.6% ($n = 64$) at 6 months to 19.2% ($n = 582$) at 12 months and then declined to 8.1% ($n = 150$) by 24 months. The prevalence of allergic rhinitis was 6.8% in 2-year-old children, and among the children with a history of wheezing ($n = 203$), 31.8% were diagnosed with asthma by physicians (Table 2).

3.3. Trajectory of allergic disease patterns from LCA

A three-class structure yielded the lowest BIC among all considered models, with the three classes listed as follows.

- 1) Healthy: 79.8% were clustered into this group and these children demonstrated some eczema or allergy at either age.
- 2) Transient allergy: this group accounted for 15.2% of the children. The group displayed a pattern of 81.5% showing food allergy and 88.4% having eczema at the age of 1 year; as the children aged, food allergy significantly decreased (to 23.7%) and rhinitis remained very low (0%). Because most children did not retain their allergy at age 2, this group was termed the "transient allergy" group.
- 3) Persistent allergy: the last group accounted for 4.9% of children. The majority in this group (62.3%) had eczema and 31.6% manifested food allergy at age one. In contrast to the "transient allergy" group, 44.7% exhibited food allergy, 66.7% showed rhinitis, and 71.1% exhibited wheezing at age 2. Given the persistence of their food allergies and eczema, this group was termed with "persistent allergy". Fig. 2 illustrates the probability distribution of the eight key variables within the identified LCA groups.

3.4. Association between maternal affective and stress-related factors during pregnancy and childhood allergic diseases

The prevalence of child eczema at 2 months (24.9%) and food allergy at 12 months (22.1%) were both significantly higher in the high maternal stress group than in the low maternal stress group (19.5% and 18.4%) during early pregnancy ($P = 0.001$ and $P = 0.04$). We also noted that the prevalence of child eczema at 2 months (30.1%) and AD and food allergy at 6 months (11.1% and 3.7%) were significantly higher in the high maternal stress group relative to the low maternal stress group (19.7%, 7.3%, and 1.5%) during late pregnancy ($P < 0.001$, $P = 0.03$, and $P = 0.01$). Similarly, the prevalence of childhood AD at 6 months (11.0%) was significantly higher in the high maternal depression group (7.4%) during late pregnancy than in the low maternal depression group ($P = 0.04$). Furthermore, the prevalence of food allergy at 24 months (14.4%) was significantly higher in the high maternal anxiety group than in the low maternal anxiety group (8.6%) during late pregnancy ($P = 0.01$).

After adjusting for the covariates (maternal age at delivery,

Table 1
Characteristics of the participants.

