Association between prenatal depressive symptoms and eczema in infants: The Born in Guangzhou Cohort Study

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Running title: Prenatal depression and infants' eczema

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59 **Abstract**

60 **Background** Eczema is a growing threat on infants' health and the role of maternal depression in the
61 risk of eczema's early onset is unclear. This study aimed to examine the associations of different
62 exposure timing of prenatal depressive symptoms with offspring's eczema in infancy.

63 **Methods** The study was part of the ongoing prospective Born in Guangzhou Cohort study. Maternal
64 depressive symptoms were assessed at both early (< 20th week of gestation) and late pregnancy ($\geq$ 33th
65 week of gestation to delivery) using Self-rating Depression Scale. Information on diagnosis of eczema
66 was collected at the 1-year-age visit. Multivariable logistic regression was used to examine the
67 association between prenatal depressive symptoms and infants' eczema and test for moderation by
68 parental history of allergic diseases.

69 **Results** In this population, 7.7% (447/5825) of mothers experienced persistent depressive symptoms
70 during pregnancy, 10.1% (590/5825) with depressive symptoms only at early pregnancy and 8.4%
71 (489/5825) of women experienced depressive symptoms only at late pregnancy. After adjusting for
72 potential confounders, higher risks of eczema were observed in infants of mothers with persistent
73 prenatal depressive symptoms when compared to those children without maternal depressive symptoms
74 throughout pregnancy (OR: 1.55, 95% CI 1.19 to 2.03). These associations were marginally more
75 pronounced among children in families without parents affected by allergic diseases than in other
76 families (P for interaction =0.064 for courses of prenatal depressive symptoms).

77 **Conclusion** Persistent maternal depressive symptoms during pregnancy increased the risk of infants'
78 eczema, especially in children without family history of allergic diseases. These associations, if proved
79 to be causal, could be intervention target not only to improve women's health but also to prevent
80 offspring's eczema.

Keywords: cohort, eczema, infant, prenatal depressive symptoms

Introduction

Prenatal depression is a common, but often overlooked major complication of pregnancy, affecting over 10% of pregnant women.¹⁻⁴ Its adverse impact is not limited to mothers but can also lead to impaired emotional and physical development in their offspring, posing a huge economic and societal burden.⁵

There is a general increasing trend in prevalence of allergic diseases, such as eczema, asthma globally.^{6,7} Growing body of evidence has implicated a potential link between prenatal depression and increased risks of children's allergic diseases,^{8,9} although the pathogenetic mechanisms underlying the association are unclear. Such observation was mainly based on the findings from studies on wheezing and asthma.^{8,9} Eczema, thought to be an early onset of allergic diseases,⁷ is a very common chronic skin disease among children,¹⁰ leading to loss in quality of life and substantial medical care burden.¹¹ However, whether prenatal depression increases the risk of offspring's eczema is unclear due to conflicting results.¹²⁻¹⁶ Such discrepancies may be, in part, explained by the differences in exposure window to depression, as exposure to stressors during the third trimester may be more relevant to the children's eczema risk than the second trimester.⁹ However, other factors such as definition and classification of stressors such as depression, major life events,¹⁷ and perceived stress,¹⁶ as well as variations in exposure duration to stressors may also explain these differences since many studies only rely on single time point measurement.

Additionally, a great deal of evidence suggests that the first-degree relatives of allergic diseases probands are at high risks of allergic diseases.¹⁸ A previous study showed that association between

maternal depressive disorders during pregnancy and childhood eczema appeared to be more evident if a potential hereditary component is absent (classified as “low risk”).¹⁹ However, the evidence of prenatal depression with children’s eczema among high risk and low risk populations is scarce.

In order to better assess the relation between the timing of prenatal exposure to mother’s depressive symptoms and subsequent offspring’s eczema risk in infancy, we examined the associations of prenatal depressive symptoms, assessed at early and late pregnancy, with offspring’s eczema during infancy in a large prospective Chinese birth cohort study. Furthermore, we explored the association separately in high-risk and low-risk children, defined as presence or absence of parental history of allergic diseases.

