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Research paper

# The impact of maternal depression, anxiety, and stress on early neurodevelopment in boys and girls

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ABSTRACT

*Objective:* To examine the effects of prenatal maternal depression, anxiety and stress, and postnatal depression on infant early neurodevelopment, and the sex dimorphism.
*Study design:* We used data from 3379 mother-infant pairs from the Shanghai Birth Cohort. Maternal mental health was assessed using the Center for Epidemiological Studies-Depression Scale, Zung Self-Rating Anxiety Scale, Perceived Stress Scale at mid-pregnancy, and the Edinburgh Postnatal Depression Scale at postpartum. Infant neurodevelopment was evaluated using the Ages & Stages Questionnaires and Bayley Scales at ages 6, 12, and 24 months, respectively. Linear mixed models and linear regression models were used.
*Results:* Among 3379 mothers, 11.07 %, 5.42 %, and 34.85 % of women experienced depression, anxiety, and elevated stress, separately. As maternal prenatal mental scores increased per 1SD, infant social-emotional scores decreased −2.82 (−3.86, −1.79) *vs* −2.86 (−3.94, −1.79) for depression, −2.34 (−3.38, −1.31) *vs* −2.72 (−3.81, −1.64) for anxiety, and −2.55 (−3.60, −1.50) *vs* −3.41 (−4.48, −2.35) for stress among boys and girls at age 24 months, respectively. Associations were also observed on social-emotional and communication scores in boys and girls, and fine motor in girls at age 6 and 12 months. These associations were not observed for postpartum depression.
*Limitation:* Generalizability of the results to other population remains to be determined.
*Conclusions:* Prenatal maternal depression, anxiety, and stress were negatively associated with infant early neurodevelopment, which were not observed for postpartum depression. We underscore the importance of maternal prenatal mental health in optimizing infant neuropsychiatric development.

## 1. Introduction

The first 1000 days of life are a critical period for neurodevelopment (Cusick and Georgieff, 2016; Schwarzenberg et al., 2018), and are sensitive to maternal factors and an adverse early environment (Suzuki, 2018). Mental disorders are an important contributor to the overall burden of 04disease in the world (Charlson et al., 2019). Perinatal mental illness was defined as maternal psychiatric disorders that existed before and persisting into pregnancy, or emerged during pregnancy, or in the postpartum period (O'Hara and Wisner, 2014). Depression affected 7.4–12.8 % (Bennett et al., 2004) of pregnant women, while anxiety affected 18.2–24.6 % (Dennis et al., 2017) of pregnant women. Prenatal maternal adversities might increase fetal corticoid levels by interrupting hypothalamic-pituitary-adrenal (HPA) axis, and "program" impaired fetal neural structures and functions (Bronson and Bale, 2016; Gluckman et al., 2010; O'Donnell and Meaney, 2017). Previous studies had reported that maternal perinatal mental illnesses, including single or combined depression (Rogers et al., 2020), anxiety (Rees et al., 2019)

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and perceived stress (Graignic-Philippe et al., 2014), were associated with adverse infant neurodevelopment in language (Rogers et al., 2020), cognitive (Wu et al., 2022), motor (Simcock et al., 2018), adaptive behavior (Rogers et al., 2020) or social-emotional (Porter et al., 2019) competences. However, the associations were less evident when comparing the types of prenatal and postpartum maternal mental problems with different domains of infant neurodevelopment domains (Burger et al., 2020). Most previous studies used self-report evaluation of child development and limited tools to take into account infant sex differences in early child development (Azak, 2012; Simcock et al., 2018) or possible mediation of postpartum depression in associations (Lahti et al., 2017), especially in low and middle income countries (LAMICs) (Burger et al., 2020).

Using data from the Shanghai Birth Cohort (SBC), a large ongoing birth cohort, our objective was to investigate the association between maternal emotional problems, including prenatal depression, anxiety and perceived stress, and postpartum depression with the neurodevelopment of boys and girls between ages 6 to 24 months assessed using ASQ-3, ASQ: SE and BSID-III. Since maternal anxiety during pregnancy can predict postpartum depression (Heron, 2004), we also examined the potential mediation role of maternal postpartum depression in associations.

## 2. Methods

### 2.1. Study design and participants

The SBC explores the impacts of genetic, social economic status, psychopathological effects, as well as environmental chemicals on pregnancy outcomes, child growth and the development, and risks of diseases on the health of women and offspring. Detailed information on the SBC was published elsewhere (Zhang et al., 2019). In summary, 4127 couples in Shanghai were recruited from six urban obstetric care centers from 2013 to 2016 and there were 3692 singleton live births recorded. For this study, we excluded infant deaths ($n = 5$) and infants with birth defects ($n = 24$), or those with missing values on child social-emotional assessments and maternal mental health status assessments ($n = 284$), resulting in 3379 participates in the final analyses (Fig. 1). The study sample for maternal mental health status was 3099 for depression assessment, 3118 for anxiety assessment, 3142 for perceived stress assessment, and 3006 for postpartum depression. Mother-baby dyads were included in follow ups at infant age 6 months ($n = 2208$), 12 months ($n = 2104$) and 24 months ($n = 2373$).

The study protocol was approved by the Institutional Research Ethics Committee of Xinhua Hospital affiliated to the Shanghai Jiao Tong University, School of Medicine. Informed consent was obtained from all study participants.

### 2.2. Assessments of maternal mental health

Maternal mental health in the 2nd trimester of pregnancy was assessed using the Center for Epidemiological Studies-Depression Scale (CES-D), which was further categorized into three classes: "<16" (*i.e.*, was "no depression symptoms"), "16~19" (that is, "depressive tendency"), and "≥20" (*i.e.*, "in depression status"). We also used the Zung self-rating Anxiety Scale (SAS) (Zung, 1971), and the Perceived Stress Scale (PSS) (Cohen et al., 1983). In this document, women were considered "without anxiety symptoms" with a SAS score < 50, "in mild

