Associations Between Maternal Distress During Early Life Periods and Offspring Respiratory Infections and Allergic Outcomes

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Background: Increasing evidence suggests that maternal distress is a risk factor for development of respiratory infections and allergic diseases in the offspring. We aim to evaluate the link between maternal distress during critical periods in early life, namely the preconception, pregnancy and postnatal periods, and development of respiratory infections and allergic diseases in the offspring from the Singapore PREConception Study of long Term maternal and child Outcomes (S-PRESTO) cohort.

Methods: Maternal perceived distress was evaluated using validated questionnaires including Beck Depression Inventory-II (BDI-II) administered during three time periods: preconception (three months apart at four timepoints), pregnancy (during each trimester) and postnatal (3 and 6 months post-delivery). Child eczema, rhinitis and wheeze outcomes were evaluated using a modified ISAAC questionnaire at ages 3, 6, 12, and 18 months. Child allergic sensitization was determined by skin prick testing at 18 months.

Results: Among 332 mother-child pairs studied, higher maternal distress during preconception and pregnancy increased the risks of wheeze development in the first 18 months; for example, preconception and pregnancy BDI-II scores ≥20 were associated with increased risks of wheeze by 18 months [adjusted risk ratios 3.2 (95%CI 1.1–9.4) and 2.5 (1.0–5.9), respectively]. Emotional and practical support from family during
Maternal Distress Increases Offspring Wheezing

preconception decreased the risks of offspring wheeze. No associations were observed between maternal distress and offspring eczema, rhinitis and allergic sensitization.

**Conclusion:** Maternal distress during critical early life periods was associated with offspring wheeze in the first 18 months of life. Supporting maternal mental health even before pregnancy could reduce the risk of offspring wheeze.

**Keywords:** maternal distress, wheeze, rhinitis, eczema, allergic sensitization, preconception, pregnancy, postnatal

**INTRODUCTION**

Allergy and respiratory infections are global health issues (1, 2) and impact the quality of life as well as school performance of children. The rapid increase in prevalence of allergic diseases and respiratory infections is postulated to be due to environmental and lifestyle factors such as psychosocial distress, which is defined as an emotional state of discomfort resulting from exposure to stress (3). Findings from epidemiological studies strongly suggest that maternal health during preconception and over the course of pregnancy and postnatal development influence child's health. The influence of early life environment on child's health forms the basis for the Developmental Origins of Health and Disease (DOHaD) paradigm which hypothesizes that early environmental stimuli during preconception, pregnancy and early life may influence fetal and neonatal immune development and cause development of diseases including eczema, asthma, allergic rhinitis and allergic sensitization during early life (4–6).

Increasing evidence suggests that maternal distress is a risk factor for development of allergic and respiratory diseases in the offspring. In a meta-analysis of 30 studies and a cross-sectional study involving 3,758 Italian mother-child pairs, prenatal maternal distress was associated with increased risk of development of eczema, rhinitis, wheeze, and asthma in the offspring (7, 8). Prenatal maternal anxiety, depression and distress were also associated with higher risk of eczema in two Korean cohorts of children at 4 and 5 years of age (9). The Generation R study from the Netherlands reported that mothers with higher distress levels had an increased risk of having offspring who wheezed at 1–4 years of age (10). In China, schoolchildren had increased risk of rhinitis if their mothers experienced symptoms of depression during and after pregancy.
MATERIALS AND METHODS

S-PRESTO Study Design and Definition of Allergic Outcomes

The S-PRESTO study is a prospective cohort study which recruited women aged 18–45 years old who planned to conceive and deliver in Singapore, out of which 373 infants were born. The detailed methodology was described by Loo et al. (26). Trained interviewers gathered information on demographic characteristics, family history of allergy, socioeconomic data, and lifestyle factors. The ISAAC modified questionnaire was used to evaluate offspring eczema, wheeze, and rhinitis symptoms at ages 3, 6, 12, and 18 months. Eczema was determined as maternally reported doctor diagnosis of eczema. Wheeze with use of nebulizer/inhaler was defined by positive responses to the questions: “Has your child ever wheezed?” and “Has your child ever been prescribed with nebulizer/inhaler treatment?”. Rhinitis was defined as a positive response to the question “Has your child had running nose, blocked or congested nose, snoring or noisy breathing during sleep or when awake that has lasted for 2 or more weeks duration?”. Cumulative eczema, wheeze with the use of nebulizer/inhaler or rhinitis by 6, 12, and 18 months were classified as “yes” when a subject answered “yes” by the time point and “no” if the subject answered “no” at all time points. Ethical approval was obtained from the SingHealth Centralised Institutional Review Board (reference 2014/692/D). This study has been registered at ClinicalTrials.gov (NCT 03531658). Written informed consent was provided by the participants.

