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An independent association of prenatal depression with wheezing and anxiety with rhinitis in infancy

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Abstract

Background: Different maternal psychological states during pregnancy have been associated with wheeze-rhinitis-eczema symptoms in children. However, previous studies were limited and it was unclear whether the type of prenatal psychological state was associated with a particular symptom. We examined the association of maternal depression and anxiety during pregnancy with wheeze-rhinitis-eczema symptoms in infancy.

Methods: In a longitudinal birth cohort (GUSTO) of 1152 mother-child pairs, wheeze-rhinitis-eczema symptoms in the infants during the first year of life were collected by parental report. Maternal depressive and anxiety symptoms were assessed at 26 weeks gestation using the Edinburgh Postnatal Depression Scale (EPDS) and State Trait Anxiety Inventory (STAI). Logistic regression analyses were performed with adjustment for potential confounders.

Results: An increased risk of wheezing was found in infants of pregnant women with probable depression (EPDS $\geq$ 15) [Odds Ratio (OR) =1.85 (95% Confidence interval (CI) 1.10-3.12)] and an increased risk of rhinitis was associated with maternal anxiety [STAI state $\geq$ 41: OR=1.42 (95% CI 1.04-

1.93); STAI trait $\geq$ 43: OR=1.38 (95% CI 1.01-1.88)]. After adjusting for known risk factors for the development of allergic disease, these associations remained significant [EPDS $\geq$ 15: adjusted OR=2.09 (95% CI 1.05-4.19); STAI state $\geq$ 41: adjusted OR=1.82 (95% CI 1.17-2.82); STAI trait $\geq$ 43: adjusted OR=1.70 (95% CI 1.10-2.61)]. However, maternal psychological states were not associated with infantile eczema.

Conclusion: This study suggests that there may be an independent effect of prenatal depression on wheezing and anxiety on rhinitis in infancy.

Key words: anxiety; depression; prenatal; rhinitis; wheeze

Abbreviations used:

HPA , hypothalamic-pituitary-adrenal; GUSTO, Growing Up in Singapore Towards healthy Outcomes;

BMI, Body mass index; EPDS, Edinburgh Postnatal Depression Scale; STAI, State Trait Anxiety Inventory; Th, T-helper

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Introduction

Allergic diseases are common in childhood and often start in infancy with wheeze-rhinitis-eczema symptoms. In 2005, prevalence of wheezing, rhinitis and eczema in young Singaporean children in the first two years of life was reported as 22.9%, 42.7% and 10.4%, respectively (1). Worldwide there seems to be a general trend towards an increase in prevalence of asthma, rhinitis and eczema (2). Although allergic diseases are not necessarily fatal, there is a considerable impact on quality of life, comorbidity and economic impact (3-5). It is therefore important to better understand the developmental origins of allergic diseases for effective prevention.

Increasingly, studies are reporting an association of maternal psychological state during pregnancy with adverse outcomes in the offspring. One possible explanation for this association is that prenatal maternal psychological state causes a dysregulation of corticotrophin releasing factor and an alteration of the hypothalamic-pituitary-adrenal (HPA) axis regulation (6-8). In support of this hypothesis, animal studies have shown that animals exposed to prenatal stress have altered HPA axis and immune function after birth, subsequently predisposing to airway inflammation and hyper-responsiveness (9-11). The programming effects on the HPA axis development of the foetus was believed to be a consequence of trans-placental passage of elevated cortisol in stressed mothers (6, 7).

Several observational studies have associated different prenatal maternal psychological state with childhood wheezing, rhinitis and eczema (12-16). However, such studies are limited and focus only on one type of psychological state. It has been reported that maternal anxiety and depressive symptoms during pregnancy are respectively associated with shorter gestation and lower birth weight (17). Therefore, the question arises as to whether the type of prenatal maternal psychological state may be associated with a particular allergy-related symptom. As there is scarce data on Asian children, we investigated the association of prenatal maternal depressive and anxiety symptoms with wheezing, rhinitis and eczema during infancy in a Singapore birth cohort.