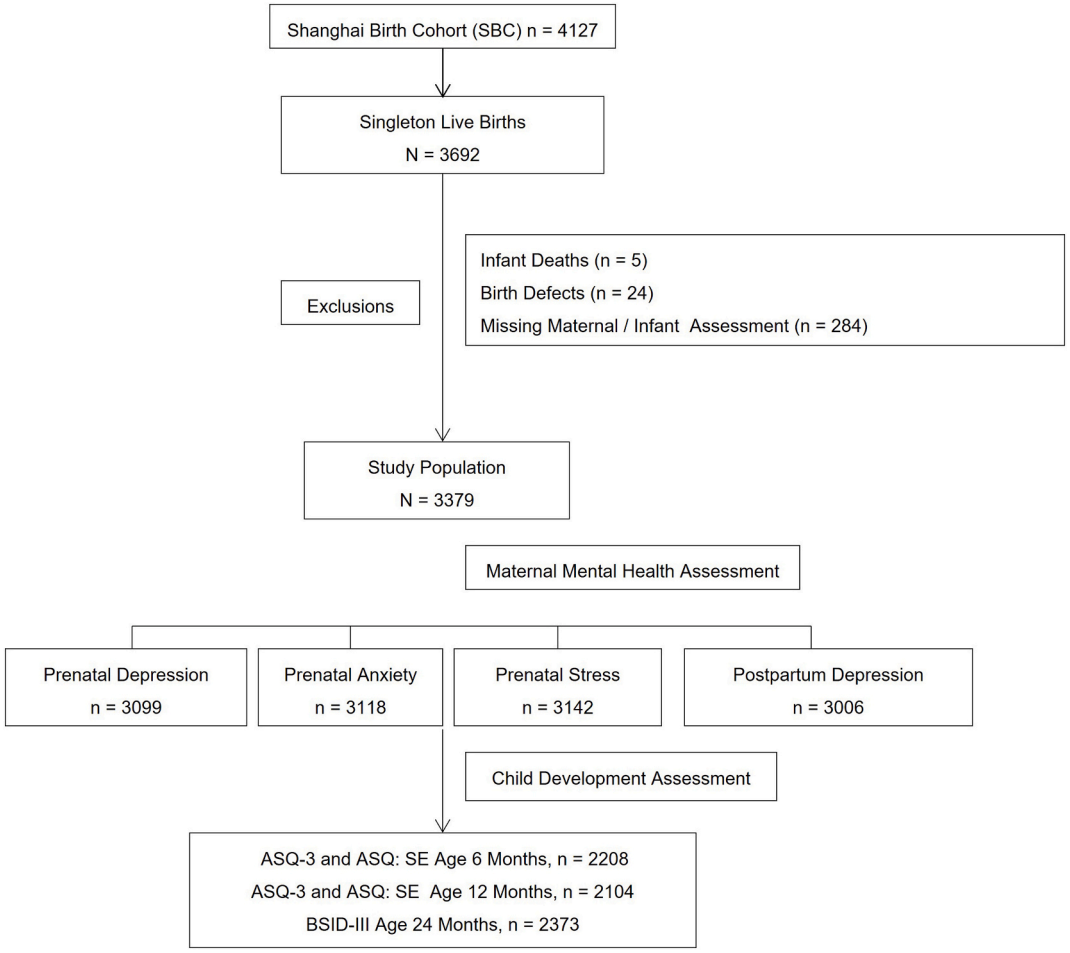


**Fig. 1.** Study flowchart in the selection of study participants.

anxiety status" with a SAS score 50–59, "in moderate anxiety status" with a SAS score 60–69 and "in serious anxiety" with a SAS score ≥ 70. Total PSS scores of 15 or higher were considered elevated maternal stress (Gholipoor et al., 2017; Wu et al., 2022). Furthermore, the Edinburgh Postnatal Depression Scale (EPDS) system was used to assess postpartum depression at 42 days after delivery, with a score ≥ 10 defined as postpartum depression (Cox et al., 1987). The Chinese versions of these three standardized scoring systems had been calibrated with good validity (Lau et al., 2010; Sun et al., 2017; Wang et al., 2011; Wang, 1984).

### 2.3. Assessment of neurodevelopment in children

As for neurodevelopmental assessment tool, we used the Ages & Stages Questionnaires-Third Edition (ASQ-3) and ASQ: SE (Social-Emotional) at the ages of 6 and 12 months. The ASQ-3 and ASQ: SE were mother self-report measures frequently used in various international studies on early child development (Squires and Twombly, 2009), which were less comprehensive than the Bayley. At the age of 2 years, we used the Bayley Scales of Infant & Toddler Development-Third Edition (BSID-III), a preferred tool which provides solid assessment of child cognitive and motor ability to children at age 2 years (Bayley, 2009).ASQ-3 contains five domains including Communication, Gross Motor, Fine Motor, Person-Social, and Problem Solving. The BSID-III contains five scales of Cognition, Language, Motor, Social-Emotional, and Adaptive Behavior. The composite scores were further dichotomized according to their corresponding cuts. Scores beyond the cut-off points were defined as "at risk of social-emotional development delay" in ASQ: SE, the explanation of evaluation criteria was reversed in ASQ-3 domains and BSID-III scales. The BSID-III scale is an instrument that can provide a solid assessment of child cognitive, language, and motor ability at 24 months of age.

### 2.4. Potential confounders

A set of confounders were adjusted as previous studies did (Cooper et al., 1993; Lahti et al., 2017; Mina et al., 2017; Napierala et al., 2016; Quinn et al., 2017), including maternal age, education (below bachelor, bachelor to master, beyond master), mode of delivery (C-section or vaginal), preterm birth (gestational age < 37 weeks), infant passive smoking (defined as living with smokers or not) and feeding pattern in the first 6 months (exclusive breastfeeding, mixed feeding, exclusive formula feeding). Infant birth weight for gestational age (GA) was classified as lower than 10th percentile (small for GA, SGA), 10th~90th percentile (appropriate for GA, AGA) and over 90th percentile (large for GA, LGA) (Zhu et al., 2015). The pre-pregnancy body mass index (BMI) was calculated as the pre-pregnancy weight divided by the square of height ($kg/m^2$).

### 2.5. Statistical analysis

Continuous variables were described by mean and standard deviation (SD), whereas categorical variables were presented as frequencies. The restricted cubic splines (RCS) were used to plot the associations between maternal prenatal mental measures (depression, anxiety, and stress) and child neurodevelopment with adjustment for covariates at the ages of 6, 12 and 24 months, respectively by using the R rms package (Supplemental Figs. S1, S2 and S3).