Allergen Sensitization

Skin prick testing (SPT) was performed at 18 months for the major relevant allergens cow’s milk, whole egg, peanut, soy, wheat, shrimp, crab, and house dust mites Dermatophagoides pteronyssinus (Der p), Dermatophagoides farina (Der f) and Blomia tropicalis (Blo t). The infant was classified as having positive SPT if any of the SPT to the allergens was positive (minimum wheal size of 3 mm) and negative if all of the SPT to the allergens were negative.

Distress Assessment

Maternal perceived distress was assessed using a battery of validated questionnaires assessing symptoms of depression [Edinburgh Postnatal Depression Scale (EPDS) and Beck Depression Inventory-II (BDI-II)], anxiety [State-Trait Anxiety Inventory (STAI) and Pregnancy Anxiety Questionnaire (PAQ)], facets of social support [Multidimensional Scale of Perceived Social Support (MSPSS)], life events [Life Experiences Survey (LES)] and levels of general perceived stress [General Health Questionnaire (GHQ), Pregnancy Experience Scale (PES) and Perceived Stress Scale (PSS)]. Depression refers to prolonged feelings of loss of interest, sadness and hopelessness (27). Anxiety refers to feelings of uneasiness or apprehension due to anticipation of future negative events (28). The MSPSS evaluates perceived support from spouse, family and friends in terms of ability to share joys and sorrows, obtain comfort, share problems and help in decision-making and solving problems (29). The questionnaires were administered at different time points from preconception to postnatal: at each trimester during pregnancy and at two time points during the postnatal period. The maximum distress during preconception, pregnancy and postnatal were computed from each of the questionnaires.

Statistical Analysis

All analyses were performed using SPSS for Windows version 26.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was set at two-sided $p < 0.05$. Descriptive statistics for numerical variables were presented as mean (SD) when normality and
homogeneity assumptions were satisfied, otherwise median (IQR) were presented and n (%) for categorical variables. Predictors for offspring allergic outcomes by ages 6, 12, and 18 months and SPT at month 18 were assessed using modified Poisson regression for prospective studies with binary outcomes (30–33), adjusting for demographic and relevant covariates period of maximum distress (if distress accessed at several time points), ethnicity, maternal age at birth, length of education, parity, smoking during pregnancy, maternal history of allergy, infant sex and gestational age at birth as assessed from literature review (7, 34). Smoking during pregnancy was not adjusted for in the postnatal period. Type 1 error for multiple comparisons were adjusted using Benjamini–Hochberg procedure with false discovery rate at 0.45.

RESULTS

Study Population Characteristics
In this study, 332 mother-child pairs with data on both maternal distress and child respiratory infections and allergic outcomes were included. The mothers’ mean age at delivery was 31.6 years (SD 3.2, Table 1). The majority of mothers were of Chinese ethnicity [254 (76.5%)], had at least 12 years of education [309 (93.1%)], had a history of allergy [235 (70.8%)], were nulliparous [203 (61.3%)] and did not smoke during pregnancy [310 (99.4%)]. Of the 332 infants, 182 (55.0%) were boys. There were 51 (17.1%), 73 (25.7%) and 87 (31.5%) infants who developed eczema by ages 6, 12, and 18 months, respectively. There were 106 (34.5%), 142 (48.0%) and 159 (55.2%) infants who developed rhinitis by ages 6, 12, and 18 months respectively. There were 10 (3.3%), 30 (10.8%) and 33 (12.8%) who wheezed and used nebulizer by ages 6, 12, and 18 months respectively. At age 18 months, 40 (16.5%) had a positive SPT.

Association Between Maternal Distress and Allergic Outcomes in the Offspring

General Distress
Univariate associations are presented in Supplementary Tables 1–4. In multivariate analyses, higher preconception GHQ scores were associated with increased risk of wheeze by 12 and 18 months after adjusting for demographic and relevant covariates (AdjRR 1.2, 95% CI 1.1–1.4 and AdjRR 1.2, 95% CI 1.1–1.3, respectively, Table 2). Higher preconception PSS scores were associated with increased risk of wheeze by 12
TABLE 1 | Characteristics of the study population.