Methods

Study recruitment

Growing Up in Singapore Towards healthy Outcomes (GUSTO) (18) is a birth cohort study which recruited 1152 pregnant women who conceived naturally and were of homogenous parental ethnicity (Chinese, Malay, Indian). During the first trimester of pregnancy, gestational age (GA) was verified using foetal ultrasonography. Mothers were administered self-reported questionnaires at the recruitment visit and at 26 weeks of gestation to record their socio-demographic characteristics. Weight and height of mothers at 26 weeks of gestation were measured and used to calculate body mass index (BMI) as weight per squared height (kg/m^2). Of the recruited mothers, 92.6% ($n=1067$) mothers gave birth between 37 and 41 weeks of gestation while the remaining ($n=85$, 7.4%) had premature deliveries between 25 and 36 weeks of gestation.

Psychological assessments

Maternal psychological state was assessed at 26 weeks of gestation using the following self-reported measures: the Edinburgh Postnatal Depression Scale (EPDS) and State Trait Anxiety Inventory (STAI). Although the EPDS was originally designed to measure postpartum depression, this self-report instrument has been shown to be valid, reliable and sensitive in measuring depressive symptoms in both pregnant and postpartum women. Based on Spitzer's Research Diagnostic Criteria, a score of ≥ 15 on EPDS was suggestive of probable prenatal depression (19). As proposed by Nasreen et al (20) and Teixeira et al (21), the cut-off for a high anxiety score on STAI was based on the top quartile scores. In our GUSTO cohort, a score of ≥ 41 and ≥ 43 identified high anxiety state and trait, respectively.

Wheeze-rhinitis-eczema symptoms

At birth of the infant, parents completed a questionnaire regarding their personal history of asthma, wheezing, rhinitis and eczema. The status of wheeze-rhinitis-eczema symptoms in the infant was also obtained, and recorded as a binary variable (presence or absence) at 3, 6, 9 and 12 months. The presence of wheezing and eczema were based on physician diagnosis. Rhinitis was defined as runny nose, blocked

or congested nose, snoring or noisy breathing during sleep or when awake that had lasted for 2 or more weeks duration (22). The presence of eczema was based on physician-diagnosed eczema. The infants were considered to have that particular symptom in the first year of life when it was reported positive at least once within 12 months.

Skin price test for allergen sensitization

Skin prick testing (SPT) was performed at 18 months to assess the presence of allergic sensitization to a panel of food (whole egg, cow's milk and peanut) and house dust mites allergens (HDM: *Blomia tropicalis*, *Dematophagoides pteronyssinus* and *Dermatophagoides farina*). Skin prick test reagents were obtained from Greer Laboratories (Lenoir, NC, USA), except for *B. tropicalis* which was obtained from our in-house laboratory. Presence of atopy was defined as a wheal size of 3 mm or larger than the negative control.

Covariates

Potential confounders for the association between prenatal maternal mood and wheeze-rhinitis-eczema symptoms in infants included baby gender, birth weight, gestational age, ethnicity, maternal age, BMI, highest education level, marital status, household monthly income, maternal asthma history, parental history of wheezing, rhinitis or eczema, maternal smoking pre-pregnancy and exposure to passive smoking during pregnancy. These variables have been reported as risk factors for the development of allergic diseases (23-30). Postnatal maternal mood was not adjusted due to its high correlation with prenatal maternal mood.

Statistical analyses

Singleton children with known status for wheezing, rhinitis or eczema in the first year of life and prenatal psychological state were included for analyses. Fisher's exact test for categorical variables and independent t-test for continuous variables were computed to explore the differences between infants with and without allergy symptoms. Crude and adjusted odds ratios (ORs) with corresponding 95% confidence

intervals (CI) for the association of prenatal maternal depression/anxiety with wheeze-rhinitis-eczema symptoms were calculated using univariate and multivariate logistic regression, respectively. Any significant associations found were re-tested in a subsample of infants with atopy using multivariate analyses. Since depression and anxiety are more likely to be comorbid, the interaction between psychological state (i.e., depression and anxiety) was tested in another multivariate model using the overall sample. Statistical significance was determined at $p < 0.05$. All statistical analyses were performed using Statistical Package for the Social Sciences, Version 20.0 (SPSS Inc. Chicago, Illinois, US).

