Maternal stressed-affective factors during pregnancy affecting the occurrence of childhood allergic diseases: Shanghai MCPC study

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Abstract

Background: Allergic diseases in offspring are suggested to originate from fetal life. The role of in-utero stress exposures in early childhood allergic diseases development has not been completely elucidated. We aimed to determine the effect of exposures to different kinds of maternal stressed-affective factors during pregnancy on the risk of childhood allergy during first 2 years of life. Methods: A sample of 4178 children born in 2016-2018 from the Shanghai Maternal-Child Pairs Cohort were included in this study. Indicators for maternal stressed-affective factors included life events stress at early and late pregnancy, respectively, and prenatal depression and anxiety at late pregnancy, which were measured by the Life Events Scale for Pregnant Women (LESPW), Self-Rating Anxiety Scale (SAS) and Center for Epidemiologic Studies, Depression Scale (CES-D). The children's allergic diseases or manifestations were assessed through the questionnaires at 2,6,12,24 months after birth, respectively, including eczema, atopic dermatitis, food allergy, wheezing, asthma, and allergic rhinitis. The impacts of maternal stressed-affective factors on child allergic diseases were analyzed using multivariable binary logistic regression adjusting for potential covariates. Results: During the first 2 years of life, all forms of allergic disease were continuously reported, with allergic diseases of skin preceded the development of other atopic diseases. Children whose mothers had high life events stress during the early pregnancy or the late pregnancy would have an increased risk of eczema at 2 months respectively (AdjOR:1.30, 95%CI:1.01-1.67; AdjOR:1.64, 95%CI:1.14-2.36). Children whose mothers with high life events stress in late pregnancy were also more likely to have food allergy at 6 months (AdjOR:3.22, 95%CI:1.27-8.12). Maternal prenatal anxiety may lead to offspring's childhood wheeze at 24 months (AdjOR:2.15, 95%CI:1.09-4.27). Conclusions: Maternal stressed-affective factors could have effects on offspring's allergic diseases, especially eczema at 2 months. Understanding the temporal-specific effects of maternal stressed-affective factors may better inform prevention strategies.

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Conflict of 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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Abstract

Background: Allergic diseases could originate from fetal life. The role of in-utero psychological exposures in early childhood allergies development has not been completely elucidated. We aimed to determine the effect of exposures to several maternal prenatal stressed-affective factors on the risk of allergies during first 2 years of life.

Methods: A sample of 4178 children born in 2016-2018 from the Shanghai Maternal-Child Pairs Cohort were included. Indicators for maternal stressed-affective factors included stress at early and late pregnancy, respectively, and depression and anxiety at late pregnancy, which were measured by the Life Events Scale for Pregnant Women, Self-Rating Anxiety Scale and Center for Epidemiologic Studies, Depression Scale. The children's allergies were assessed through the questionnaires at 2,6,12,24 months after birth, respectively, including eczema, atopic dermatitis, food allergy, wheezing, asthma, and allergic rhinitis. The impacts of maternal stressed-affective factors on childhood allergies were analyzed using multivariable binary logistic regression adjusting for potential covariates.

Results: During the first 2 years of life, allergies of skin preceded the development of other allergies. Children whose mothers had high stress during the early pregnancy or the late pregnancy would have an increased risk of eczema at 2 months respectively (AdjOR:1.30, 95%CI:1.01-1.67; AdjOR:1.64, 95%CI:1.14-2.36). Children whose mothers with high stress in late pregnancy were also more likely to have food allergy at 6 months (AdjOR:3.22, 95%CI:1.27-8.12). Maternal prenatal anxiety may lead to offspring's childhood wheeze at 24 months (AdjOR:2.15, 95%CI:1.09-4.27).

Conclusions: Maternal stressed-affective factors could have negative impacts on offspring's allergies, especially eczema at 2 months. Understanding the temporal-specific effects of maternal stressed-affective factors may better inform prevention strategies.

Keywords:

maternal stressed-affective factors; allergic diseases; birth cohort study, in-utero exposure

Key Message

The effects of maternal psychological stress on offspring's childhood allergies vary in types and occurrence timing of disease. Maternal prenatal emotional problems could increase the risk of offspring's allergic diseases, especially eczema at 2 months. Lower incidence but severer effect was found among maternal stress in late pregnancy in comparison with early pregnancy. The risk during the late trimester may represent cumulative stress exposure throughout pregnancy.