Sociodemographic characteristics	2-month-old survey n (%), N = 4178	6-month-old survey n (%), N = 3938	12-month-old survey n (%), N = 3882	24-month-old survey n (%), N = 3252	P value ^b
Maternal age at delivery, y					
≤24	534 (12.8)	503 (12.8)	482 (12.4)	420 (12.9)	0.98
25–29	1963 (47.0)	1837 (46.6)	1788 (46.1)	1509 (46.4)	
30–34	1177 (28.2)	1106 (28.1)	1079 (27.8)	895 (27.5)	
≥35	458 (11.0)	452 (11.5)	430 (11.1)	334 (10.3)	
Socioeconomic status					
Low	563 (13.5)	526 (13.4)	511 (13.2)	408 (12.5)	0.76
Medium	2194 (52.5)	2084 (52.9)	2047 (52.7)	1758 (54.1)	
High	581 (13.9)	546 (13.9)	522 (13.4)	425 (13.1)	
Maternal education					
Middle school and below	332 (7.9)	302 (7.7)	277 (7.1)	211 (6.5)	0.60
High school or same level	466 (11.2)	456 (11.6)	441 (11.4)	375 (11.5)	
College and above	2830 (67.7)	2671 (67.8)	2616 (67.4)	2239 (68.8)	
Household income per year					
Low (<¥100,000)	873 (20.9)	818 (20.8)	788 (20.3)	639 (19.6)	0.09
Moderate (¥100,000–200,000)	1671 (40.0)	1598 (40.6)	1600 (41.2)	1393 (42.8)	
High (>¥200,000)	979 (23.4)	917 (23.3)	817 (22.4)	716 (22.0)	
Maternal work status					<0.001
Currently working	102 (2.4)	1797 (45.6)	2302 (59.3)	2071 (63.7)	
Not working	3838 (91.9)	1142 (29.0)	912 (18.0)	1149 (11.2)	
Maternal parity					
Primiparous	2222 (53.2)	2184 (55.5)	2072 (53.4)	1760 (54.1)	0.67
Non-primiparous	1731 (41.4)	1683 (42.7)	1600 (42.2)	1295 (39.8)	
Maternal second-hand smoking during pregnancy					
Yes	867 (20.8)	825 (20.9)	795 (20.5)	683 (21.0)	0.93
No	3074 (73.6)	2900 (73.6)	2823 (72.7)	2343 (72.0)	
Family history of asthma					
Yes	150 (3.6)	137 (3.5)	135 (3.5)	110 (3.4)	0.98
No	3746 (89.7)	3548 (90.1)	3445 (88.7)	2889 (88.8)	
Child's birth weight, grams ^a	3330.0 (445.2)	3330.7 (442.0)	3326.4 (440.4)	329.7 (442.5)	0.97
Child's gestational age, weeks ^a	39.09 (1.30)	39.08 (1.28)	39.06 (1.26)	39.07 (1.29)	0.74
Child's gender					
Male	2126 (50.9)	1984 (50.4)	1956 (50.4)	1651 (50.8)	0.69
Female	2051 (40.1)	1954 (49.6)	1858 (47.9)	1539 (47.3)	
Ever breastfeeding					
Yes	2634 (63.0)	2756 (70.0)	2686 (69.2)	2372 (72.9)	<0.001
No	198 (4.7)	235 (6.0)	201 (5.2)	121 (3.7)	
Maternal psychological state during pregnancy					
Maternal stress in 12–16 weeks of pregnancy					
High	703 (16.8)	660 (16.8)	647 (16.7)	531 (6.3)	0.93
Low	2937 (70.3)	2780 (70.6)	2700 (9.6)	2305 (70.9)	
Median (IQR)	151 (66–282)	152 (69–280)	154 (72–281)	153 (69–277)	
Maternal stress in 32–36 weeks of pregnancy					
High	304 (7.3)	284 (7.2)	271 (7.0)	219 (6.7)	0.81
Low	2831 (67.8)	2672 (67.9)	2647 (68.2)	2214 (68.1)	
Median (IQR)	95 (0–195)	94 (0–193)	97 (0–195)	98 (0–194)	
Anxiety during late pregnancy					
Yes	279 (6.7)	282 (7.2)	267 (6.9)	225 (6.9)	0.87
No	2700 (64.6)	2536 (64.4)	2512 (64.7)	2096 (4.5)	
Median (IQR)	40 (36–45)	40 (36–45)	40 (36–45)	40 (36–45)	
Depression during late pregnancy					
Yes	304 (7.3)	304 (7.7)	287 (7.4)	248 (7.6)	0.87
No	2490 (59.6)	2329 (59.1)	2321 (59.8)	1944 (59.8)	
Median (IQR)	8 (4–12)	8 (4–12)	8 (4–12)	8 (4–12)	

^a Values are expressed as mean (standard deviation).

^b Differences in categorical variables tested using Pearson Chi-Square test. Differences in continuous variables tested using Kruskal-Wallis test.

socioeconomic status, maternal parity, exposure to second-hand smoke during pregnancy, family history of asthma, child's birth weight, gestational age, sex, and feeding styles), children with mothers who experienced high stress in early and late pregnancy were at an increased risk of eczema at 2 months of age (AdjOR:1.30, 95% CI:1.01–1.67; and AdjOR:1.64, 95% CI:1.14–2.36). Mothers who showed high stress in late pregnancy were more likely to have children with a food allergy at 6 months (AdjOR:3.22, 95%CI:1.27–8.12) and allergic rhinitis at 2 years of age (AdjOR:1.78, 95%CI:1.01–3.15). We also observed a positive association between maternal anxiety during late pregnancy and the occurrence of child food allergy at 24 months (AdjOR:1.76, 95% CI:1.06–2.92) (Fig. 3).

As shown in Table 3, high maternal stress in late pregnancy was

associated with an increased risk of persistent atopic symptoms.