We used linear mixed models with random intercepts to examine the effects of maternal prenatal mental measures (depression, anxiety, and stress) on infant ASQ and ASQ: SE measures at age 6 and 12 months simultaneously, with adjustment for child age, maternal age, education, mode of delivery, delivery mode, preterm birth, infant passive smoking, and feeding pattern in the first 6 months and infant ages at the time of ASQ measurement. For neurodevelopment assessed by BSID-III at age 24 months, linear regression models were used to evaluate these associations with maternal mental health measures. Original child neurodevelopment scores were used as dependent variables in all the models. The regression coefficients reflected the changes in the neurodevelopment scores, on the original scale per 1 SD changes in the predictors (*i.e.*, maternal depression, anxiety, and stress scores) or by its categories. Missing data of covariates were treated by multiple imputation using the chained equation approach (MICE), under assumed mechanism of missing at random (MAR), and the impacts of missing values of selected confounders on our results were assessed. Missing percentage for covariates ranged from 0.24 % to 28.32 % Specifically, SAS PROC MI and MIANALYZE procedures were applied for linear models, and 25 imputed data sets were generated; The final results were pooled across imputed datasets using Rubin's rule (Rubin, 2004) to examine the adjusted mean differences in infant development scores according to maternal mid-pregnancy psychometric measurement scores (depression, anxiety, and perceived stress), and postpartum depression scores, separately. The models were also adjusted with postpartum depression scores to determine potential mediation or interactive effects on associations between maternal mid pregnancy mental problems and infant outcomes. Considering multiple tests, two-sided $p$ value <0.01 was set statistically significant.

Analyzes were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC, USA) and R 4.0.3 (R Development Core Team).

## 3. Results

### 3.1. Study population

The mean age of the women was 28.64 years and most of them had a bachelor or higher degree (77.60 %). According to the Chinese BMI category standards (Chen, 2004), 66.49 % of the women had normal weight. The cesarean section delivery rate was 47.24 %. The infants had an even gender distribution, most of whom were born full-term (95.36 %). The SGA and LGA infants accounted for 4.62 % and 11.22 %, respectively. Mixed feeding was the dominant feeding pattern (71.03 %) at age 6 months. Differences between groups were found to be not significant for the basic characteristics of the participants (Table 1). The neurodevelopment scores in boys and girls were shown in Table 2. Compared to the boys, the girls had better scores in communication, problem solving and person social at the age of 12 months, and higher scores in all five domains (cognition, language, motor, adaptive behavior and social- emotional) at the age of 24 months.

The prevalence of maternal depression symptoms was 11.07 % ($n$ = 343), while 10.49 % ($n$ = 325) of women experienced possible depressive symptoms (depressive tendency). Postpartum depression affected 11.48 % ($n$ = 345) of women. One hundred and fifty-one women (4.84 %) had mild anxiety, 18 women (0.58 %) had moderate anxiety and no severe anxiety at mid-pregnancy. The PSS assessment indicated that 34.85 % ($n$ = 1095) of the women had elevated perceived stress at mid-pregnancy. The mean and standard deviation (SD) of maternal mental health scores were as follows: prenatal depression (CES—D) score 10.29 (6.98), anxiety (SAS) 37.65 (6.67), perceived stress (PSS) 12.29 (5.13), and postnatal depression (EPDS) 4.12 (4.25), respectively. Correlations (Table S1) were found in prenatal depression and anxiety ($r$ = 0.67, $p$ < 0.001), prenatal depression and perceived stress ($r$ = 0.64, $p$ < 0.001), and prenatal anxiety and perceived stress ($r$ = 0.54, $p$ < 0.001).

### 3.2. Prenatal maternal depression and infant neurodevelopment

Results shown that both boys and girls at ages 6, 12 and 24 months had weakened social-emotional performance (Tables 3–4). The mean social-emotional scores were 7.44(95 % CI -10.80, −4.09) and 6.38 (95 % CI -9.83, −2.93) lower for boys and girls of depressed mothers at age 24 months as compared to that of the infants of non-depressed mothers, respectively ($p$ < 0.001). The infants also had lower communication scores in boys and girls, and fine motor scores in girls, problem solving

**Table 1**
Characteristics of study mothers and their children by prenatal maternal depression status.

| Characteristics | | Prenatal depression status | | | p | Characteristics | | Prenatal depression status | | | p |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | No | Possible | Depressed | | | | No | Possible | Depressed | |
| Mean ± SD or n (%) | | | | | | | | | | | |
| Age, years | | 28.63 ± 3.60 | 28.38 ± 3.58 | 28.84 ± 3.91 | 0.258 | GA: | SGA | 108 (4.62) | 16 (5.11) | 11 (3.38) | |
| ≥35 | | 157 (6.48) | 21 (6.48) | 34 (9.91) | | | AGA | 1949 (83.43) | 269 (85.94) | 279 (85.85) | |
| <35 | | 2267 (93.52) | 303 (93.52) | 309 (90.09) | 0.035 | | LGA | 279 (11.94) | 28 (8.95) | 35 (10.77) | 0.621 |
| BMI, kg/m$^2$ | | 22.44 ± 3.25 | 22.04 ± 3.15 | 22.53 ± 3.90 | 0.109 | Preterm birth | No | 2248 (95.58) | 296 (93.97) | 312 (95.12) | |
| GDM | Yes | 258 (11.01) | 28 (9.06) | 36 (10.88) | | | Yes | 104 (4.42) | 19 (6.03) | 16 (4.88) | 0.436 |
| | No | 2085 (89.0) | 281 (90.94) | 295 (89.12) | 0.669 | Infant passive smoking | | | | | |
| Gestational hypertension/ (pre) eclampsia | | | | | | Age 0–6 months | | | | | |
| Yes | | 94 (4.01) | 10 (3.24) | 12 (3.63) | | None | | 1140 (59.97) | 149 (59.60) | 162 (59.556) | |
| No | | 2250 (95.99) | 299 (96.76) | 319 (96.37) | 0.593 | Occasionally | | 739 (38.87) | 98 (39.20) | 98 (36.03) | |
| Mode of delivery | | | | | | Frequently | | 22 (1.16) | 3 (1.20) | 12 (4.41) | 0.312 |
| C-section | | 1104 (46.72) | 155 (49.36) | 155 (46.41) | | Age 0–12 months | | | | | |
| Vaginal | | 1259 (53.28) | 159 (50.64) | 179 (53.59) | 0.833 | None | | 878 (49.97) | 106 (46.70) | 127 (49.80) | |
| Parity | ≥1 | 351 (14.52) | 52 (16.20) | 59 (17.30) | | Occasionally | | 828 (47.13) | 117 (51.54) | 112 (43.92) | |
| | 0 | 2066 (85.48) | 269 (83.80) | 282 (82.70) | 0.139 | Frequently | | 51 (2.90) | 4 (1.76) | 16 (6.27) | 0.301 |
| Education | | | | | | Age 0–24 months | | | | | |
| Beyond master | | 192 (7.92) | 33 (10.19) | 38 (11.08) | | None | | 649 (37.02) | 73 (32.59) | 91 (35.97) | |
| Bachelor to master | | 1901 (78.39) | 244 (75.31) | 263 (76.68) | | Occasionally | | 1004 (57.27) | 141 (62.95) | 140 (55.34) | |
| Lower than bachelor | | 332 (13.69) | 47 (14.51) | 42 (12.24) | 0.087 | Frequently | | 100 (5.70) | 10 (4.46) | 22 (8.70) | 0.227 |
| Infant sex | Girl | 1163 (48.52) | 158 (49.07) | 167 (49.70) | | Feeding in first 6 months | | | | | |
| | Boy | 1234 (51.48) | 164 (50.93) | 169 (50.30) | 0.668 | Exclusive breast feeding | | 457 (25.04) | 70 (28.81) | 64 (25.40) | |
| Gestational age, week | | 38.97 ± 1.51 | 38.93 ± 1.37 | 38.95 ± 1.51 | 0.886 | Exclusive formula feeding | | 72 (3.95) | 5 (2.06) | 12 (4.76) | |
| Birth weight, g | | 3391.33 ± 448.75 | 3342.81 ± 432.28 | 3387.99 ± 451.57 | 0.197 | Mixed feeding | | 1296 (71.01) | 168 (69.14) | 176 (69.84) | 0.850 |