| Table 1 | Continued |
|-----------------|-----------------|
| **Period of maximum PES Hassles/Uplifts frequency ratio (week)** | n | Median (IQR), Mean (SD) or n (%) |
| **Period of maximum PES Hassles/Uplifts frequency ratio** | 293 | 26.0 (8.0–36.0) |
| **Period of maximum PES Hassles/Uplifts intensity ratio (week)** | 293 | 26.0 (8.0–36.0) |
| **PSS** | 292 | 17.3 ± 5.6 |
| **Period of maximum PSS (week)** | 292 | 26.0 (8.0–36.0) |
| **Depression** | 311 | 10.0 (6.0–15.0) |
| **BDI** | 311 | 26.0 (8.0–36.0) |
| **Period of maximum BDI (week)** | 311 | 26.0 (8.0–36.0) |
| **EPDS** | 312 | 8.0 (5.0–11.0) |
| **Period of maximum EPDS (week)** | 312 | 26.0 (8.0–36.0) |
| **Anxiety** | 313 | 39.2 ± 10.9 |
| **STAI state** | 313 | 26.0 (8.0–36.0) |
| **Period of maximum STAI state (week)** | 313 | 26.0 (8.0–36.0) |
| **STAI trait** | 313 | 26.0 (8.0–36.0) |
| **Period of maximum STAI trait (week)** | 313 | 26.0 (8.0–36.0) |
| **PAQ** | 289 | 2.9 ± 0.6 |
| **Period of maximum PAQ (week)** | 289 | 26.0 (8.0–36.0) |
| **Social support** | 290 | 5.0 (4.3–5.0) |
| **MSPSS emotional support from partner** | 290 | 36.0 (26.0–36.0) |
| **Period of maximum MSPSS emotional support from partner (week)** | 290 | 26.0 (8.0–36.0) |
| **MSPSS emotional support from family** | 290 | 5.0 (4.0–5.0) |
| **Period of maximum MSPSS emotional support from family (week)** | 290 | 26.0 (8.0–36.0) |
| **MSPSS emotional support from friend** | 290 | 4.5 (4.0–5.0) |
| **Period of maximum MSPSS emotional support from friend (week)** | 290 | 26.0 (8.0–36.0) |
| **MSPSS practical support from family** | 290 | 4.5 (4.0–5.0) |
| **Period of maximum MSPSS practical support from family (week)** | 290 | 26.0 (8.0–36.0) |
| **MSPSS practical support from friend** | 290 | 4.0 (3.5–5.0) |
| **Period of maximum MSPSS practical support from friend (week)** | 290 | 26.0 (8.0–36.0) |
| **Postnatal** | 290 | 4.5 (4.0–5.0) |
| **General distress** | 290 | 26.0 (8.0–36.0) |
| **PSS at month 6** | 172 | 15.4 ± 5.9 |
| **Depression** | 250 | 9.0 (4.0–14.0) |
| **BDI (included month 6)** | 250 | 3.0 (3.0–6.0) |
| **Period of maximum BDI (month)** | 250 | 7.0 (4.0–12.0) |
| **BDI (excluded month 6)** | 211 | 7.0 (3.0–10.0) |
| **Period of maximum EPDS (month)** | 250 | 6.0 (3.0–6.0) |
| **EPDS (excluded month 6)** | 211 | 5.0 (2.0–9.0) |
| **Anxiety** | 249 | 35.0 (29.5–44.0) |
| **STAI state (included month 6)** | 249 | 3.0 (3.0–6.0) |
| **Period of maximum STAI state(month)** | 249 | 33.0 (25.0–41.0) |
| **STAI state (excluded month 6)** | 211 | 38.0 (31.0–46.0) |

(Continued)
TABLE 1 | Continued

|                                | n  | Median (IQR), Mean (SD) or n (%) |
|--------------------------------|----|----------------------------------|
| **Period of maximum STAI trait (month)** | 249 | 3.0 (3.0–6.0) |
| STAI trait (excluded month 6) | 211 | 36.0 (28.0–43.0) |
| **Social support** |    |                                  |
| MSPSS emotional support from partner at month 6 | 179 | 4.7 (4.0–5.0) |
| MSPSS emotional support from family at month 6 | 179 | 4.0 (3.5–5.0) |
| MSPSS emotional support from friend at month 6 | 178 | 4.0 (3.5–5.0) |
| MSPSS practical support from family at month 6 | 179 | 4.0 (3.5–5.0) |
| MSPSS practical support from friend at month 6 | 179 | 4.0 (3.0–4.5) |
| **Life event** |    |                                  |
| LES positive at month 6 | 173 | 6.0 (3.0–10.0) |
| LES negative at month 6 | 173 | 5.0 (2.0–9.0) |
| Eczema by 6 months Yes | 299 | 51 (17.1%) |
| No | 248 (82.9%) |
| Eczema by 12 months Yes | 284 | 73 (25.7%) |
| No | 211 (74.3%) |
| Eczema by 18 months Yes | 276 | 87 (31.5%) |
| No | 189 (68.5%) |
| Rhinitis by 6 months Yes | 307 | 106 (34.5%) |
| No | 201 (65.5%) |
| Rhinitis by 12 months Yes | 296 | 142 (48.0%) |
| No | 154 (52.0%) |
| Rhinitis by 18 months Yes | 288 | 159 (55.2%) |
| No | 129 (44.8%) |
| Wheeze by 6 months Yes | 299 | 10 (3.3%) |
| No | 289 (96.7%) |
| Wheeze by 12 months Yes | 277 | 30 (10.8%) |
| No | 247 (89.2%) |
| Wheeze by 18 months Yes | 258 | 33 (12.8%) |
| No | 225 (87.2%) |
| Month 18 SPT Positive | 242 | 40 (16.5%) |
| Negative | 202 (83.5%) |