4. Discussion

In this prospective birth cohort study, we observed that childhood skin allergies preceded the development of other atopic diseases. We noted that eczema occurred in children aged 2 months and that the highest prevalence of food allergy symptoms was seen at 12 months of age, and we ascertained an association between maternal psychological stress and childhood allergies in offspring that varied in type and disease onset. Additionally, maternal stress in late pregnancy reflected a lower incidence but a more severe effect than in early pregnancy, which was consistent with previous evidence [9]. Regarding asthma during

Table 2

Prevalence of allergic diseases in children during their first 2 years of life.

Prevalence		No. of Responses	No. of Cases (%)
Skin allergies	Eczema at 2 months	4097	821 (20.0)
	AD at 6 months	3356	247 (7.4)
	Eczema at 12 months	3103	1372 (44.2)
Food allergy	Food allergy at 6 months	3356	64 (1.9)
	Food allergy at 12 months	3300	629 (19.1)
	Food allergy at 24 months	2425	206 (8.5)
Respiratory allergies	Wheezing at 24 months	2428	245 (10.1)
	Asthma at 24 months	2428	78 (3.2)
	Allergic rhinitis at 24 months	2420	157 (6.5)

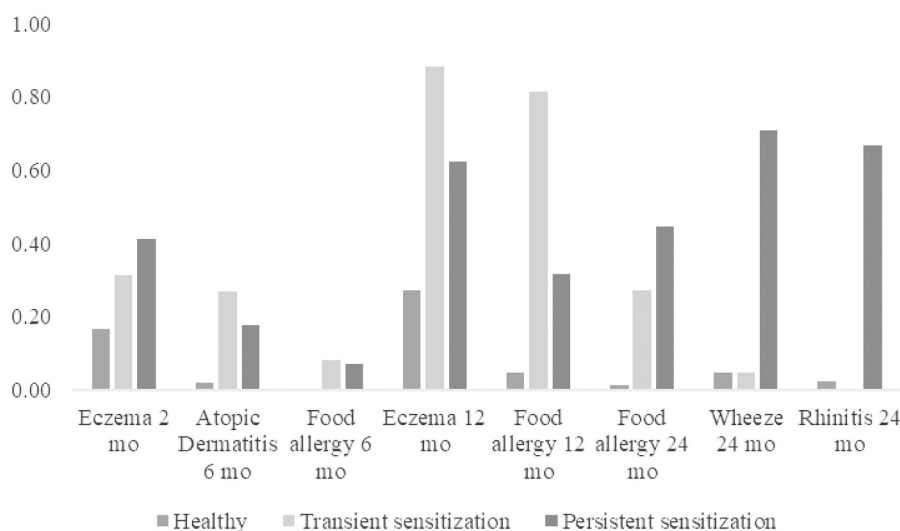
Note: Atopic dermatitis (AD).

childhood, Cookson, et al. [49] demonstrated a stronger association with maternal anxiety at 32 weeks compared with 18 weeks of gestation, while other studies suggested that severe stress in the first trimester was notably associated with an elevated risk of schizophrenia [11]. Our findings herein suggested that the fetal immune system was more susceptible to maternal stress during the critical time window of 32–36 weeks. Insights into why maternal stress occurring in late pregnancy increased the risk of atopic diseases in children are still lacking, although this phenomenon might constitute an adaptive response to environmental demands [50].

Several studies have assessed the association between maternal mental health during pregnancy and one or more allergies in children [8,20]. To the best of our knowledge, the present study is the first to incorporate multiple common allergies in young children, in which we tested our hypothesis in a longitudinal study with multiple follow-ups; this was done without adjusting for maternal affective and stress-related factors as covariates due to the correlations among them. Previous work has suggested that maternal anxiety, depression [20], and stress [18] during pregnancy increased the risk of eczema and AD in children 12 months to 10 years of age, whereas some authors did not uncover a significant link [22]. In the present study, we found that higher maternal stress during both early and late pregnancy—rather than anxiety or depression during late pregnancy—was associated with child eczema at 2 months of age. However, it remains to be determined whether this discrepancy can be explained by the disparate effects of