Note: GDM, gestational diabetes mellitus; GA, Birth weight for gestational age; SGA, small for gestational age; AGA, appropriate for gestational age; LGA, large for gestational age.

**Table 2**
Distribution of Infant Neurodevelopment scores in boys and girls.

| Domains | n | Boys ($n$ = 1715) | n | Girls ($n$ = 1618) | p |
|---|---|---|---|---|---|
| 6 months | 1126 | Mean ± SD | 1047 | Mean ± SD | |
| Communication | | 52.0 ± 7 0.9 | | 52.4 ± 7.3 | 0.208 |
| Gross motor | | 42.4 ± 12.1 | | 41.8 ± 11.9 | 0.194 |
| Fine motor | | 49.9 ± 11.0 | | 50.1 ± 11.4 | 0.666 |
| Problem solving | | 50.1 ± 11.2 | | 49.5 ± 11.7 | 0.210 |
| Person-social | | 43.9 ± 13.2 | | 44.6 ± 12.7 | 0.213 |
| Social-emotional | | 16.7 ± 13.9 | | 16.3 ± 13.7 | 0.504 |
| 12 months | 1079 | | 1004 | | |
| Communication | | 53.6 ± 8.3 | | 55.7 ± 7.0 | <0.001 |
| Gross motor | | 45.9 ± 14.1 | | 46.3 ± 14.3 | 0.478 |
| Fine motor | | 52.5 ± 9.1 | | 53.3 ± 7.8 | 0.029 |
| Problem solving | | 49.8 ± 10.3 | | 51.5 ± 9.1 | <0.001 |
| Person-social | | 47.7 ± 11.6 | | 50.3 ± 10.5 | <0.001 |
| Social-emotional | | 21.4 ± 15.8 | | 19.8 ± 15.8 | 0.025 |
| 24 months | 1231 | | 1142 | | |
| Cognition | | 114.2 ± 22.8 | | 117.6 ± 22.4 | <0.001 |
| Language | | 94.6 ± 15.8 | | 99.3 ± 15.8 | <0.001 |
| Motor | | 106.3 ± 14.9 | | 109.4 ± 15.6 | <0.001 |
| Adaptation behavior | | 102.0 ± 19.1 | | 107.5 ± 18.4 | <0.001 |
| Social-emotional | | 103.8 ± 17.8 | | 105.7 ± 18.0 | 0.009 |

scores in girls at ages 6 and 12 months. Cognition scores decreased in boys 2.18 (95 % CI -3.46, −0.91) at 24 months as maternal depression scores increased per 1SD, without significant effects on girls (Table 4, Fig. S3). We tested the interaction effects between maternal prenatal mental measures and child age on ASQ measures and ASQ: SE at the age of 6 and 12 months, and none of them were statistically significant. So, the overall associations were assessed between maternal mental measures and infant ASQ measures and ASQ: SE at the age of 6 and 12 months simultaneously. The non-linear relationships were not statistically significant in associations between maternal mental measures (depression, anxiety, and stress) and child neurodevelopment at the age of 6 (Fig. S1), 12 (Fig. S2), and 24 months (Fig. S3).

### 3.3. Prenatal maternal anxiety and infant neurodevelopment

Consistently, prenatal maternal anxiety was associated with weakened social-emotional performance in both boys and girls at the age of 6, 12 and 24 months. Specifically, boys and girls at 24 months had 2.34 (95 % CI -3.38, −1.31) and 2.72 (95 % CI -3.81, −1.64) lower scores for social-emotional development ($p < 0.001$) respectively, as maternal anxiety scores increased per 1SD (Table 4, Fig. S3). Communication and gross motor scores in boys decreased 0.54 (95 % CI – 0.92, −0.17) and 0.99 (95 % CI -1.63, −0.36) with maternal anxiety scores increased per 1SD, separately, and girls had decreased fine motor scores at ages 6 and 12 months, ($p < 0.01$, (Table 3, Fig. S2). At 24 months of infant age, language (−1.30, 95 % CI -2.23, −0.38; $p = 0.006$) and adaptive behavior (−1.96, 95 % CI -3.10, −0.83; $p < 0.001$) scores only changed in girls with increased maternal anxiety scores per 1SD.