1 Introduction

Allergic diseases and manifestations such as atopic dermatitis (AD) and food or inhalant allergies are the most common chronic diseases among children.[1] Previous studies have showed an increasing prevalence of childhood allergies in parallel with growing maternal stressed-affective factors during pregnancy.[2] Accumulating evidence suggests an etiologic role that maternal prenatal stressed-affective factors impact negatively on immune system development in children.[3, 4] Animal studies showed that stress during pregnancy may impact the development of the offspring's immune system through hypothalamus-pituitary-adrenal(HPA) axis and sympathetic adrenomedullary system, leading to Th2-biased cell differentiation in the fetus[5], and increasing immunoglobulin E production and allergies during childhood[6]. However, there is a lack of causal relationship between maternal stressed-affective factors and childhood allergies from large-scale prospective cohort studies.

Evidence of the effects of maternal prenatal stress exposure on childhood skin allergies is inconsistent. For instance, Elbert et al. [7] found that maternal psychiatric symptoms during pregnancy were associated with increased risk of childhood eczema, which is consistent with another study in England [8]. The link between maternal prenatal stress and atopic dermatitis symptoms has been demonstrated by While Braig et al. [9], however, the association with atopic dermatitis diagnoses was limited. In addition, few studies have investigated the correlation between maternal stressed-affective factors and childhood food allergies, and the results remains controversial. A previous research has shown that compared to siblings, higher number in-utero stress exposures have been found in food-allergic children.[10] In contrast, another study showed no significant association between maternal stress and childhood food allergy during the first year of life.[11] Study found that an early food sensitization may play an important role in the development of asthma.[12] Wheezing episodes in young children may mark the beginning of asthma and lung function deficits.[13] Ramratnam et al. showed that maternal prenatal depression and early life stress may affect the incidence of wheezing or subsequent asthma in the preschoolers and the schoolers.[4] Magnus et al. found that maternal anxiety/depression and negative life events were associated with offspring asthma.[14] Study by Brew et al. revealed that cumulative exposure of maternal depression or anxiety increased the risk of asthma in offspring.[15] Epidemiological and genetic evidence have suggested that early-onset AD is associated with other subsequent allergic manifestations.[16]

Thus, prospective cohort studies investigating the impact of maternal psychological stress on the offspring allergic disease in early life are urgently needed. This study aim to assess the impact of the maternal prenatal stressed-affective factors, including high stress during pregnancy, anxiety, and depression on the occurrence of eczema, atopic dermatitis, food allergy, wheezing, asthma, and allergic rhinitis in the offspring during the first 2 years of life.

2 Methods

2.1 Study design

Participants of this study were a subgroup of Shanghai Maternal-Child Pairs Cohort (Shanghai MCPC), which was the first prospective birth cohort study in China since the implementation of the comprehensive 2-child policy.[17] Pregnant women were recruited in two regional maternity hospitals of Shanghai Pudong District and Songjiang District from April 2016. A baseline questionnaire was conducted by trained personnel to obtain sociodemographic characteristics, perinatal psychological stress, living situation and lifestyle at 12-16 gestational weeks. Different questionnaires and biological samples were obtained at 24-28, 32-36 gestational weeks and childbirth. The health information of children was collected by questionnaires completed by a parent (usually Mother) or a primary caregiver at 2, 6, 12, 24 months after childbirth. The inclusion criteria were as follows: women with a singleton pregnancy, living in Shanghai currently, willing to participate in the cohort study, and being able to read Chinese. Pregnant women with syphilis or AIDS were excluded. The study was approved by the ethics committee of the School of Public Health, Fudan University (IRB number 2016-04-0587), and written informed consent was obtained from each mother participant. Pregnant women recruited from April 2016 and April 2018 were selected in this study. We analyzed data of

4178 children who born before October 2018 in MCPC cohort. All of the requisite data were available for 3938 children at 6 months, for 3039 children at 12 months, and for 1854 at 24 months (Figure 1).