Results

Subject characteristics

For this cohort, data was obtained in 86.8% ($n=1000$), 86.8% ($n=1000$) and 78.8% ($n=908$) for wheezing, rhinitis and eczema, respectively. Of these, 187 (18.7%), 297 (29.7%) and 115 (12.7%) infants were reported to have wheezing, rhinitis and eczema in the first year of life. A total of 707 infants have undergone SPT, of which, 108 were identified to be atopic.

Table 1 shows the comparison of parental and infant characteristics between absence and presence of infantile wheeze-rhinitis-eczema symptoms. Compared to infants without wheezing, infants who wheezed were less likely to be Chinese (46.0% vs 57.3%; $p=0.018$) but more likely to have mothers with higher BMI (26.76 ± 4.86 vs 25.92 ± 4.34 kg/m²; $p=0.032$) and have a history of asthma (22.7% vs 10.9%; $p < 0.001$) and wheezing (10.9% vs 4.0%; $p=0.001$).

In addition to ethnicity, maternal BMI and maternal asthma, significant difference between absence and presence of infant rhinitis was found in infant gender (Table 1). More male (59.3% vs 49.4%; $p=0.005$) and Malay (33.7% vs 23.5%; $p=0.004$) infants experienced rhinitis than those who did not. Also, mothers of infants with rhinitis were more likely to have higher BMI (26.69 ± 4.62 vs 25.82 ± 4.35 kg/m²; $p=0.005$) and a history of asthma (16.2% vs 8.6%; $p=0.002$) and rhinitis (15.0% vs 9.0%; $p=0.029$) than mothers of infants without rhinitis.

Characteristics that showed significant difference varied slightly for eczema. Indian (7.0% vs 19.9%; $p=0.001$) and female (35.7% vs 49.7%; $p=0.005$) infants were less likely to have eczema in the first year of life. However, those in the higher household monthly income group of $\geq$ SGD6000 (40.5% vs 27.4%; $p=0.020$) and those having mothers (14.3% vs 6.1%; $p=0.008$) and fathers (8.8% vs 2.8%; $p=0.009$) with a history of eczema tended to have eczema.

Prenatal psychological state and wheeze-rhinitis-eczema symptoms

Completion rates for EPDS and STAI were 92.2% ($n=1062$) and 92.4% ($n=1065$), respectively. 7.7% ($n=82$) of mothers were probable cases of prenatal depression, and they were also found to have higher proportions of concurrent state- (78.8% vs 21.9%; $p<0.001$) and trait-anxiety (83.8% vs 20.6%; $p<0.001$).

As shown in Table 2, an increased risk of wheezing was found in infants of pregnant women with probable depression ($EPDS \geq 15$) [OR=1.85 (95% CI 1.10-3.12)]. After adjusting for potential confounders, the association between prenatal maternal depression and infantile wheezing remained significant [adjusted OR=2.09 (95% CI 1.05-4.19)]. High anxiety state and trait were not associated with infantile wheezing.

Maternal anxiety in pregnancy was associated with an increased risk of rhinitis in their infants [STAI state ≥ 41 : OR=1.42 (95% CI 1.04-1.93); STAI trait ≥ 43 : OR=1.38 (95% CI 1.01-1.88)]. After adjustment, prenatal maternal anxiety, both state and trait, remained significantly associated with increased risk of the infantile rhinitis [STAI state ≥ 41 : adjusted OR=1.82 (95% CI 1.17-2.82); STAI trait ≥ 43 : adjusted OR=1.70 (95% CI 1.10-2.61)]. No significant association between prenatal depression and infantile rhinitis was found (Table 2).