Method

Study population and design

The present study was part of the ongoing prospective Born in Guangzhou Cohort study (BIGCS) conducted in Guangzhou Women and Children’s Medical Center, China; details of which have been described previously.²⁰ Self-administered questionnaires were conducted at recruitment (<20 gestational weeks), 24-27 weeks of gestation and late pregnancy (after 33th gestational week and prior to delivery). In the children’s first year, face-to-face interview of mothers and health checks of infants were performed in hospital at 6-weeks, 6-months and 1-year, or telephone interview for those mothers who were unable to bring their child to the health care clinic at each follow-up time point.

In the present work, pregnant women recruited between February 2012 and August 2016 and their infants were included. Those with multiple pregnancies, terminations of pregnancy, death of infants, missing information on birth characteristics, depressive symptoms and eczema, and who dropped out

were excluded (Figure 1). The study was approved by The Institute Ethics Committee of the Guangzhou Women and Children's Medical Center and all participants provided written informed consent prior to their inclusion.

Measurement of prenatal depressive symptoms

Maternal depressive symptoms during pregnancy were assessed by a Self-rating Depression Scale (SDS)²¹ at early pregnancy (<20th week of gestation) and late pregnancy($\geq$ 33th week of gestation) via questionnaire, which have been validated in the Chinese population.^{22,23} For each of the 20 items in the SDS, participants chose the frequency that they felt or behaved during the past seven days on a four-point Likert scale (1, a little of the time; 2, some of the time; 3, good part of the time; and 4, most of the time). The sum of scores for all items was then multiplied by 1.25 to give a range between 25 and 100, where a higher score indicated a greater level of depressive symptoms. Presence of depressive symptoms was defined as $\geq$ 53 on the score.²³ Depressive symptoms were further categorized into four different courses throughout pregnancy (1) absent, no depressive symptoms at early and late pregnancy, (2) early pregnant only, depressive symptoms at early pregnancy but no symptoms at late pregnancy, (3) late pregnancy only, no depressive symptoms at early pregnancy but presence of symptoms at late pregnancy, and (4) persistent, depressive symptoms at early and late pregnancy.

Measurement of infants' eczema

Cases of infants' eczema were defined as parental report of physician-diagnosed eczema through the questions, collected when the infants were at 1 year old 'Have your child been diagnosed with eczema by a doctor since he/she was 6 months of age?'. Information on eczema symptoms (defined as recurrent

itchy rash) in children's first 6 months of life was also collected at 6 months old via the question 'Have your child had recurrent itchy rash since he/she was 2 months of age?'.
Covariates

Covariates

Information on maternal age at recruitment, maternal education level and monthly income, active smoking during pregnancy, passive smoking during pregnancy, maternal height and pre-pregnancy weight, maternal and paternal history of asthma, allergic rhinitis, atopic dermatitis, and other allergic diseases, and parity were collected from questionnaires at baseline and at late pregnancy. Infants with at least one of parents having history of allergic diseases (including asthma, allergic rhinitis, atopic dermatitis, and other allergic diseases) were categorized in high-risk group, while all others were in the low-risk group. Pre-pregnancy body mass index (BMI) (kg/m^2) was calculated by dividing pre-pregnancy weight by height squared. Based on the Guidelines of Prevention and Control of Overweight and Obesity in Chinese Adults, pre-pregnancy nutrition status of mother was categorized as four groups as follows: underweight ($\text{BMI} < 18.5 \text{ kg/m}^2$), normal ($\text{BMI} 18.5\text{--}23.9 \text{ kg/m}^2$), overweight ($\text{BMI} 24.0\text{--}27.9 \text{ kg/m}^2$) and obesity ($\text{BMI} \geq 29.0 \text{ kg/m}^2$).²⁴ Birth information (including offspring's gender, birth weight and gestational age) and pregnancy complications (including gestational diabetes mellitus, gestational hypertension, and preeclampsia) were extracted from the medical records after delivery.

Statistical analysis

Differences in maternal and children's characteristics by depressive symptoms at early pregnancy were examined using chi-square test or Fisher exact test for categorical data, and Student's t test or Whitney

U test for continuous variables.