IQR, Interquartile range; SD, standard deviation; BDI-II, Beck Depression Inventory-II; EPDS, Edinburgh Postnatal Depression Scale; GHQ, General Health Questionnaire; LES, Life Experiences Survey; MSPSS, Multidimensional Scale of Perceived Social Support; PAQ, Pregnancy Anxiety Questionnaire; PES, General Health Questionnaire; PSS, Perceived Stress Scale; STAI, State-Trait Anxiety Inventory.

and 18 months (AdjRR 1.1, 95% CI 1.0–1.2 and AdjRR 1.1, 95% CI 1.0–1.2, respectively). There were no associations between GHQ and Perceived Stress Scale scores and PES Hassles/Uplifts frequency and intensity ratios with child eczema, rhinitis and allergic sensitization outcomes (Supplementary Tables 5–7).

**Depression**

Higher preconception BDI scores were associated with increased risk of wheeze by 12 and 18 months (AdjRR 1.07, 95% CI 1.01–1.13 and AdjRR 1.06, 95% CI 1.00–1.12, respectively, Table 2). Further analysis with BDI categories showed that preconception BDI scores ≥ 20 increased the risk of wheeze by 12 months (AdjRR 3.5, 95% CI 1.2–10.9). Preconception and pregnancy BDI scores ≥ 20 were associated with increased risk of wheeze by 18 months (AdjRR 3.2, 95% CI 1.1–9.4, respectively, AdjRR 2.5, 95% CI 1.0–5.9, respectively).

Higher preconception EPDS scores were associated with increased risk of wheeze by 12 and 18 months (AdjRR 1.1, 95% CI 1.0–1.3 and AdjRR 1.1, 95% CI 1.0–1.2, respectively).

There were no associations between BDI and EPDS scores and child eczema, rhinitis and allergic sensitization outcomes (Supplementary Tables 5–7).

**Anxiety**

Higher preconception STAI trait scores were associated with increased risk of wheeze by 12 and 18 months, respectively (AdjRR 1.06, 95% CI 1.00–1.13 and AdjRR 1.07, 95% CI 1.01–1.13, respectively, Table 2). Higher pregnancy STAI state scores were associated with increased risk of wheeze by 12 months (AdjRR 1.04, 95% CI 1.00–1.08).

There were no associations between STAI trait and state scores and Pregnancy Anxiety Questionnaire scores and child eczema, rhinitis and allergic sensitization outcomes (Supplementary Tables 5–7).

**Social Support**

Higher preconception MSPSS emotional support from family scores and practical support from family scores were associated with a lower risk of wheeze by age 18 months (AdjRR 0.58, 95% CI 0.38–0.89) and AdjRR 0.66, 95% CI 0.43–0.99, respectively, Table 2).

There were no associations between MSPSS emotional and physical support scores and child eczema, rhinitis and allergic sensitization outcomes (Supplementary Tables 5–7).

**Life Events**

There were no associations between positive and negative LES scores and child eczema, rhinitis, wheeze with the use of nebuliser and allergic sensitization outcomes (Supplementary Tables 5–7).