Logistic regression displayed different results for infants with eczema from wheezing and rhinitis.

Probable depression, and high anxiety state and trait- in pregnant women were not significantly associated with infantile eczema (Table 2).

The associations of prenatal depression with infantile wheezing and anxiety with rhinitis were still seen when these were tested in a subsample of infants, despite statistical insignificance. Using the overall

sample, we found that the interaction between prenatal maternal depression and anxiety state were not significantly associated with wheezing and rhinitis during infancy. Similar findings were found when the interaction between prenatal maternal depression and anxiety trait was tested.

Discussion

This is the first study which demonstrates that maternal depression and anxiety during pregnancy were both independently associated with increased risk of wheezing and rhinitis in infants. The strength of the association was consistent after adjustment for multiple confounding factors including baby gender, birth weight, gestational age, ethnicity, maternal age, BMI, highest education level, marital status, household monthly income, maternal asthma history, parental history of wheezing, rhinitis or eczema, maternal smoking pre-pregnancy and exposure to passive smoking during pregnancy. Our findings suggest that adverse prenatal depression and anxiety may be causal for wheezing and rhinitis in infancy. However, such an association was not present for infantile eczema.

Previous studies have reported the association of childhood wheezing with maternal stress during pregnancy (14, 15, 31). In this study, we measured maternal psychological stress by assessing the presence of symptoms of depression and anxiety. Our results further elucidate that prenatal maternal depression but not anxiety was associated with wheezing in infants. Though the EPDS contains an anxiety sub-scale (32), infantile wheezing was less likely to be influenced by comorbid effect of depression and anxiety since interaction between depression and anxiety did not show significant association with infantile wheezing. On the other hand, Lefevre et al (16) found that prenatal depression was not associated with childhood wheezing. This inconsistency may be due to differences in study design. In the study by Lefevre et al (16), it was a case-control study using an earlier version of the BDI which was administered postnatally to assess prenatal depression.

Consistent with previous studies (12, 16), this study demonstrated that prenatal anxiety was not associated with childhood wheezing. We found, however, an association with prenatal anxiety and infantile rhinitis.

This finding has not been definitively reported though it has been suggested (12) based on the link seen between asthma and allergic rhinitis (33). Moreover, our study has also demonstrated a new finding that mothers' depression during pregnancy was less likely to be associated with rhinitis in their infants during the first year of life. These observations suggest that prenatal depression and anxiety during pregnancy may affect the infants through different mechanisms (34).

As wheezing and rhinitis are respiratory disorders, it can be postulated that the aberrant or excessive pro-inflammatory immune responses resulting from prenatal exposures to environmental toxins or factors may alter the normal course of morphogenesis and maturation of the respiratory system, leading to changes that affect both structure and function (35, 36). Animal studies have shown that prenatal stress can cause dysregulation between lung function and airway response from the increased corticosteroid secreted by the stressed pregnant rat (7, 10). Using this information, a possible explanation for the development of the respiratory symptoms in the infants of mothers who demonstrate depressive or anxiety-traits during pregnancy is that the glucocorticoids cross the placenta and alter the neuroendocrine system including hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system in the offspring (6), resulting in the production of higher levels of Type 2 T-helper cells (Th2) than Th1, which in turn leads to airway inflammation and reactivity and diminished lung function after birth (7). Another possible mechanism is that it has been shown that early life stress during critical periods of prenatal development may also induce epigenetic changes that program the HPA axis (37). This in turn can lead to a greater Th2 response by the immune system.

To the best of our knowledge, only one study reported that maternal stress during pregnancy was positively related to childhood eczema (13). Our study did not find an association of prenatal psychological state with infantile eczema. A possible explanation for this may be due to population and ethnic differences. A higher percentage of mothers with psychological problems during pregnancy was found in our study than that reported by Sausenthaler et al (13), while the prevalence of infant eczema at 0-1 year in both cohorts were similar. Nonetheless, our findings suggest that prenatal psychological state

might not be the direct cause of early childhood eczema. Another possible explanation is that eczema is not an allergic disease but primarily a skin barrier defect in which allergy is not the cause but the consequence of that defect.