We performed multivariable logistic regression to investigate the associations between maternal depressive symptoms scores (continuous) or depressive symptoms (categorical) in early or late pregnancy and eczema in the offspring within the first year, adjusting for potential confounders, including maternal age, maternal income and education, active or passive smoke during pregnancy, pre-pregnancy BMI, parental history of allergic diseases, parity, and pregnancy complications. We also examined the association of the courses of prenatal depressive symptoms across pregnancy with children's eczema in first year. Prespecified analyses of infants' eczema were performed in subgroups defined according to parental history of allergic diseases. Interaction tests were expected to be significant.

In sensitivity analysis, we re-ran our main analyses by additionally including the pregnant women whose depressive symptoms were assessed during the period between 28-32 gestational weeks and between 20-32 gestational weeks, respectively, to examine the robustness of the results in definitions of late pregnancy. We also performed an analysis by using the data of eczema symptoms reported in the first 6 months and the diagnosed information in the second half of the first year of life to explore the association of prenatal depressive symptoms with the four subtypes of offspring's eczema during infancy (i.e. "no eczema symptoms and diagnosed eczema throughout infancy", "eczema symptoms in early infancy but no diagnosed eczema in late infancy", "no eczema symptoms in early infancy but diagnosed eczema in late infancy", and "eczema symptoms in early infancy with diagnosed eczema in late infancy").

The significance level was set at 0.05 with two sides. All analyses were performed in SAS software version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

A total of 19 231 pregnant women were recruited between February 2012 and August 2016 in BIGCS. After applying the exclusion criteria, 8580 mother-child pairs were included in this study as presented in Figure 1. In the analytical population, 18.79% (1458/8194) and 16.08% (995/6188) of mothers were identified as having depressive symptoms at early and late pregnancy, respectively. There were 5825 women with information on depressive symptoms at both early and late pregnancy, of which, 73.8% (n=4299), 10.1% (n=590), 8.4% (n=489), and 7.7% (n=447) were categorized into “absent”, “early pregnancy only”, “late pregnancy only”, and “persistent”, respectively. Maternal and infants’ characteristics by depressive symptoms at early pregnancy are summarized in Table 1. Mothers with depressive symptoms before 20th gestational week were more likely to be younger, be of lower socioeconomic position, smoke actively or be exposure to passive smoking during pregnancy, and have the parents with history of allergic diseases. The mean follow-up time of children was 11 months and 27 days (SD 18 days). There were 17.28% (1483/8580) of infants having parent-reported diagnosed eczema.

Figure 2 shows that maternal depressive symptom scores at early pregnancy or late pregnancy were positively associated with infants’ eczema risks ($P<0.05$ in both). Table 2 shows the association between the maternal depressive symptoms at early or late pregnancy and courses of depressive symptoms throughout pregnancy, and children’s eczema in first year. After adjusting for potential confounders, presence of maternal depressive symptoms at early pregnancy were associated with higher risks of infants’ eczema (Odds ratio (OR): 1.30, 95% Confidence Interval (CI) 1.09 to 1.55). Similar association was observed for depressive symptoms at late pregnancy (OR: 1.27, 95% CI 1.05 to 1.54). Compared to those children with mothers not experiencing depressive symptoms during

pregnancy (“absent”), the children of mothers with persistent depressive symptoms were at higher risks of eczema (OR: 1.55, 95% CI 1.19 to 2.03). However, the associations for the presence of prenatal depressive symptoms at early or late pregnancy only were not statistically significant.

Results of the prespecified subgroup analyses according to parental history of allergic diseases are presented in Figure 3 and Supplementary eFigure 1. Associations for maternal depressive symptoms at early pregnancy (OR: 1.38, 95% CI 1.13 to 1.69) with infants’ eczema were only observed in the low-risk group, but not in the high-risk group. Associations between maternal depressive symptoms at late pregnancy and infants’ eczema were not obvious in both low-risk and high-risk groups. Persistent prenatal depressive symptoms were associated with elevated risks of infants’ eczema when compared to the “absent” group (OR: 1.73, 95% CI 1.28 to 2.35) in low-risk group. In contrary, the associations for depressive symptoms during early or late pregnancy only and the association for persistent depressive symptoms were not observed in the high-risk group. The interaction tests for depressive symptoms at early pregnancy and at late pregnancy, and courses of depressive symptoms and parental history of allergic diseases were 0.384, 0.109, and 0.064 respectively in adjusted models.