pregnancy stress, anxiety, and depression or the variety of measurements used to evaluate mental symptoms and childhood diseases. The association between maternal affective and stress-related factors and food allergy in offspring thus remains controversial. A retrospective study conducted in Italy showed that stressful events that occurred during the perinatal period increased the risk of food allergy in school-aged children [17], while another study of 370 mother–child pairs in Poland did not discern any association between prenatal stress and food allergy in offspring aged 12 months [23]. The effects of stress are controversial as stress might also be influenced by unmeasured factors such as inherited personality traits. While we found that higher maternal stress in late pregnancy increased the risk of food allergy in children at 6 months, the exact underlying mechanisms are unknown. Previous research indicated that children exposed to maternal affective and stress-related factors in utero were more likely to develop wheezing and asthma [8,24]. However, our findings did not support a significant association between maternal affective and stress-related factors and offspring wheezing symptoms or asthma at 2 years of age. In contrast, our findings suggested that higher stress in late pregnancy increased the risk of allergic rhinitis at 2 years of age and of persistent allergy in offspring.

In contrast with a previous study, we herein found a significant association between maternal life-events stress/anxiety symptoms rather than depression and a higher risk for allergies in infants. The exact mechanisms underlying the associations between maternal stress and offspring allergic diseases remain arcane, but they may relate to inter-related stress regulation and immune systems [19,51]. During pregnancy, the immune system is modified to allow developmental tolerance of the semi-allogeneic fetus and placenta until term [52]. It was previously revealed that mothers who were exposed to comorbidity of prenatal anxiety and depression manifested a major downregulation of placental transcripts related to immune processes such as T-cell regulation, interleukin and cytokine signaling, or innate immune responses [21]. Throughout pregnancy, exposure to maternal depression or anxiety may lead to increased secretion of stress hormones such as cortisol or serotonin in both the mother and the fetus [24], which may predispose the fetus to develop allergies during childhood and thereby hinder offspring cytokine production toward a Th2 type immune response [53]. In addition, the release of glucocorticoids is a pivotal mediator that is triggered in response to stress, affecting gene expression by binding to glucocorticoids receptors and affecting fetal immune system development in general and atopic risk in particular [54]. Although the extant research has indicated that anxiety and depression share several