The large sample size is one of the strengths in this study. Despite it being a longitudinal study, selection bias due to missing data was low as there was good compliance to follow up (18). We also adjusted for multiple possible confounders to increase the reliability of the results. Nonetheless, our study does present some limitations. We did not capture information on medication for depression or anxiety in the participating mothers. Wheeze-rhinitis-eczema symptoms were largely self-reported but our findings in the overall sample were consistent with those in the subsample of infants with atopy. Since the sample size for the subsample was small because of the young age, we intend to re-examine the data when children are older as more children show evidence of sensitization. In addition, depressed or anxious mothers might be more prone to report wheeze-rhinitis-eczema symptoms in their children. We are also unable to provide any biological data to elucidate the underlying mechanisms linking prenatal psychological state and the development of wheeze-rhinitis symptoms in infants.

In conclusion, our study suggests that maternal depression and anxiety during pregnancy may independently lead to development of wheezing and rhinitis in their children. Also, maternal psychological problems may not be the causal factor for infantile eczema. Our findings highlight the importance of screening for and the timely treatment of maternal depression and anxiety during pregnancy as it may be a risk factor for the development of allergic respiratory disease in their offspring. Further experimental studies are needed to better define the mechanisms linking prenatal depression with wheezing and anxiety with rhinitis in infants so that specific intervention strategies can be implemented in the future.

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Table 1: Comparisons of parental and infant characteristics

Characteristics	Wheezing			Rhinitis			Eczema		
	No (n=813)	Yes (n=187)	<i>p</i>	No (n=703)	Yes (n=297)	<i>p</i>	No (n=793)	Yes (n=115)	<i>p</i>
Ethnicity (n, %)			0.018			0.004			0.001
Chinese	466 (57.3)	86 (46.0)		407 (57.9)	145 (48.8)		433 (54.6)	77 (67.0)	
Malay	205 (25.2)	60 (32.1)		165 (23.5)	100 (33.7)		202 (25.5)	30 (26.1)	
Indian	142 (17.5)	41 (21.9)		131 (18.6)	52 (17.5)		158 (19.9)	8 (7.0)	
Mother									
Age (years) (SD)	30.68 (5.16)	30.10 (4.97)	0.166	30.58 (5.11)	30.54 (5.20)	0.911	30.54 (5.09)	31.47 (5.06)	0.067
BMI (kg/m ²) (SD)	25.92 (4.34)	26.76 (4.86)	0.032	25.82 (4.35)	26.69 (4.62)	0.005	26.19 (4.49)	25.71 (4.17)	0.281
Education (n, %)			0.657			0.880			0.271
None/Primary/Secondary	249 (31.0)	53 (29.0)		212 (30.5)	90 (30.9)		236 (30.1)	28 (24.6)	
Tertiary	555 (69.0)	130 (71.0)		484 (69.5)	201 (69.1)		548 (69.9)	86 (75.4)	
Marital Status (n, %)			0.820			0.848			0.162
Single/Divorced	28 (3.5)	5 (2.8)		23 (3.3)	10 (3.5)		29 (3.7)	1 (0.9)	
Married	770 (96.5)	175 (97.2)		670 (96.7)	275 (96.5)		747 (96.3)	112 (99.1)	
Household monthly income (n, %)			0.290			0.066			0.020
≤SGD 1999	118 (15.6)	26 (14.6)		102 (15.4)	42 (15.3)		119 (16.1)	13 (11.7)	
SGD 2000-5999	416 (55.0)	109 (61.2)		357 (54.0)	168 (61.3)		418 (56.5)	53 (47.7)	
≥SGD 6000	223 (29.5)	43 (24.2)		202 (30.6)	64 (23.4)		203 (27.4)	45 (40.5)	
Asthma (n, %)	87 (10.9)	41 (22.7)	<0.001	50 (8.6)	40 (16.2)	0.002	66 (10.0)	14 (15.4)	0.144
Pre-pregnancy smoking (n, %)	99 (12.3)	32 (17.3)	0.091	93 (13.4)	38 (13.0)	0.918	97 (12.4)	16 (14.2)	0.547
Passive smoking during pregnancy (n, %)	285 (36.0)	72 (40.0)	0.346	240 (35.1)	117 (40.6)	0.109	282 (36.5)	36 (32.7)	0.460
Related parental allergy history (n, %)									
Mother – Wheezing/Rhinitis/Eczema	30 (4.0)	18 (10.9)	0.001	40 (9.0)	30 (15.0)	0.029	40 (6.1)	13 (14.3)	0.008
Father - Wheezing/Rhinitis/Eczema	18 (2.4)	5 (3.1)	0.583	41 (9.3)	24 (12.1)	0.323	18 (2.8)	8 (8.8)	0.009
Infant									
Birth weight (kg) (SD)	3.11 (0.44)	3.07 (0.48)	0.305	3.09 (0.45)	3.14 (0.45)	0.100	3.10 (0.44)	3.14 (0.52)	0.383
Gestational age (weeks) (SD)	38.33 (1.34)	38.20 (1.80)	0.370	38.29 (1.45)	38.34 (1.41)	0.650	38.35 (1.31)	38.11 (2.17)	0.097
Gender (n, %)			0.331			0.005			0.005
Male	419 (51.5)	104 (55.6)		347 (49.4)	176 (59.3)		399 (50.3)	74 (64.3)	
Female	394 (48.5)	83 (44.4)		356 (50.6)	121 (40.7)		394 (49.7)	41 (35.7)	