**DISCUSSION**

In this study, we examined aspects of maternal distress during preconception, pregnancy and postnatal periods using a battery of validated questionnaires to assess maternal distress and
| TABLE 2 | Multivariate poisson regression of wheeze by 6, 12, and 18 months. |
|---|---|---|---|---|---|---|---|
| | 6 months | 12 months | 18 months |
| | n | RR (95% CI) | p-value<sup>b</sup> | n | RR (95% CI) | p-value<sup>b</sup> | n | RR (95% CI) | p-value<sup>b</sup> |
| **Preconception** | | | | | | | | | |
| **General distress** | | | | | | | | | |
| GHQ | 160 | 1.4 (1.0–2.1) | 0.08 | 146 | 1.2 (1.1–1.4) | <0.001 | 136 | 1.2 (1.1–1.3) | <0.001 |
| PSS | 159 | 1.0 (0.8–1.2) | 0.855 | 145 | 1.1 (1.0–1.2) | 0.038 | 136 | 1.1 (1.0–1.2) | 0.044 |
| PSS ≥ 14 | 159 | 0.44 (0.05–4.00) | 0.469 | 145 | 1.4 (0.4–4.1) | 0.593 | 136 | 1.3 (0.5–3.9) | 0.588 |
| **Depression** | | | | | | | | | |
| BDI | 154 | 1.0 (0.9–1.2) | 0.549 | 138 | 1.07 (1.01–1.13) | 0.026 | 126 | 1.06 (1.00–1.12) | 0.037 |
| BDI | 154 | 1.0 (0.9–1.2) | 0.549 | 138 | 1.07 (1.01–1.13) | 0.026 | 126 | 1.06 (1.00–1.12) | 0.037 |
| 0–13 | 1 | 4.5 (0.3–70.5) | 0.28 | 1 | 0.69 (0.06–7.97) | 0.768 | 1 | 0.87 (0.09–8.15) | 0.905 |
| 14–19 | 7.5 (0.5–101.7) | 0.131 | 3.5 (1.2–10.9) | 0.026 | 3.2 (1.1–9.4) | 0.032 |
| ≥ 20 | 189 | 0.95 (0.76–1.20) | 0.688 | 170 | 1.1 (1.0–1.3) | 0.036 | 158 | 1.1 (1.0–1.2) | 0.04 |
| EPDS | 189 | 1.3 (0.1–22.0) | 0.866 | 170 | 2.3 (0.7–7.3) | 0.173 | 158 | 1.9 (0.6–5.9) | 0.281 |
| **Anxiety** | | | | | | | | | |
| STAI state | 188 | 0.98 (0.88–1.09) | 0.684 | 169 | 1.05 (0.99–1.10) | 0.108 | 157 | 1.04 (0.99–1.10) | 0.083 |
| STAI trait | 188 | 1.0 (0.9–1.2) | 0.788 | 170 | 1.06 (1.00–1.13) | 0.037 | 158 | 1.07 (1.01–1.13) | 0.016 |
| STAI trait ≥ 40 | 189 | 0.63 (0.08–4.89) | 0.657 | 170 | 1.6 (0.6–4.5) | 0.334 | 158 | 1.8 (0.7–4.6) | 0.195 |
| **Social support** | | | | | | | | | |
| MSPSS emotional support from partner | 159 | 0.61 (0.10–3.68) | 0.588 | 145 | 1.0 (0.6–1.9) | 0.883 | 136 | 0.84 (0.53–1.33) | 0.457 |
| MSPSS emotional support from family | 159 | 1.1 (0.2–7.1) | 0.89 | 145 | 0.64 (0.40–1.02) | 0.061 | 136 | 0.58 (0.38–0.89) | 0.012 |
| MSPSS emotional support from friend | 159 | 0.99 (0.13–7.34) | 0.992 | 145 | 1.1 (0.6–1.9) | 0.745 | 136 | 0.86 (0.51–1.45) | 0.575 |
| MSPSS practical support from family | 159 | 1.0 (0.2–4.4) | 0.964 | 145 | 0.67 (0.42–1.06) | 0.085 | 136 | 0.66 (0.43–0.99) | 0.047 |
| MSPSS practical support from friend | 159 | 1.4 (0.2–8.2) | 0.69 | 145 | 1.2 (0.6–2.2) | 0.623 | 136 | 1.0 (0.6–1.7) | 0.973 |
| **Life event** | | | | | | | | | |
| LES positive | 151 | 1.2 (1.0–1.4) | 0.117 | 136 | 1.0 (0.9–1.1) | 0.847 | 127 | 0.99 (0.89–1.09) | 0.795 |
| LES negative | 151 | 1.1 (0.9–1.4) | 0.257 | 136 | 1.1 (1.0–1.2) | 0.101 | 127 | 1.1 (1.0–1.2) | 0.243 |
| **Pregnancy** | | | | | | | | | |
| General distress | | | | | | | | | |
| BDI | 266 | 1.0 (0.9–1.1) | 0.637 | 246 | 1.04 (0.99–1.08) | 0.116 | 231 | 1.03 (0.99–1.08) | 0.156 |
| BDI | 266 | 1.0 (0.9–1.1) | 0.637 | 246 | 1.04 (0.99–1.08) | 0.116 | 231 | 1.03 (0.99–1.08) | 0.156 |
| 0–13 | 1 | 3.1 (0.5–20.6) | 0.246 | 1 | 1.5 (0.5–4.2) | 0.49 | 1 | 1.4 (0.5–3.9) | 0.561 |
| 14–19 | 1.3 (0.1–11.8) | 0.807 | 2.3 (0.9–5.8) | 0.071 | 2.5 (1.0–5.9) | 0.042 |
| ≥ 20 | 266 | 1.0 (0.9–1.2) | 0.649 | 246 | 1.1 (1.0–1.2) | 0.098 | 231 | 1.06 (0.99–1.14) | 0.115 |
| EPDS | 266 | NA | NA | 246 | 1.1 (0.4–2.7) | 0.912 | 231 | 1.1 (0.5–2.7) | 0.786 |
| **Anxiety** | | | | | | | | | |
| STAI state | 267 | 1.02 (0.95–1.09) | 0.568 | 247 | 1.04 (1.00–1.08) | 0.03 | 232 | 1.03 (1.00–1.06) | 0.087 |
| STAI trait | 267 | 1.0 (0.9–1.1) | 0.888 | 247 | 1.03 (0.99–1.07) | 0.211 | 232 | 1.02 (0.98–1.06) | 0.309 |
| STAI trait ≥ 40 | 267 | 2.3 (0.4–12.4) | 0.32 | 247 | 2.3 (1.0–5.2) | 0.056 | 232 | 1.9 (0.9–4.1) | 0.104 |
| PAQ | 248 | 1.2 (0.3–4.5) | 0.827 | 231 | 1.6 (0.8–3.0) | 0.183 | 218 | 1.4 (0.8–2.6) | 0.247 |
| **Social support** | | | | | | | | | |
| MSPSS emotional support from partner | 249 | 0.94 (0.19–4.70) | 0.937 | 232 | 0.93 (0.43–2.01) | 0.854 | 219 | 0.95 (0.43–2.09) | 0.895 |