**Fig. 2.** Probability of eczema, food allergy, and wheezing with respect to latent class memberships.

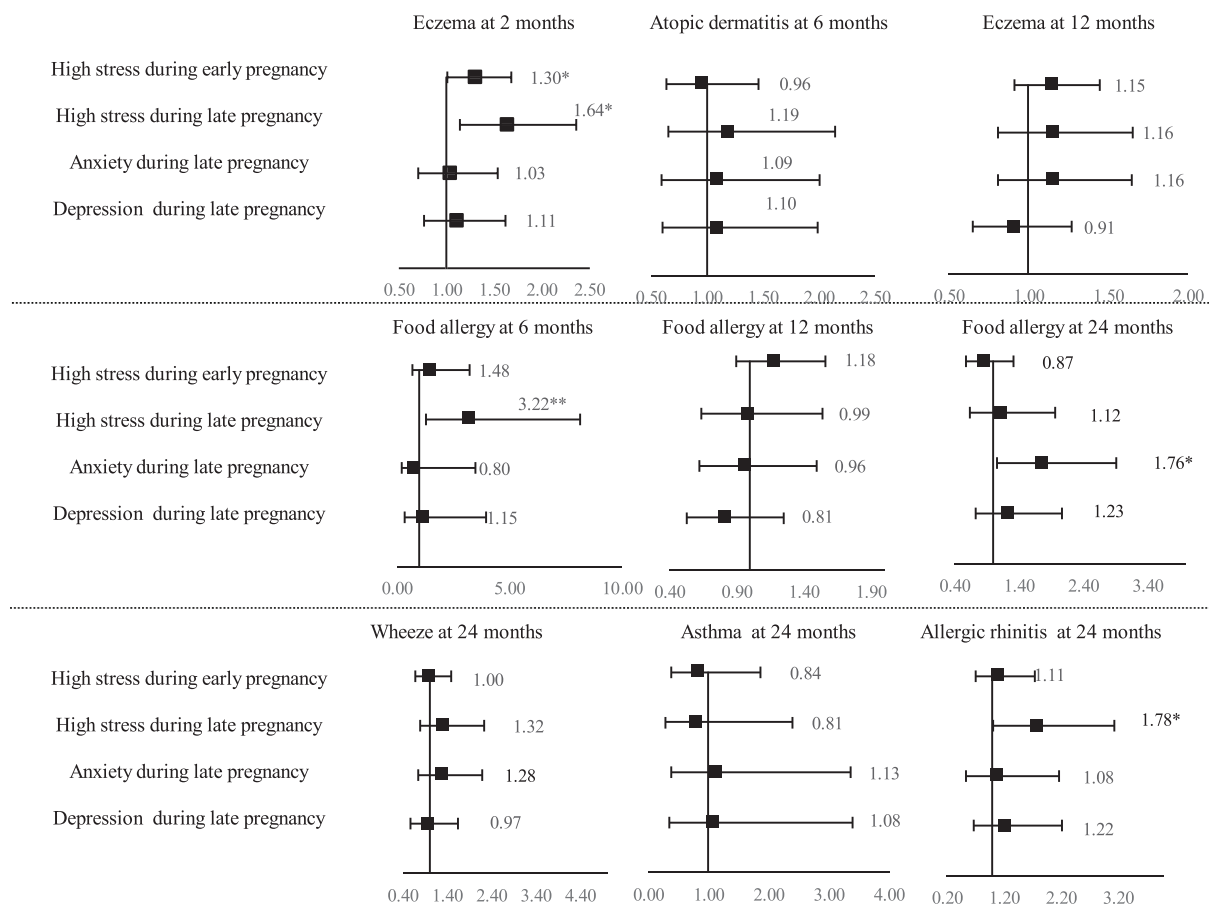


Fig. 3. Multivariate logistic regression analysis of the categories for LESPW score, SAS and CES-D scores (i.e., high stress level at 12–16 gestational weeks; high stress level at 32–36 gestational weeks; anxiety at 32–36 weeks of pregnancy; and depressive mood at 32–36 weeks of pregnancy) and outcomes in offspring. Reference category: low stress level, no anxiety, no depressive mood; the physician-diagnosis includes 0–24 months. All of the models adjusted for maternal age at delivery, socioeconomic status, maternal parity, exposure to second-hand smoke during pregnancy, family history of asthma, child's birth weight, gestational age. Feeding styles (exclusive breastfeeding or not) for two-month-old infants were adjusted in the analysis of two-months-old eczema. Ever breastfeeding was adjusted in the rest models. * $0.01 \leq P < 0.05$, ** $0.001 \leq P < 0.01$.

putative risk factors [55], emerging evidence suggests that the presence and type of hypothalamus-pituitary-adrenocortical (HPA) axis abnormalities may differ across various subtypes of depression [56]; moreover, the endogenous depression subtype may be associated with hypo-function of the HPA axis [57]. Furthermore, depression as reflected in the current study indicated a higher depressive symptom without satisfying the diagnosis of mental disorder; stress was defined as an unexpected stressful life event during pregnancy rather than a response to a stressor involving anxiety and distress. These results were probably related in part to the disparities between stress and depression in our study.

The present study was strengthened by its prospective cohort design, which facilitated the establishment of a temporal relationship between maternal mental health and childhood outcomes. We also enhanced the specification of vulnerable periods, and we posited that mothers who exhibit high psychosocial stress during their entire pregnancy were more severely affected. In this longitudinal cohort, we were able to track the progression of atopic march in the children.

There were some limitations to this study. First, reporting bias likely existed as the maternal affective and stress-related factors were self-reported, albeit with well-validated questionnaires. Second, the lack of laboratory testing measures limited our results to a degree. Nonetheless, the questionnaires on allergic diseases in our survey were completed under the supervision of community physicians. Lastly, a higher SES level for participants may have limited the study's extrapolability, as

Shanghai is one of the most developed cities in China.

5. Conclusions

The associations between maternal psychological stress and offspring childhood allergies vary in type and disease onset. We herein reported that young children of mothers who were exposed to affective and stress-related factors during pregnancy were more likely to develop allergies before 2 years of age. This was especially true for those children whose mothers were exposed to stress in late pregnancy. Given our findings, mental health promotion among pregnant women might be one of effective strategies to reduce the risks of their children from developing allergic diseases.