n, number; %, percentage; SD, standard deviation; BMI, Body Mass index; kg, kilogram; m, meter; SGD, Singapore dollars

Table 2: The association between prenatal mood and allergic diseases in infancy

Psychological assessments at 26 weeks of gestation	Wheezing		Rhinitis		Eczema	
	crude OR (95% CI)	adjusted OR ^a (95% CI)	crude OR (95% CI)	adjusted OR ^b (95% CI)	crude OR (95% CI)	adjusted OR ^c (95% CI)
EPDS (≥15)	1.85 (1.10-3.12)*	2.09 (1.05-4.19)*	1.31 (0.81-2.14)	1.13 (0.54-2.36)	0.76 (0.34-1.71)	1.13 (0.43-2.99)
STAI state (≥41)	1.05 (0.72-1.51)	1.01 (0.63-1.61)	1.42 (1.04-1.93)*	1.82 (1.17-2.82)*	0.98 (0.62-1.54)	1.01 (0.56-1.81)
STAI trait (≥43)	1.17 (0.81-1.68)	1.23 (0.78-1.94)	1.38 (1.01-1.88)*	1.70 (1.10-2.61)*	0.87 (0.55-1.39)	1.02 (0.58-1.81)

OR, Odds ratio; CI, Confidence Interval

*<0.05

^aadjusted for baby gender, birth weight, gestational age, ethnicity, maternal age, maternal BMI, education, marital status, household monthly income, maternal wheezing history, paternal wheezing history, maternal asthma history, maternal pre-pregnancy smoking and passive smoking during pregnancy

^badjusted for baby gender, birth weight, gestational age, ethnicity, maternal age, maternal BMI, education, marital status, household monthly income, maternal rhinitis history, paternal rhinitis history, maternal asthma history, maternal pre-pregnancy smoking and passive smoking during pregnancy

^cadjusted for baby gender, birth weight, gestational age, ethnicity, maternal age, maternal BMI, education, marital status, household monthly income, maternal eczema history, paternal eczema history, maternal asthma history, maternal pre-pregnancy smoking and passive smoking during pregnancy