(Continued)
their associations with eczema, rhinitis, wheeze, and allergic sensitization outcomes in the offspring in early life.

We observed associations of higher maternal distress during preconception and pregnancy with higher risks of wheeze development by ages 12 and 18 months, while social support decreased the risk. Supportive evidence is provided by the GUSTO cohort from Singapore which reported significant associations between maternal depression during pregnancy and child wheeze by age 1 year (35) and a meta-analysis which reported a 56% higher risk of wheeze in offspring whose mothers experienced prenatal psychological distress levels (36), suggesting that control of maternal distress through social support can reduce offspring wheeze risk.

Wheezing illnesses are mainly caused by respiratory viruses, and not by allergy, in young children (37). Supporting evidence of the role of viruses in the etiology of wheeze has been provided by a number of studies. The COAST study in the US identified 90% of wheezing in children up to 3 years of age to be associated with viral etiology (37). A US study of children who visited the emergency department for wheezing reported

### TABLE 2 | Continued

|                          | 6 months | 12 months | 18 months |
|--------------------------|----------|-----------|-----------|
|                          | n        | RR (95% CI) | p-value<sup>b</sup> | n        | RR (95% CI) | p-value<sup>b</sup> | n        | RR (95% CI) | p-value<sup>b</sup> |
| MSPSS emotional support from family | 249 | 1.1 (0.4–2.9) | 0.886 | 232 | 0.96 (0.58–1.59) | 0.878 | 219 | 0.88 (0.55–1.41) | 0.586 |
| MSPSS emotional support from friend | 249 | 0.76 (0.32–1.83) | 0.538 | 232 | 1.1 (0.7–1.9) | 0.61 | 219 | 1.08 (0.67–1.73) | 0.754 |
| MSPSS practical support from family | 249 | 0.65 (0.27–1.53) | 0.323 | 232 | 0.76 (0.47–1.20) | 0.238 | 219 | 0.71 (0.45–1.12) | 0.144 |
| MSPSS practical support from friend | 249 | 0.66 (0.29–1.50) | 0.319 | 232 | 1.1 (0.7–1.8) | 0.698 | 219 | 1.1 (0.7–1.8) | 0.661 |

<sup>a</sup>Month 3 postnatal stress.
<sup>b</sup>Adjusted for period of maximum stress (if stress accessed at several time points), ethnicity, maternal age at birth, length of education, parity, smoking during pregnancy, maternal history of allergy, infant sex and gestational age at birth.

**General distress**

**PSS**

| Age group | n | RR (95% CI) | p-value<sup>a</sup> | n | RR (95% CI) | p-value<sup>a</sup> | n | RR (95% CI) | p-value<sup>a</sup> |
|-----------|---|-------------|----------------|---|-------------|----------------|---|-------------|----------------|
| 0–13      | 154 | 1.04 (0.95–1.15) | 0.359 | 136 | 1.0 (0.9–1.1) | 0.484 |
| 14–26     | 154 | 1.0 (0.9–1.1) | 0.538 | 136 | 1.0 (0.9–1.1) | 0.484 |
| ≥27       | 154 | 1.0 (0.9–1.1) | 0.538 | 136 | 1.0 (0.9–1.1) | 0.484 |