In the sensitivity analyses, the results were consistent with the main results when we additionally included those women whose late-pregnancy depressive symptoms were collected between 28-32 gestational weeks or 20-32 gestational weeks (data not shown). When exploring the association of prenatal depressive symptoms and offspring’s eczema subtypes, evident associations were found between prenatal depressive symptoms and infants’ eczema diagnosed in late infancy irrespective of eczema symptoms in early infancy, but no obvious associations were shown in infants with eczema symptoms in early infancy but free of diagnosed eczema in late infancy (Supplementary eTable 1).

Discussion

In this large prospective cohort study in an understudied population, we found that presence of maternal depressive symptoms at either early or late pregnancy were both associated with higher risks of childhood eczema in infancy, especially in those with persistent prenatal depression. In addition, maternal depressive symptoms increased the risk of infants' eczema particular in the child without parental history of allergic diseases.

Few studies have assessed the relationship between maternal depression during pregnancy and children's eczema at early age; and these studies only assessed maternal depression at a single time point.¹²⁻¹⁶ Three of these previous studies showed no association between prenatal depressive symptoms at second trimester and children's eczema,^{12,15,16} while the other three reported positive associations when the maternal depressive symptoms were assessed at third trimester.^{13,14} To some extent, the difference could be due to the different windows and methods of assessment of depressive symptoms or children's eczema. However, none of these studies have been able to differentiate the effects from maternal depressive symptoms in early pregnancy or in late pregnancy or from cumulative exposure of symptoms across pregnancy. The pronounced risk of maternal depressive symptoms measured at the third trimester in previous studies may reflect cumulative exposure of mood state throughout pregnancy rather than specific trimester effect.

Concern has been raised that mother's depressive symptoms may influence the recognition and reporting of eczema in their child,¹⁹ which may influence the association between prenatal depressive symptoms and infants' eczema. We had assessed mothers' postpartum depressive symptoms using Edinburgh Postnatal Depression Scale when their children were at 6 weeks, 6 months and 1 year old. There was no difference in the rate of infants' eczema between mothers with and without postnatal

depressive symptoms at children's age of 1 year (18.32% vs 18.06%) as well as no difference between women with persistent postnatal depressive symptoms and no postnatal depressive symptoms throughout infancy (16.76% vs 18.62%), which indicates no influence of postpartum depressive symptoms on parental reporting of eczema in our study, and postpartum depressive symptoms are unlikely to have mediation effect.

Our study adds by showing that children who were persistently exposed to maternal depressive symptoms had higher risks of eczema in infancy, while the infants whose mother had depressive symptoms only in specific pregnancy windows were not at increased risks of eczema. There is evidence from animal studies that prenatal stress exposure can affect the development process of immunity system at the earliest stage,²⁵ which may explain the cumulative effects of prenatal depressive symptoms on offspring's eczema, although this has been rarely investigated in humans.

Our subgroup analysis was suggestive of a higher risk of infants' eczema given maternal depressive symptoms during pregnancy in families without history of allergic diseases than those with, although the interaction test did not reach significance. This is consistent with a previous study showing a stronger association between maternal depressive disorders and childhood eczema if children were in families with siblings not affected by atopic diseases than other families.¹⁹ The consistent findings suggest the association of prenatal depressive disorders with offspring's eczema appeared to be more evident in children without pre-existing parental hereditary component. We speculate that these "first-generation" individuals with allergic diseases may confer an elevated risk for eczema to their children, such that additional contribution from maternal depression during pregnancy would be minimal. Nevertheless, the role of parental disease history in modifying the relation between prenatal depression and offspring's eczema risk requires further investigation, such as larger cohorts

with more refined phenotyping of depressive symptoms to allow for adequately powered interaction analyses.