Availability of data and materials

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Preprint

An earlier version of this manuscript is available as a preprint at <http://www.authorea.com/users/368356/articles/487515> (DOI: 10.22541/au.160315202.23074983/v1).

Table 3

Multivariate logistic regression analysis of the categories for LESPW score, SAS and CES-D scores and patterns of allergic diseases.

		Persistent allergy	Transient allergy
Stress in early pregnancy	high	25(6.7)	70(16.4)
	low	89(5.6)	282(15.9)
	Odds Ratio (95% CI) ^a	0.98 (0.60,1.61)	1.01 (0.74,1.37)
Stress in late pregnancy	high	19(9.5)	33(16.1)
	low	95(5.4)	319(16.0)
	Odds Ratio (95% CI)	1.93 (1.10,3.40)*	0.98 (0.64,1.48)
Anxiety in late pregnancy	high	11(6.0)	41(17.8)
	low	103(5.8)	311(15.8)
	Odds Ratio (95% CI)	0.91 (0.44,1.88)	1.20 (0.79,1.82)
Depression in late pregnancy	high	15(6.4)	37(15.0)
	low	99(5.8)	315(16.2)
	Odds Ratio (95% CI)	1.02 (0.54,1.93)	0.81 (0.45,1.44)

Note. Reference: Healthy group. All of the models adjusted for maternal age at delivery, socioeconomic status, maternal parity, exposure to second-hand smoke during pregnancy, family history of asthma, child's birth weight, gestational age, sex, and feeding styles for two-month-old infants.

* $0.01 \leq P < 0.05$.

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Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000.

Contributors' statement

Conceptualization, H.S. and Y.S.; data curation, Q.W. and X.M.; formal analysis, Y.S.; funding acquisition, H.S. and Y.Z.; investigation, X.M.; methodology, Y.S.; project administration, H.S. and Y.Z.; resources, H.S. and L.W.; supervision, H.S., L.W. and Y.Z.; validation, Y.S. and Q.W.; writing—original draft preparation, Y.S.; writing—review and editing, Y.S., Q.W., X.M. and H.S. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Declaration of Competing Interest

The authors declare that: (i) no support, financial or otherwise, has been received from any organization that may have an interest in the submitted work; and (ii) there are no other relationships or activities that could appear to have influenced the submitted work.