**Depression**

**BDI**

| Age group | n | RR (95% CI) | p-value<sup>a</sup> | n | RR (95% CI) | p-value<sup>a</sup> | n | RR (95% CI) | p-value<sup>a</sup> |
|-----------|---|-------------|----------------|---|-------------|----------------|---|-------------|----------------|
| 0–13      | 219 | 1.02 (0.98–1.07) | 0.302 | 203 | 1.02 (0.98–1.06) | 0.415 |
| 14–26     | 219 | 1.4 (0.5–3.9) | 0.521 | 203 | 1.2 (0.4–3.4) | 0.697 |
| ≥27       | 219 | 1.1 (0.4–3.5) | 0.816 | 203 | 1.0 (0.3–3.1) | 0.957 |

**EPDS**

| Age group | n | RR (95% CI) | p-value<sup>a</sup> | n | RR (95% CI) | p-value<sup>a</sup> | n | RR (95% CI) | p-value<sup>a</sup> |
|-----------|---|-------------|----------------|---|-------------|----------------|---|-------------|----------------|
| 0–13      | 219 | 0.99 (0.91–1.08) | 0.873 | 203 | 0.98 (0.90–1.06) | 0.588 |
| 14–26     | 219 | 1.1 (0.4–3.5) | 0.816 | 203 | 1.0 (0.3–3.1) | 0.957 |
| ≥27       | 219 | 1.1 (0.4–3.5) | 0.816 | 203 | 1.0 (0.3–3.1) | 0.957 |

**Anxiety**

**STAI state**

| Age group | n | RR (95% CI) | p-value<sup>a</sup> | n | RR (95% CI) | p-value<sup>a</sup> | n | RR (95% CI) | p-value<sup>a</sup> |
|-----------|---|-------------|----------------|---|-------------|----------------|---|-------------|----------------|
| 0–13      | 218 | 1.03 (1.00–1.07) | 0.067 | 202 | 1.02 (0.99–1.06) | 0.162 |
| 14–26     | 218 | 1.02 (0.98–1.06) | 0.264 | 202 | 1.02 (0.98–1.06) | 0.244 |
| ≥27       | 218 | 1.2 (0.5–2.7) | 0.687 | 202 | 1.3 (0.6–2.8) | 0.519 |

**Social support**

**MSPSS emotional support from family**

| Age group | n | RR (95% CI) | p-value<sup>a</sup> | n | RR (95% CI) | p-value<sup>a</sup> | n | RR (95% CI) | p-value<sup>a</sup> |
|-----------|---|-------------|----------------|---|-------------|----------------|---|-------------|----------------|
| 0–13      | 163 | 0.87 (0.5–1.52) | 0.622 | 152 | 0.91 (0.52–1.59) | 0.745 |
| 14–26     | 163 | 0.90 (0.55–1.49) | 0.691 | 152 | 0.88 (0.55–1.40) | 0.579 |
| ≥27       | 163 | 1.2 (0.7–2.1) | 0.543 | 152 | 1.1 (0.6–1.8) | 0.844 |

**MSPSS emotional support from friend**

| Age group | n | RR (95% CI) | p-value<sup>a</sup> | n | RR (95% CI) | p-value<sup>a</sup> | n | RR (95% CI) | p-value<sup>a</sup> |
|-----------|---|-------------|----------------|---|-------------|----------------|---|-------------|----------------|
| 0–13      | 163 | 0.73 (0.43–1.25) | 0.255 | 152 | 0.74 (0.45–1.22) | 0.233 |
| 14–26     | 163 | 1.0 (0.6–1.8) | 0.941 | 152 | 1.1 (0.6–1.8) | 0.766 |
| ≥27       | 163 | 1.0 (0.6–1.8) | 0.941 | 152 | 1.1 (0.6–1.8) | 0.766 |

**LES positive**

| Age group | n | RR (95% CI) | p-value<sup>a</sup> | n | RR (95% CI) | p-value<sup>a</sup> | n | RR (95% CI) | p-value<sup>a</sup> |
|-----------|---|-------------|----------------|---|-------------|----------------|---|-------------|----------------|
| 0–13      | 158 | 1.0 (0.9–1.1) | 0.957 | 149 | 1.0 (0.9–1.1) | 0.927 |
| 14–26     | 158 | 1.04 (0.97–1.12) | 0.305 | 149 | 1.02 (0.95–1.10) | 0.564 |

**LES negative**

| Age group | n | RR (95% CI) | p-value<sup>a</sup> | n | RR (95% CI) | p-value<sup>a</sup> | n | RR (95% CI) | p-value<sup>a</sup> |
|-----------|---|-------------|----------------|---|-------------|----------------|---|-------------|----------------|
| 0–13      | 158 | 1.04 (0.97–1.12) | 0.305 | 149 | 1.02 (0.95–1.10) | 0.564 |
that respiratory viruses were detected in 82% of wheezing infants younger than age 2 years (38). We postulate that the associations between maternal distress and wheeze may be due to lower anti-viral responses in the offspring (Figure 1). Hyper-reactivity of the HPA axis to stress is linked to enhanced production of glucocorticoids which inhibit Th1 responses that are essential in anti-viral responses (39, 40). Maternal distress during preconception and pregnancy can also result in persisting and epigenetic changes in genes involved in stress responses (41, 42) which may be passed to the offspring. For example, murine models showed that maternal preconception distress resulted in increased expression of corticotropin releasing factor type 1, a protein key in stress responses, in mature oocytes and offspring brain (43). Higher cord blood Nuclear Receptor Subfamily 3 Group C Member 1 (NR3C1) CpG3 methylation is also linked to higher maternal depression and anxiety during third trimester of pregnancy and increased infant salivary cortisol stress responses at 3 months of age, suggesting increased HPA stress response in infants (44).