### 3.4. Prenatal maternal perceived stress and infant neurodevelopment

Similarly, prenatal maternal stress was associated with weakened social-emotional performance in both boys and girls at age 6, 12 and 24 months, which were consistent with the results of prenatal maternal depression and anxiety. With elevated maternal stress scores for 1SD, social-emotional scores changed −2.55 (95 % CI -3.60, −1.50) and −3.41 (95 % CI -4.48, −2.35) at 24 months in boys and girls, respectively ($p < 0.001$, Table 4, Fig. S3). Girls had decreased fine motor scores

at ages 6 and 12 months (Table 3, Fig. S1). Communication scores decreased with elevated maternal stress scores per 1SD (Table 3, Fig. S2) in boys and girls at ages 6 and 12 months.

### 3.5. Postpartum maternal depression and infant neurodevelopment

Maternal postpartum depression was associated with adverse effects only on the person-social and gross motor development at ages 6 and 12 months (Table 5). Person-social in boys changed −0.25 (95 % CI -0.39, −0.11; $p < 0.001$), and gross motor scores in boys and girls changed −0.33 (95%CI -0.48, −0.18; $p < 0.001$) and − 0.21 (95 % CI -0.36, −0.07; $p < 0.01$) at ages 6 and 12 months per 1SD increase in EPDS scores, separately. No effects were found on majority of the other aspects of infant development domains at age 6, 12 and 24 months.

### 3.6. Mediation effect of maternal postpartum depression

We examined the potential mediation of maternal postpartum depression on the associations between mid-pregnancy mental health problems and infant neurodevelopment domains (Tables S2∼S3). With postpartum depression additionally included in the models, the effect estimation remains similar for maternal prenatal depression, anxiety, and stress on the gross motor domain in boys at ages 6 and 12 months, while the effects between maternal prenatal depression and child person social developments at ages 6 and 12 months disappeared. The results indicated that most associations between maternal prenatal mental health and child neurodevelopment aspects (for example, social-emotional domain) were not mediated (or explained) by 42-days postpartum depression, except for associations between prenatal maternal depression and child person social development at ages 6 and 12 months.

## 4. Discussion

To our knowledge, this was the first study using comprehensive and multidimensional assessments both for maternal mental health and infant neurodevelopment out comes in a large-scale prospective cohort to explore impacts of perinatal maternal mental problems on infant neurodevelopment outcomes in LAMICs.

We found that maternal prenatal depression, anxiety, and stress were

**Table 3**
Associations of maternal mental health at mid-pregnancy with child neurodevelopment at 6 and 12 months in 1002 boys and 945 girls.

| Maternal mental status | | n | Child neurodevelopment measures $\beta$ (95 % CI) with linear mixed models | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Communication | Gross motor | Fine motor | Problem solving | Person-social | ASQ: SE |
| | | | | | | | | Social-emotional |
| Boys | | | | | | | | |
| Depression | No (<16) | 785 | *ref* | *ref* | *ref* | *ref* | *ref* | *ref* |
| | Possible (16 ~ 19) | 99 | −0.82 [−2.09, 0.45] | −0.29 [−2.37, 1.80] | 0.90 [−0.63, 2.44] | 0.62 [−1.05, 2.28] | −1.32 [−3.24, 0.60] | 2.89 [0.53, 5.25]* |
| | Depressed (>19) | 103 | −1.28 [−2.51, −0.04]* | −2.58 [−4.60, −0.56]* | −0.22 [−1.71, 1.28] | 0.25 [−1.36, 1.87] | −1.46 [−3.33, 0.40] | **4.61 [2.30, 6.93]** *** |
| | Per 1SD | 987 | **−0.65 [−1.03, −0.26]** ** | **−1.04 [−1.68, −0.41]** ** | −0.10 [−0.57, 0.37] | −0.18 [−0.69, 0.33] | **−0.80 [−1.38, −0.21]** ** | **1.86 [1.14, 2.58]** *** |
| Anxiety | No (<50) | 942 | *ref* | *ref* | *ref* | *ref* | *ref* | *ref* |
| | Mild or moderate (50–69) | 52 | −0.51 [−2.18, 1.16] | −2.73 [−5.49, 0.04] | −0.15 [−2.17, 1.88] | −0.75 [−2.96, 1.47] | −0.64 [−3.19, 1.92] | **6.02 [2.81, 9.23]** *** |
| | Per 1SD | 994 | **−0.54 [−0.92, −0.17]** ** | **−0.99 [−1.63, −0.36]** ** | −0.02 [−0.49, 0.45] | −0.37 [−0.88, 0.13] | −0.20 [−0.78, 0.38] | **2.19 [1.48, 2.90]** *** |
| Stress | No (<15) | 640 | *ref* | *ref* | *ref* | *ref* | *ref* | *ref* |
| | Yes (≥15) | 362 | **−1.30 [−2.09, −0.52]** ** | −1.20 [−2.52, 0.12] | −0.24 [−1.20, 0.71] | −0.48 [−1.53, 0.56] | −1.28 [−2.48, −0.08]* | **3.76 [2.28, 5.25]** *** |
| | Per 1SD | 1002 | −0.40 [−0.78, −0.03]* | −0.35 [−0.98, 0.28] | −0.20 [−0.66, 0.26] | −0.07 [−0.57, 0.42] | −0.48 [−1.05, 0.09] | **1.84 [1.14, 2.54]** *** |
| Girls | | | | | | | | |
| Depression | No (<16) | 731 | *ref* | *ref* | *ref* | *ref* | *ref* | *ref* |
| | Possible (16 ~ 19) | 92 | −0.43 [−1.55, 0.68] | 0.05 [−2.09, 2.20] | 0.44 [−1.09, 1.97] | −0.06 [−1.72, 1.59] | −0.05 [−1.88, 1.77] | 1.59 [−0.83, 4.02] |
| | Depressed (>19) | 111 | **−1.94 [−2.99, −0.90]** *** | −1.02 [−3.05, 1.01] | **−2.53 [−3.97, −1.09]** *** | **−2.05 [−3.61, −0.50]** ** | −1.56 [−3.27, 0.15] | **4.05 [1.77, 6.33]** *** |
| | Per 1SD | 934 | **−0.53 [−0.86, −0.20]** ** | −0.35 [−0.98, 0.28] | −0.48 [−0.91, −0.05]* | −0.55 [−1.05, −0.04]* | −0.28 [−0.82, 0.27] | **2.00 [1.28, 2.72]** *** |
| Anxiety | No (<50) | 891 | *ref* | *ref* | *ref* | *ref* | *ref* | *ref* |
| | Mild or moderate (50–69) | 48 | 0.11 [−1.39, 1.61] | 0.79 [−2.05, 3.62] | −0.26 [−2.19, 1.67] | −0.89 [−3.16, 1.37] | −0.48 [−2.95, 1.98] | 3.70 [0.50, 6.90]* |
| | Per 1SD | 939 | −0.31 [−0.65, 0.03] | −0.30 [−0.93, 0.32] | **−0.69 [−1.15, −0.23]** ** | −0.50 [−0.99, −0.001]* | −0.40 [−0.96, 0.16] | **1.88 [1.15, 2.60]** *** |
| Stress | No (<15) | 632 | *ref* | *ref* | *ref* | *ref* | *ref* | *ref* |
| | Yes (≥15) | 313 | −0.86 [−1.57, −0.14]* | −0.82 [−2.19, 0.55] | −1.03 [−1.95, −0.11]* | −0.96 [−2.05, 0.13] | −0.88 [−2.07, 0.31] | **3.49 [1.93, 5.05]** *** |
| | Per 1SD | 945 | **−0.70 [−1.04, −0.37]** *** | −0.66 [−1.9, −0.03]* | **−0.72 [−1.15, −0.28]** ** | **−0.78 [−1.28, −0.29]** ** | −0.66 [−1.21, −0.11]* | **2.19 [1.46, 2.92]** *** |