2.2 Maternal stressed-affective factors assessments

Maternal stressed-affective factors were measured by maternal self-administered questionnaires, including life events stress, anxiety, and depression.

The Life Events Scale for Pregnant Women (LESPW) was used to assess perceived stress comes from family life, work, study, social relationships and other aspects over the last 3 months in 12-16 weeks and 32-36 weeks during pregnancy, respectively. Events are classified into different subscales and the demarcation points for total score and subscales' scores are 375, 130 (subjective events), 310 (positive objective events), 235 (general negative objective events), and 145 (severe negative objective events), respectively.[18] The LESPW has demonstrated good reliability with a Cronbach's alpha of 0.961 for total and 0.776, 0.880, 0.892, 0.902 for subscales respectively.[19] The correlation coefficients of criterion related validity between total score of LESPW and the social readjustment rating scale are 0.727.[20]

The Self-Rating Anxiety Scale (SAS) [21], scored on a 4-point scale, was used to evaluate a general tendency to anxiety over the previous week at 32-36 weeks of pregnancy. Twenty item scores are summed up and standardized according to the formula: standardized score equals to integer ($1.25 \times$ item score). The standardized score is used as an index of anxiety, and the cutoff value is 50.[21] The SAS has excellent psychometric properties in both clinical and epidemiological studies for the detection of anxiety with Cronbach's alpha of 0.897 and acceptable reliability in previous studies.[22]

The Chinese version of Center for Epidemiologic Studies, Depression Scale (CES-D) was used to measure levels of depressive symptoms over the last week at 32–36 weeks' gestation.[19] As a primary screening tool in research and in clinical practice, the CES-D is widely . It contains 20 items with scores ranging from 0-60 and a score of 16 or above represents a depressive mood. A higher score indicates more severe depression symptoms. The Cronbach's alpha of the scale was 0.86, with 100% sensitivity (95% CI: 44% to 100%) and 76% specificity (95% CI: 69% to 82%) of cut-off score of 16.[23]

2.3 Child allergic diseases assessments

The occurrence of childhood allergies (including eczema, atopic dermatitis, food allergy, wheezing, asthma, and allergic rhinitis) were defined based on parental positive answers to the following questions [24]:

"Has your child had eczema in last 2 weeks?" (at 2 months and 12 months)

"Has your child had atopic dermatitis in last 2 weeks?" (at 6 months)

"Has your child had food allergy in last 2 weeks?" (at 6 months and 12 months)

"Has your child ever been diagnosed with food allergy?" (at 24 months)

"Has your child had wheezing symptoms in last 4 weeks?" (at 24 months)

"Has your child ever been diagnosed with an allergic rhinitis?" (at 24 months)

In the 24-month-old survey, the family history of allergic disease (food allergy, asthma, and allergic rhinitis) was also noted. The food allergens and symptoms were specified to guarantee the authenticity of the report. If the child ever had wheezing symptoms, parents or primary caregivers need to answer if their child was ever diagnosed with asthma, in combination with either current symptoms or used asthma medication in the past 4 weeks. For each type of medications, examples were given (including short-acting β2-agonists, inhaled corticosteroids, leukotriene antagonists, and oral glucocorticoids) for respondents to understand. The duration of allergic rhinitis, medical treatments and hospitalizations were also collected, which allowed us to identify children with allergic rhinitis with a minimal false-positive inclusion.

2.4 Covariates

Maternal information was obtained by questionnaires at enrollment (12-16 gestational weeks), including age at delivery, education level, household income, parity, personal and family history of asthma (self-reported asthma 'ever', first-degree relatives), maternal and paternal occupational status. Additionally, information on tobacco exposure during pregnancy and breastfeeding was collected by questionnaires at late pregnancy (32-36 gestational weeks) and at multiple visits after delivery. Child characteristics were obtained by obstetric medical records at birth, including sex, birth weight and gestational age. The socioeconomic status (SES) variable was derived from family income, and the education level and occupational status of the mothers and her husband. Composite scores were standardized, with an average of 0 and a standard deviation of 1. Low SES was defined by scores below -1 and high SES was defined by scores above +1.[25]