The mechanisms underpinning the associations between prenatal depressive symptoms and offspring's eczema are still unclear. Maternal stress may disrupt fetal hypothalamic-pituitary-adrenal (HPA) axis and sympathetic adrenomedullary system, via elevated levels of cortisol,^{26,27} which may induce a type 2 T-helper cell (Th2) predominance and increase the production of pro-inflammatory and Th2 cytokines,^{28,29} and eventually resulting in the up-regulation of immune susceptibility to childhood eczema.³⁰ Alternatively, increased oxidative stress in the fetal environment, driven by mother's distress during pregnancy might damage keratinocytes,³¹ which would enhance the offspring's vulnerability to eczema in later life. Furthermore, microbiota may play a role since infants' intestinal microbiota composition and colonization pattern differed by status of maternal prenatal stress and the altered colonization pattern was related to more infants' allergic reactions.³² Gut immunity that involves intestinal secretory immunoglobulin A (sIgA) may also be a potential pathway. Infants with mothers experiencing antepartum depressive symptoms have been reported to exhibit lower intestinal sIgA concentrations,^{33,34} and lower production of sIgA is associated with greater risk of allergic diseases, such as eczema.³⁵ Further investigation is required to verify the causal pathway of sIgA.

Despite using a large prospective study to assess maternal depressive symptoms at different stages of gestation, the present study has some limitations. First, we could not rule out the possibility of residual confounding given this was an observational study. Alternative approaches such as Mendelian randomization studies could be explored to assess the impact of maternal attributes to offspring's outcomes.³⁶ Second, information on diagnosis of eczema and eczema symptoms was based on parental report instead of medical records or physical examinations, leading to potential misclassification bias.

However, such approach appears to be sufficiently valid for investigating childhood eczema in previous studies.³⁷ Third, data on the severity of eczema was unavailable in our study. Further investigation is required to examine whether the effects of prenatal depressive symptoms on infants' eczema differed by the severity of eczema.

In conclusion, our study suggested that a possible intrauterine programming effect of persistent prenatal depressive symptoms on the offspring's risk of developing eczema in infancy, especially in children without parental history of allergic diseases. As eczema is thought to predispose patients to other allergic diseases later in life and given the regular contact pregnant women have with health care providers, evaluation and management of women's depressive symptoms during pregnancy could be important not only for improving women's health but also for reducing the risk of offspring's developing eczema and other allergic disorders, and improve offspring's quality of life later in life.

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Contributors: XQ, DW, and SLAY conceived and designed the study; DW and SLAY analyzed and interpreted the data, and drafted the manuscript; JL analyzed and interpreted the data; ML and WX collected and assembled the data; SS and KBHL interpreted the data. All authors reviewed and revised the manuscript critically for important intellectual content. All authors have approved the final version

to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data sharing: No additional data available.

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Figure legends

Figure 1. Flowchart of participant inclusion. BIGCS, Born in Guangzhou Cohort Study.

Figure 2. Associations between prenatal depressive symptoms scores and predicted probability of infants' eczema. Adjusting for maternal age, maternal income, maternal education, maternal active or passive smoke during pregnancy, pre-pregnant BMI, maternal and paternal history of allergic diseases, parity, and pregnancy complications. Blue lines represent the fitting results; Red lines represents the 95% prediction limits; Grey dot represents individuals' scatter dot. Figure A represents maternal depressive symptoms scores at early pregnancy; Figure B represents maternal depressive symptoms scores at late pregnancy. For all the figures, *P* value was less than 0.05.

Figure 3. The associations between maternal depressive symptoms and infants' eczema among low-risk and high-risk population. CI, confidence interval; OR, odds ratio. Low-risk group, infants without parental history of allergic diseases; High-risk, infants with parental history of allergic diseases. The reference groups for depressive symptoms at early or late pregnancy were absence of depressive symptoms. *P* values for interaction between depressive symptoms at early pregnancy, at late pregnancy, and courses of depressive symptoms and parental history of allergic diseases were 0.384, 0.109, and 0.064 respectively in adjusted model. ^a Adjusting for maternal age, maternal income, maternal education, maternal active or passive smoke during pregnancy, pre-pregnant BMI, parity, and pregnancy complications.