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References

- [1] J.I. Silverberg, Public health burden and epidemiology of atopic dermatitis, *Dermatol. Clin.* 35 (3) (2017) 283–289.
- [2] W. Loh, M.L.K. Tang, The epidemiology of food allergy in the global context, *Int. J. Environ. Res. Public Health* 15 (9) (2018).
- [3] S.C. Dharmage, J.L. Perret, A. Custovic, Epidemiology of asthma in children and adults, *Front. Pediatr.* 7 (2019) 246.
- [4] G.W.K. Wong, et al., Pediatric allergy and immunology in China, *Pediatr. Allergy Immunol.* 29 (2) (2018) 127–132.
- [5] R.J. Turner, B.W.D.A. Lloyd, The epidemiology of social stress, *Am. Sociol. Rev.* 60 (1995) 104–125.
- [6] WHO, Investing in Treatment for Depression and Anxiety Leads to Fourfold Return, World Health Organization, Geneva, Switzerland, 2016.
- [7] S. Nazzari, et al., Beyond the HPA-axis: exploring maternal prenatal influences on birth outcomes and stress reactivity, *Psychoneuroendocrinology* 101 (2019) 253–262.
- [8] S.K. Ramratnam, et al., Relationships among maternal stress and depression, type 2 responses, and recurrent wheezing at age 3 years in low-income urban families, *Am. J. Respir. Crit. Care Med.* 195 (5) (2017) 674–681.
- [9] I.R. Hartwig, et al., Prenatal adverse life events increase the risk for atopic diseases in children, which is enhanced in the absence of a maternal atopic predisposition, *J. Allergy Clin. Immunol.* 134 (1) (2014) 160–169.
- [10] B.K. Brew, et al., Longitudinal depression or anxiety in mothers and offspring asthma: a Swedish population-based study, *Int. J. Epidemiol.* 47 (1) (2018) 166–174.
- [11] C. Guo, et al., Long-term effects of prenatal exposure to earthquake on adult schizophrenia, *Br. J. Psychiatry* 215 (6) (2019) 730–735.
- [12] X. Ma, et al., The impact of resilience on prenatal anxiety and depression among pregnant women in Shanghai, *J. Affect. Disord.* 250 (2019) 57–64.
- [13] A. Lee, et al., Prenatal and postnatal stress and asthma in children: temporal- and sex-specific associations, *J. Allergy Clin. Immunol.* 138 (3) (2016) 740–747.e3.
- [14] R. de Marco, et al., Foetal exposure to maternal stressful events increases the risk of having asthma and atopic diseases in childhood, *Pediatr. Allergy Immunol.* 23 (8) (2012) 724–729.
- [15] Y.H. Chiu, et al., Prenatal and postnatal maternal stress and wheeze in urban children: effect of maternal sensitization, *Am. J. Respir. Crit. Care Med.* 186 (2) (2012) 147–154.
- [16] M.J. Rosa, et al., Prenatal and postnatal stress and wheeze in Mexican children: sex-specific differences, *Ann. Allergy Asthma Immunol.* 116 (4) (2016) 306–312.e1.
- [17] L. Polloni, et al., Perinatal stress and food allergy: a preliminary study on maternal reports, *Psychol. Health Med.* 20 (6) (2015) 732–741.
- [18] S. El-Heis, et al., Maternal stress and psychological distress preconception: association with offspring atopic eczema at age 12 months, *Clin. Exp. Allergy* 47 (6) (2017) 760–769.
- [19] S. Trump, et al., Prenatal maternal stress and wheeze in children: novel insights into epigenetic regulation, *Sci. Rep.* 6 (2016) 28616.
- [20] H.Y. Chang, et al., Prenatal maternal distress affects atopic dermatitis in offspring mediated by oxidative stress, *J. Allergy Clin. Immunol.* 138 (2) (2016) 468–475.e5.
- [21] C.A. Martinez, et al., Prenatal stress, anxiety and depression alter transcripts, proteins and pathways associated with immune responses at the maternal-fetal interface, *Biol. Reprod.* 106 (3) (2022) 449–462.
- [22] S. Braig, et al., Maternal prenatal stress and child atopic dermatitis up to age 2 years: the Ulm SPATZ health study, *Pediatr. Allergy Immunol.* 28 (2) (2017) 144–151.
- [23] K. Smejda, et al., Maternal stress during pregnancy and allergic diseases in children during the first year of life, *Respir. Care* 63 (1) (2018) 70–76.
- [24] M.C. Magnus, et al., Association of Maternal Psychosocial Stress with Increased Risk of asthma development in offspring, *Am. J. Epidemiol.* 187 (6) (2018) 1199–1209.
- [25] H.A. Brough, et al., Epicutaneous sensitization in the development of food allergy: what is the evidence and how can this be prevented? *Allergy* 75 (9) (2020) 2185–2205.
- [26] E.H. Tham, et al., Epicutaneous sensitization to food allergens in atopic dermatitis: what do we know? *Pediatr. Allergy Immunol.* 31 (1) (2020) 7–18.
- [27] H.A. Brough, et al., Atopic dermatitis increases the effect of exposure to peanut antigen in dust on peanut sensitization and likely peanut allergy, *J. Allergy Clin. Immunol.* 135 (1) (2015) 164–170.
- [28] G. Du Toit, et al., Randomized trial of peanut consumption in infants at risk for peanut allergy, *N. Engl. J. Med.* 372 (9) (2015) 803–813.
- [29] C. Caffarelli, et al., Asthma and food allergy in children: is there a connection or interaction? *Front. Pediatr.* 4 (2016) 34.
- [30] M.J. McGeachie, et al., Patterns of growth and decline in lung function in persistent childhood asthma, *N. Engl. J. Med.* 374 (19) (2016) 1842–1852.
- [31] H. Han, F. Roan, S.F. Ziegler, The atopic march: current insights into skin barrier dysfunction and epithelial cell-derived cytokines, *Immunol. Rev.* 278 (1) (2017) 116–130.
- [32] Y. Lin, et al., Association between temperature and maternal stress during pregnancy, *Environ. Res.* 158 (2017) 421–430.
- [33] S. Li, et al., The non-linear association between low-level lead exposure and maternal stress among pregnant women, *Neurotoxicology* 59 (2017) 191–196.
- [34] Q. Su, et al., Maternal stress in gestation: birth outcomes and stress-related hormone response of the neonates, *Pediatr. Neonatol.* 56 (6) (2015) 376–381.
- [35] Z. Zhang, Behavioral medicine scale manual, in: Behavioral Medicine Scale Manual, Chinese Medicine Multimedia Press, 2005, pp. 265–267.