Supporting evidence of the link between maternal distress and lower immunity in the offspring is also provided by a number of studies; Rusconi et al. reported that higher maternal GHQ scores i.e. poorer mental health during and after pregnancy increased the risk of wheezing as well as respiratory and gastroenteric infections in the offspring at 1–2 years (45). In another cohort of more than 1.6 million Danish children, maternal stressful events up to 11 months before pregnancy were linked to higher risk of infectious disease hospitalization in the offspring (46).

In this study, we did not observe any associations between maternal distress experienced preconception, or during the pregnancy or postnatal periods and eczema, rhinitis and allergic sensitization in the offspring. Existing studies have yielded conflicting results on the association between maternal distress and these allergic outcomes (47). In support of our findings, the Ulm SPATZ Health Study reported that mothers belonging to the highest quartile in relation to prenatal distress, anxiety and depression did not observe more parental report of child eczema diagnosis by 2 years (48). The GUSTO cohort reported non-significant associations between maternal depression and anxiety during pregnancy as assessed by EPDS and STAI, respectively, with child eczema by age 1 year (35). The LISA Study did not observe significant associations between maternal distress during pregnancy and child eczema in the first 6 years of life (49). Similarly, the ALSPAC study reported no associations between maternal anxiety at 18 and 32 weeks of pregnancy and child allergic sensitization at 7.5 years (34). The Western Australian Pregnancy Cohort also did not observe significant associations between maternal distress during pregnancy and child rhinitis at ages 6 and 14 years (50). Contrary to our observations, the UK Southampton Women’s Survey observed that preconception distress as assessed by the Short Form (36) Health Survey was linked to higher risk of eczema development in the offspring at 12 months (24). The China National Birth Cohort Study also reported an association between maternal distress during pregnancy and infant eczema development at 6 months (51). Another study of 24200 mother-child pairs in Taiwan reported that postpartum depression at 6 months was associated with an increased risk of child eczema at 3 years (52). The Viadana study reported that maternal stressful life events during pregnancy increased the risk of allergic rhinitis in children aged ~8.5 years (8). Possible explanations for these discrepancies include the use of different types of distress assessments methods. For example, the Ulm SPATZ study used Trier Inventory of Chronic Stress, Pregnancy Related Anxiety Questionnaire and Hospital Anxiety and Depression Scale while the UK Southampton Women’s Survey used the Short Form (36) Health Survey. Moreover, although rhinitis can also be viral-induced (53), our study did not differentiate between allergic and infectious rhinitis which might have reduced the strength of associations between maternal distress and rhinitis. Taken together, our observations suggest that maternal distress may result in specific lower anti-viral immune responses to respiratory viruses in the offspring rather than allergic disease development.

The strengths of this study include the comprehensive assessment of maternal distress at multiple time points via a battery of validated questionnaires from preconception to pregnancy and after birth. The specific design of this preconceptional study can offer new insights into the earliest precursors and risk factors of child’s health in an Asian population. A limitation of our study is the modest sample size. However, we have increased the reliability of our results using robust statistical methods. Although we used questionnaires to gather information on allergic disease diagnosis and maternal mental health, these questionnaires had also been used by numerous studies in the field (54–71). This limitation is also mitigated by regular follow-ups to reduce recall bias. We also did not assess physiological responses to maternal distress in both mothers and offspring and this should be evaluated in future research.

In conclusion, maternal distress during critical early life periods was associated with an increased risk of wheeze development in children in the first 18 months of life. This study highlights the importance of supporting maternal mental health, even before pregnancy, to improve offspring’s health.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by SingHealth Centralised Institutional Review Board (reference 2014/692/D). Written informed consent to participate in this study was provided by the participants’ legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

HL and QY analyzed the data and wrote the manuscript. MK provided intellectual input and wrote the manuscript. YHC...
provided statistical advice and intellectual input. ET, AG, OT, JE, KG, PG, YSC, JC, HV, BL, LS and MM contributed to the study design and provided intellectual input. EL conceptualized the study design, contributed to the analysis and wrote the manuscript. All authors critically reviewed the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.749323/full#supplementary-material

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