Note: Data in bold: significant; CI, Confidence Interval; Infant neurodevelopment was assessed with Ages & Stages Questionnaires-Third Edition and Social-Emotional, Maternal depression was assessed with Center for Epidemiologic Studies-Depression Scale, maternal anxiety was assessed with Zung's Self-rating Anxiety Scale, maternal stress was assessed with Perceived Stress Scale. All models were adjusted for child age at assessment, maternal age, education, mode of delivery, preterm birth, infant passive smoking, and feeding pattern in the first 6 months.

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.

**Table 4**
Associations of maternal depression, anxiety, and stress at mid-pregnancy with child neurodevelopment in 1137 boys and 1060 girls at age 24 months.

| Maternal mental status | | n | Child neurodevelopment measures $\beta$ (95 % CI) with linear models | | | | |
|---|---|---|---|---|---|---|---|
| | | | Cognition | Language | Motor | Adaptive behavior | Social-emotional |
| Boys | | | | | | | |
| Depression | No (<16) | 892 | *ref* | *ref* | *ref* | *ref* | *ref* |
| | Possible (16 ~ 19) | 111 | 0.19 [−4.06, 4.44] | −1.03 [−4.07, 2.02] | −1.15 [−4.12, 1.82] | −2.38 [−6.41, 1.34] | −3.27 [−6.72, 0.18] |
| | Depressed (>19) | 118 | −4.63 [−8.76, −0.50]* | −1.84 [−4.80, 1.12] | −2.22 [−5.11, 0.67] | −1.08[−4.73, 2.57] | **−7.44 [−10.80, −4.09]*** |
| | Per 1SD | 1121 | **−2.18 [−3.46, −0.91]*** | −1.12 [−2.03, −0.21]* | −1.15 [−2.04, −0.26]* | −1.23 [−2.35, −0.11]* | **−2.82 [−3.86, −1.79]*** |
| Anxiety | No (<50) | 1074 | *ref* | *ref* | *ref* | *ref* | *ref* |
| | Mild or moderate (50–69) | 60 | −6.21 [−11.84, −0.58]* | −1.62 [−5.64, 2.39] | −0.18 [−4.09, 3.73] | −2.25 [−7.18, 2.69] | **−7.75 [−12.33, −3.17]*** |
| | Per 1SD | 1134 | −1.10 [−2.38, 0.17] | −0.75 [−1.66, 0.16] | −0.80 [−1.68, 0.09] | −1.25 [−2.38, −0.13] | **−2.34 [−3.38, −1.31]*** |
| Stress | No (<15) | 742 | Ref | Ref | Ref | Ref | Ref |
| | Yes (≥15) | 395 | −2.28 [−4.96, 0.39] | −0.88 [−2.80, 1.03] | −0.34 [−2.21, 1.52] | −1.31 [−3.68, 1.07] | **−4.31 [−6.50, −2.12]*** |
| | Per 1SD | 1137 | −0.90 [−2.19, 0.39] | −0.65 [−1.57, 0.27] | −0.41 [−1.31, 0.49] | −0.44 [−1.58, 0.70] | **−2.55 [−3.60, −1.50]*** |
| Girls | | | | | | | |
| Depression | No (<16) | 823 | *ref* | *ref* | *ref* | *ref* | *ref* |
| | Possible (16 ~ 19) | 111 | −2.56 [−6.58, 1.47] | −2.45 [−5.43, 0.52] | −1.09 [−4.07, 1.89] | −2.87 [−6.52, 0.77] | −5.16 [−8.67, −1.65]** |
| | Depressed (>19) | 116 | 1.32 [−2.65, 5.29] | −0.98 [−3.91, 1.95] | −1.82 [−4.76, 1.12] | −2.04 [−5.63, 1.54] | **−6.38 [−9.83, −2.93]*** |
| | Per 1SD | 1050 | 0.19 [−1.05, 1.43] | −0.48 [−1.39, 0.44] | −0.37 [−1.29, 0.55] | −1.45 [−2.57, −0.33]* | **−2.86 [−3.94, −1.79]*** |
| Anxiety | No (<50) | 998 | Ref | Ref | Ref | Ref | Ref |
| | Mild or moderate (50–69) | 53 | 0.68 [−4.98, 6.33] | −2.45 [−6.61, 1.71] | 0.54 [−3.63, 4.70] | −0.17 [−5.27, 4.92] | −1.40 [−6.32, 3.52] |
| | Per 1SD | 1051 | −0.64 [−1.90, 0.62] | **−1.30 [−2.23, −0.38]**** | −0.58 [−1.50, 0.35] | **−1.96 [−3.10, −0.83]**** | **−2.72 [−3.81, −1.64]*** |
| Stress | No (<15) | 705 | *ref* | *ref* | *ref* | *ref* | *ref* |
| | Yes (≥15) | 355 | −0.57 [−3.19, 2.05] | −0.54 [−2.47, 1.39] | −1.19 [−3.12, 0.75] | −1.90 [−4.26, 0.46] | **−4.74 [−7.00, −2.48]*** |
| | Per 1SD | 1060 | −0.26 [−1.50, 0.98] | −0.50 [−1.41, 0.42] | −0.75 [−1.67, 0.16] | −1.34 [−2.46, −0.22]* | **−3.41 [−4.48, −2.35]*** |

Note: Data in bold: significant; CI: Confidence Interval; *ref*: Reference; SD: Standard Deviation; Infant neurodevelopment was assessed with Bayley Scales of Infant & Toddler Development-Third Edition. Maternal depression was assessed with Center for Epidemiologic Studies-Depression Scale, maternal anxiety was assessed with Zung's Self-rating Anxiety Scale, maternal stress was assessed with Perceived Stress Scale. All models were adjusted for maternal age, education, mode of delivery, preterm birth, infant passive smoking, and feeding pattern in the first 6 months.

* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

associated with less optimal early child development outcomes. Such associations remained persistent with the social-emotional development in both girls and boys throughout the first two years. The development of infant communication at age 12 months were adversely affected by prenatal maternal depression, anxiety, and stress, with effects of depression not specified by sex. The gross motor development at 12 months and cognition development at 24 months in boys were vulnerable to maternal prenatal anxiety and depression, separately. The fine motor development in girls was affected by maternal prenatal depression, anxiety, and stress at 6 months. These associations were not observed for postpartum depression, and remained significant after further adjusted for postpartum depression.

The deleterious effects of maternal emotional problems on infant neurodevelopment have been reported (Hentges et al., 2020; Li et al., 2018; Madigan et al., 2018; Polte et al., 2019; Porter et al., 2019). Even after adjusting for maternal postpartum depression, the association between maternal depressive symptoms at 20 weeks of gestational age and offspring developmental problems remained significant in another study (El Marroun et al., 2014). Our results were in line with current evidence with a comparable effect size as summarized in a recent review (Rogers et al., 2020). We found that prenatal maternal depression, anxiety, and stress were associated with reduced infant neurodevelopment capacity between ages 6 and 24 months even after adjustment for postpartum depression. The effects on infant social-emotional development were strong. Recently, Wu et al. (2022) reported that elevated maternal psychological distress during pregnancy was associated with altered fetal brain development and offspring cognitive and social-emotional outcomes. The volume of the left fetal hippocampal mediated the association between maternal prenatal stress and infant cognition outcomes, the cortical local gyrification index, and sulcal depth were related to social-emotional competence. Other studies reported that the negative association between maternal depression during pregnancy and cortical thickness of girls was found stronger than that in boys (Lebel et al., 2016), and a larger right amygdale volume in girls from depressed mothers was found at the age of 4.5 (Wen et al., 2017). The alteration of amygdale volume indicated a reduction in structural connectivity and maturation that was associated with anxiety and mood. In our study, the specific effects of sex on infant cognition, gross motor, and fine motor may be explained by changes of sex specific brain structures. The difference in infant brain structure may be the potential resource of sex special neurodevelopment outcomes and indicate a different vulnerable window for boys and girls with exposed maternal depression

**Table 5**
Associations of maternal 42-days postpartum depression with child neurodevelopment in 1128 boys and 1060 girls at age 6, 12 and 24 months.

| Maternal postpartum depression | | n | Child neurodevelopment measures, $\beta$ (95 % CI) | | | | | |
|---|---|---|---|---|---|---|---|---|
| Boys | | | | | | | | |
| | | | Communication | Gross motor | Fine motor | Problem solving | Person-social | Social-emotional |
| No | 6 and 12 | 889 | *ref* | *ref* | *ref* | *ref* | *ref* | *ref* |
| Depressed (≥10) | Months | 104 | −1.35 [−2.61, −0.10]* | **−3.19 [−5.25, −1.13]** ** | 0.62 [−0.91, 2.14] | −1.16 [−2.79, 0.47] | −2.40 [−4.30, −0.49]* | 2.48 [0.14, 4.82]* |
| Per 1SD | | 993 | −0.11 [−0.20, −0.01]* | **−0.33 [−0.48, −0.18]** *** | 0.01 [−0.10, 0.13] | −0.10 [−0.22, 0.02] | **−0.25 [−0.39, −0.11]** *** | 0.11 [−0.06, 0.28] |
| | | | Cognition | Language | Motor | Adaptive Behavior | Social-Emotional | |
| No | 24 Months | 1019 | *ref* | *ref* | *ref* | *ref* | *ref* | |
| Depressed (≥10) | | 109 | 2.29 [−1.66, 6.84] | 0.84 [−2.15, 3.83] | −1.37 [−4.30, 1.56] | −1.94 [−5.73, 1.85] | −3.13 [−6.61, 0.34] | |
| Per 1SD | | 1128 | 0.80 [−0.52, 2.11] | −0.54 [−1.47, 0.38] | −1.05 [−1.95, −0.15] | −0.16 [−1.32, 1.01] | −1.23 [−2.30, −0.16]* | |
| Girls | | | | | | | | |
| | | | Communication | Gross motor | Fine motor | Problem solving | Person-social | Social-emotional |
| No | 6 and 12 | 838 | *ref* | *ref* | *ref* | *ref* | *ref* | *ref* |
| Depressed (≥10) | Months | 118 | −0.11 [−1.11, 0.88] | −0.53 [−2.43, 1.37] | 0.62 [−0.91, 2.14] | 0.98 [−0.55, 2.50] | 0.96 [−0.69, 2.61] | −0.12 [−2.32, 2.08] |
| Per 1SD | | 956 | −0.03 [−0.10, 0.05] | **−0.21 [−0.36, −0.07]** ** | 0.03 [−0.07, 0.12] | 0.01 [−0.20, 0.12] | 0.03 [−0.10, 0.15] | −0.02 [−0.19, 0.15] |
| | | | Cognition | Language | Motor | Adaptive behavior | Social-emotional | |
| No | 24 Months | 919 | *ref* | *ref* | *ref* | *ref* | *ref* | |
| Depressed (≥10) | | 141 | −1.27 [−4.91, 2.36] | −1.50 [−4.19, 1.19] | −0.39 [−3.05, 2.26] | 1.83 [−1.47, 5.12] | −0.89 [−4.03, 2.25] | |
| Per 1SD | | 1060 | 0.13 [−1.06, 1.31] | −0.79 [−1.67, 0.09] | −0.47 [−1.33, 0.40] | 0.85 [−0.23, 1.93] | −0.04 [−0.99, 1.07] | |

Note: Data in bold: significant; CI: Confidence Interval; *ref*: Reference; SD: Standard Deviation; Infant neurodevelopment was assessed with Ages & Stages Questionnaires-Third Edition and Social-Emotional at ages of 6 and 12 months, and Bayley Scales of Infant & Toddler Development-Third Edition at age 24 months. Maternal depression was assessed with Edinburgh Postnatal Depression Scale. All models were adjusted for maternal age, education, mode of delivery, preterm birth, infant passive smoking and feeding pattern in the first 6 months. Mixed models were used for repeated assessments at 6 and 12 months. Linear models were used for assessments at 24 months.

* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

with different intrauterine brain development stages (Lebel et al., 2016). On the other hand, a current study found that maternal prenatal depression and anxiety were associated with maternal perceptions of negative temperament and behavior in daughters but not in sons one year after birth (Savory et al., 2020). This further proved the reliability of our results. Our study is based on infant BSID-III assessments rather than maternal self-report assessments, which can exclude the possibility of sex biases caused by maternal self-report in the results.

Another interesting result we found was that prenatal and postpartum maternal depression was differently associated with neurodevelopment in offspring. The part of postpartum depression assessment was to explore the vulnerable susceptible window for the impact of maternal depression on infant neurodevelopment and to exam the potential mediation role in the association of prenatal maternal depression and infant neurodevelopment. Previous studies of this topic focused on the period of prenatal, postpartum or both prenatal and postpartum. Prenatal depression and postpartum depression were strongly correlated. The mediation role and joint effect of postpartum depression should be considered in association between prenatal maternal depression and infant outcomes. Although, the results of the current study shown postpartum depression did not play a significant mediator role in the most association between prenatal maternal depression and infant development. Especially, maternal postpartum depression was not significantly associated with infant social-emotional development in the first 2 years, which was consistent with a recent study (Fransson et al., 2020). The discrepancy in infant outcome for pre- and postpartum depressed mothers indicated that mid-pregnancy is an important exposure window, while postpartum may participate in limited mediation or joint modification effects in associations. Previous studies revealed that maternal depression in mid pregnancy rather than late pregnancy is negatively correlated with children of preschool right hemisphere cortical thickness which are involved in inhibition and attention control. This may further demonstrate that the onset time of depression during pregnancy differentially affects infant development (Lebel et al., 2016). Intrauterine fetal programming (Fransson et al., 2020) rather than postpartum bonding may be related to the underlying mechanisms. Neurodevelopment originates from the fetal stage, maternal depression, or anxiety can change the intrauterine environment and affect brain development and function. However, it is not yet well understood how maternal emotional problems in such a susceptible period might interfere with infant neurodevelopment. The key role of maternal HPA activation in the fetal brain and HPA development for women experiencing prenatal stress was described before (Graignic-Philippe et al., 2014). Maternal prenatal stress resulting in HPA dysregulation was associated with lower expression of placental HSD11B2, which can lead to infant exaggerated cortisol reactivity and injury to fetal HPA (Jahnke et al., 2021). This effect on fetal HPA disruption could result in long-term deterioration of neurobehavioral development. The decreased volume of the amygdala and prefrontal cortex, changes in the functioning of the autonomic nervous and immune system, and differs in the programming of the developing 'gut-brain axis' were also observed in prenatally stressed infants (Kang et al., 2018; O'Mahony et al., 2017; Van den Bergh et al., 2020). Studies also hypothesized that the epigenetic mechanisms of placental gene expression regulating fetoplacental

glucocorticoid and changes in serotonin exposure and infant DNA cord blood methylation may play a critical role in mediating the association between prenatal stress exposure and less than optimal child development outcomes (Provenzi et al., 2020; Raikkonen et al., 2015).

The varied effects of types of prenatal maternal anxiety and depression were considered to have apparently different effects on infants (Reissland et al., 2018). However, a recent meta-analysis (Madigan et al., 2018) reported a result of the mean effects of maternal prenatal stress (OR = 1.66), depression (OR = 1.79), and anxiety (OR = 1.50) on children (range 0.2 months to 17 years) socioemotional problems, which was consistent with our results. The adjusted mean differences between infant neurodevelopment scores for the effects of maternal depression, anxiety, and stress scores increasing with 1SD in the current study were close. As the hidden links between multiple dimensions of mental illnesses had been reported (Marshall, 2020), the effects of prenatal maternal depression, anxiety, and stress on child development may be interrelated.

The strength of this prospective study included its large sample size, which allowed us to acquire more reliable results. We used BSID-III to assess child development, which is a gold standard series of behavioral assessments in clinics (Del Rosario et al., 2021). Also, this was a multicenter study, thus avoid the potential selection bias to a better extent that might occur in a single-center study.

Our study had limitations. Data on maternal perinatal mental symptoms were based on maternal self-reports. Infant neurodevelopment assessed by using ASQ and ASQ: SE at 6 and 12 months were reported by caregivers. Second, all study subjects were Chinese, generalizability to other ethnic groups remains to be determined. Still, there might be residual confounding. A major potential confounder was genetics, which may predispose both mothers and children to more mental/psychological problems. However, this was less likely given the specificity of prenatal as opposed to postnatal mental health effects, but still, it cannot be excluded.

## 5. Conclusion

Prenatal maternal mental problems were associated with less optimal infant early neurodevelopment including social-emotional, communication, cognition, and motor competences in the first 2 years, with strong effects on social-emotional development in both boys and girls. The sex modification effect appeared in the associations. Prenatal period is an important susceptible window for the effect of maternal depression on infant neurodevelopment. Postpartum depression had limited mediation and joint effects. This study underscores the importance of intervention in mothers' emotions during pregnancy to optimize child neuropsychiatric.

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## CRediT authorship contribution statement

F. Ouyang conceptualized and designed the study, and contributed to data analysis, data interpretation and manuscript writing; T. Zhang conducted the analyses and drafted the manuscript; Z. Luo and J. Zhang contributed to data interpretation and manuscript revision; J. Li, Y. Ji, and Y. Tian contributed to manuscript revision; Y. Chen, R. Ma and P. Fan contributed to study conduction and data analysis.

All authors reviewed and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

## Conflict of interest

The authors have no conflicts of interest relevant to this article to disclose.

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