- [36] T.H. Holmes, R.H. Rahe, The social readjustment rating scale, *J. Psychosom. Res.* 11 (2) (1967) 213–218.
- [37] P. Svanborg, M. Asberg, A new self-rating scale for depression and anxiety states based on the comprehensive psychopathological rating scale, *Acta Psychiatr. Scand.* 89 (1) (1994) 21–28.
- [38] M. Samakouri, et al., Standardization of the Greek version of Zung's self-rating anxiety scale (SAS), *Psychiatriki* 23 (3) (2012) 212–220.
- [39] Z. Li, M.H. Hicks, The CES-D in Chinese American women: construct validity, diagnostic validity for major depression, and cultural response bias, *Psychiatry Res.* 175 (3) (2010) 227–232.
- [40] M.I. Asher, et al., International study of asthma and allergies in childhood (ISAAC): rationale and methods, *Eur. Respir. J.* 8 (3) (1995) 483–491.
- [41] M.I. Asher, et al., 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) (2006) 733–743.
- [42] M. Santer, S. Lewis-Jones, T. Fahey, Childhood eczema, *Bmj* 331 (7515) (2005) 497.
- [43] S. Weidinger, N. Novak, Atopic dermatitis, *Lancet* 387 (10023) (2016) 1109–1122.
- [44] E. Castro-Nallar, et al., Integrating microbial and host transcriptomics to characterize asthma-associated microbial communities, *BMC Med. Genet.* 8 (2015) 50.
- [45] Y. Luo, J. Gao, X. Zheng, Individual-level and area-level socioeconomic inequalities in hearing impairment among Chinese adults: a population-based study, *J. Epidemiol. Community Health* 74 (6) (2020) 541–547.
- [46] L.M. Glover, et al., Life course socioeconomic status and hypertension in African American adults: the Jackson heart study, *Am. J. Hypertens.* 33 (1) (2020) 84–91.
- [47] E.G.L. Zeger, Latent Class Model Diagnosis, *Biometrics* 56 (2000) 1055–1067.
- [48] J.B.L.D.A. Linzer, polCA: an R package for Polytomous variable latent class analysis, *J. Stat. Softw.* 42 (2011) 1–29.
- [49] H. Cookson, et al., Mothers' anxiety during pregnancy is associated with asthma in their children, *J. Allergy Clin. Immunol.* 123 (4) (2009) 847–853.e11.
- [50] S.T. Holgate, et al., Asthma, *Nat. Rev. Dis. Primer.* 1 (1) (2015) 15025.
- [51] D.W. Cain, J.A. Cidlowski, Immune regulation by glucocorticoids, *Nat. Rev. Immunol.* 17 (4) (2017) 233–247.
- [52] B. Abu-Raya, et al., Maternal immunological adaptation during Normal pregnancy, *Front. Immunol.* 11 (2020), 575197.
- [53] D.I. Suh, et al., Prenatal maternal distress and allergic diseases in offspring: review of evidence and possible pathways, *Allergy, Asthma Immunol. Res.* 9 (3) (2017) 200–211.
- [54] M. Moustaki, et al., Prenatal stress enhances susceptibility to allergic diseases of offspring, *Endocr Metab Immune Disord Drug Targets* 17 (4) (2017) 255–263.
- [55] B. Leuner, T.J. Shors, Stress, anxiety, and dendritic spines: what are the connections? *Neuroscience* 251 (2013) 108–119.
- [56] P.W. Gold, The organization of the stress system and its dysregulation in depressive illness, *Mol. Psychiatry* 20 (1) (2015) 32–47.
- [57] M.F. Juruena, et al., Atypical depression and non-atypical depression: is HPA axis function a biomarker? A systematic review, *Affect. Disord.* 233 (2018) 45–67.