2.5 Statistical analysis

Descriptive statistics were calculated for the demographic characteristics of mothers and their children. The scores of the LESPW, SAS, and CES-D presented a non-normally distribution and were expressed as medians and interquartile ranges (IQR 25-75). We used Chi-square tests to compare the distribution of child allergies at 2, 6, 12, 24 months by maternal stressed-affective factors. To examine the effect sizes of maternal stressed-affective factors during pregnancy on the risk of child allergies, we used binary logistic regression model to calculate the odds ratios (OR s) and their 95% confidence intervals (CI s) by adjusting confounding clinical and socio-demographic covariates, including maternal age at delivery, socioeconomic status, maternal parity, maternal prenatal tobacco smoke exposure status, family history of asthma, child' s birth weight, child' s gestational age, child' s sex, and ever breastfeeding. The reference group was low stress level, no anxiety, no depressive mood in logistic regression. Given the multicollinearity was present among the psychosocial risk factors, they were considered individually in a series of regression models. Analyses were performed using SPSS version 20.0 (IBM Corp., College Station).

3 Results

3.1 Participants' characteristics

Of the participants (N=4178), 703(16.8%) and 304(7.3%) had high stress at early and late pregnancy, respectively. The presence of anxiety and depressive symptoms was 279(6.7%) and 304(7.3%), respectively. The mean age of pregnant mothers was 28.90 years (SD=4.11), ranging from 17 to 43 years, and 563(13.4%) of them were in low SES. Half of pregnancies were nulliparity and 867(20.8%) of them were exposed to tobacco or second-hand smoke during pregnancy. As for their offspring, 105(2.5%) of them were born with low birth weight (<2500 gram), and 1852(44.3%) were breastfed until 6 months of age. (Table 1)

3.2 Prevalence of allergic diseases in children

During the first 2 years of life, the most common allergic disease was skin allergy (eczema), with a prevalence of 19.7% (n=821) and 41.3% (n=1255) at 2 months of age and 12 months of age, respectively (Table 2), while 6.3% (n=247) at age 6 months were defined as atopic dermatitis. The prevalence of parental reported food allergy increased from 1.6% (n=64) to 19.2% (n=582) in 6-month-old survey and 12-month-old survey, while the prevalence of physician-diagnosed food allergy was 8.1% (n=150) at age 24 months. From a total of 1854 questionnaires for 2-year-old children, physician-diagnosed allergic rhinitis was 6.8%. Of the children with wheezing (n=203), 27.6% reported physician-diagnosed asthma.

3.3 Effects of maternal prenatal stressed-affective factors on childhood allergic diseases

As shown in table 3, the prevalence of child eczema at 2 months was significantly higher in high maternal stress group than that in low maternal stress group both at early (p <0.01) and late pregnancy (p <0.001). The prevalence of childhood atopic dermatitis at 6 months was significantly higher in high maternal stress group than that in low maternal stress group during late pregnancy(p <0.05). Likewise, the prevalence of childhood atopic dermatitis at 6 months was significantly higher in high prenatal depression group than that in low prenatal depression group. Furthermore, the prevalence of childhood food allergy at 6 months was significantly higher in high maternal life stress group than that in low maternal stress group during late pregnancy(p <0.05).

After adjusting for confounders (Maternal age at delivery, Socioeconomic status, Maternal parity, Maternal prenatal tobacco smoke exposure status, Family history of asthma, Child' s birth weight, Child' s gestational age, Child' s sex, and Ever breastfeeding), children whose mothers having a high life stress at early pregnancy and late pregnancy were at an increased risk of eczema (AdjOR:1.30, 95%CI:1.01-1.67; AdjOR:1.64, 95%CI:1.14-2.36) at 2-month-old. Mothers with high stress in the late pregnancy were more likely to have children with food allergy at 6 months (AdjOR:3.22, 95%CI:1.27-8.12). Additionally, there was a positive association between prenatal anxiety and occurrence of childhood wheeze at 24 months (AdjOR:2.15, 95%CI:1.09-4.27). (Figure 2)

4 Discussion

In this prospective birth cohort study, we observed that childhood allergies of skin preceded the development of other atopic diseases. The eczema could occur in children aged 2 months and the highest prevalence of food allergy symptoms was at age 6-12 months. We found the effects of maternal psychological stress on offspring's childhood allergies vary in types and occurrence timing of disease. Additionally, lower incidence but severer effect was found among maternal stress in late pregnancy in comparison with early pregnancy. The risk during the late trimester may represent cumulative stress exposure throughout pregnancy.

Although there are a number of studies that have assessed the association between maternal prenatal mental health and one or a few allergies [4, 7], this is the first study that has embraced multiple common allergies in young children and applied hypothesis testing based on multiple observations. We did not adjust for multiple testing due to the correlation between the measures of maternal stressed-affective factors. Previous works have suggested that maternal anxiety, depression [7] and stress during pregnancy [8] increase the risk of eczema and atopic dermatitis in children aged 12 months to 10 years old, whereas some studies did not find the link [9]. In this study, we found that maternal higher stress during pregnancy—but not prenatal anxiety or depression—was associated with child eczema at 2 months old. The difference indicated that the effect of pregnancy stress starts to appear as early as 2 months of age, much more earlier than the effects of maternal prenatal anxiety and depression. In addition, different measurements of mental symptoms and childhood diseases may also contribute to the differences.

The association between maternal stressed-affective factors and food allergy of offspring still remains controversial. A study from Italy showed that more stressful events which occurred during patients' perinatal period increased the risk of developing food allergy in childhood.[10] However, another study found the absence of this association.[11] The results of stress are more controversial and stress might be influenced by unmeasured factors such as heritable personality traits. We found that higher maternal stress in the late pregnancy increased the risk of developing child food allergy at 6 months. Most of infancy in Shanghai were added supplementary food since 4-month-old.[26] That may be one source of the differences, despite that we tried to control the factors of breastfeeding in the model.

Evidence indicated that children exposed to maternal stressed-affective factors in utero had an increased risk of wheezing and asthma.[4, 14] Consistent with previous study, our results here found an association between maternal prenatal anxiety and offspring wheezing symptoms at 2 years old. Putative mechanisms linking stress in pregnancy and childhood allergic disease include a dysregulation of maternal and child HPA axis and an immune dysregulation in offspring.[27] Maternal stressed-affective factors during pregnancy impact the development of the immune system of offspring through HPA axis-related epigenetic pathways.[28] Throughout pregnancy, exposure to maternal depression or anxiety can lead to increased secretion of stress hormones such as cortisol or serotonin, in both the mother and the fetus, which may predispose the fetus to develop allergies during childhood and hinder the subsequent process in the offspring's cytokine production towards a Th2 type immune response.[29] In addition to HPA-related pathway, the release of glucocorticoids (GC) is also a pivotal mediator triggered in response to stress, which may affect gene expression through binding to GC receptors, thus affecting fetal development of immune system in general, and atopic risk in particular.[5] These mechanism could explain an enhanced susceptibility to childhood atopic disorders.

The present study is strengthened by its prospective cohort design. Since outcomes were ascertained after

the occurrence of exposures, we could establish a temporal relationship between maternal mental health and childhood outcomes. With our approach, we could better specify the vulnerable periods and speculate that mothers with high psychosocial stress in both prenatal periods are possibly more severely affected. The study also has some limitations. First, reporting bias exits because the measurement of allergic disease symptoms was self-reported by parents or guardians, despite the method was widely used in epidemiologic studies. This bias is mitigated in the present study by every six months survey with parents' high attention to their children. Second, the prevalence of wheezing might be overestimated, as some parents might label a single episode of noisy breathing as wheezing. Third, we did not analyze the effect of mothers' postpartum psychological state on children's allergies, but evidence suggested that self-reported stress as well as anxiety/depressive symptoms during pregnancy is relatively stable for a period of time, even after pregnancy. The postpartum psychological problems may be the continuation of prenatal mental disorders.[30]

In conclusion, we found that young children born to mothers with stressed-affective factors during pregnancy increased the risk of allergies in aged 0-2 years, especially eczema at 2 months. Given that eczema may play an important role in the development of allergic disease, children exposed to maternal stressed-affective factors in utero need more careful skin care from birth as well as more careful supplementary food adding later in life.

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