Eur Child Adolesc Psychiatry (2015) 24:1139–1147
DOI 10.1007/s00787-015-0701-9

ORIGINAL CONTRIBUTION

Sex-specific and time-dependent effects of prenatal stress on the early behavioral symptoms of ADHD: a longitudinal study in China

Peng Zhu[1] · Jia-Hu Hao[1] · Rui-Xue Tao[2] · Kun Huang[1] · Xiao-Min Jiang[3] · Yuan-Duo Zhu[1] · Fang-Biao Tao[1]

Received: 21 September 2014 / Accepted: 6 March 2015 / Published online: 20 March 2015

Abstract There is increasing evidence that prenatal stressful life events (SLEs) may be a potential risk factor for attention-deficit hyperactivity disorder (ADHD), but the sex-specific and time-dependent effects of prenatal stress on ADHD are less clear. In this prospective longitudinal study, data on prenatal SLEs during different stages of gestation and indicators of buffers against stress, including maternal social support and avoidance coping, were obtained from 1765 pregnant women at 32 weeks of gestation. The behavioral symptoms of ADHD in children aged 48–54 months were evaluated by reports from the parents. There were 226 children (12.8 %) above the clinically significant cutoff for ADHD. After adjusting for potential confounders, boys whose mother experienced severe SLEs in the second trimester had a significantly increased risk (OR = 2.41, 95 % CI: 1.03–5.66) of developing ADHD symptoms compared with boys whose mothers did not experience severe SLEs at this time. However, no significantly increased risk of ADHD symptoms was observed in girls born to mothers experienced prenatal severe SLEs. Additionally, significant interaction effects of prenatal SLEs, social support and coping style on ADHD symptoms were found in males. Boys whose mothers experienced severe SLEs during the second trimester accompanied by a higher score for avoidance coping (OR = 3.31, 95 % CI: 1.13–9.70) or a lower score for social support (OR = 4.39, 95 % CI: 1.05–18.31) were likely to be at a higher risk for ADHD symptoms. The epidemiological evidence in this prospective follow-up study suggests that the effect of prenatal SLEs on ADHD symptoms in offspring may depend on the timing of prenatal stress and may vary according to the sex of the offspring.

Keywords Attention-deficit hyperactivity disorder (ADHD) · Pregnancy · Prenatal stress · Life events · Social support · Coping style · Longitudinal

Abbreviations

ADHD	Attention-deficit hyperactivity disorder
BMI	Body mass index
PNMS	Prenatal maternal stress
SLEs	Stressful life events

Introduction

Attention-deficit hyperactivity disorder (ADHD) is believed to be a multifactorial disorder [1, 2]. It has a worldwide prevalence ranging from 5 to 10 % of all school-aged children [3, 4]. Evidence from a significant body of independent prospective studies suggested that prenatal maternal stress (PNMS) had long-term effects on neurobehavioral development in offspring [5–7]. To date, a small but growing number of studies highlighted that maternal exposure to prenatal stressful life events (SLEs) is a potential risk factor for ADHD [8–10]. These studies were independent and different in terms of design (registration system based, retrospective or prospective investigations).

✉ Fang-Biao Tao
fbtao@ahmu.edu.cn

[1] Anhui Provincial Key Laboratory of Population Health and Aristogenics, Department of Maternal and Child Health, Anhui Medical University, 81 Mei Shan Road, Hefei 230032, Anhui, China

[2] Department of Gynecology and Obstetrics, Hefei First People's Hospital, Hefei, Anhui, China

[3] Department of Gynecology and Obstetrics, Hefei Maternal and Child Health Hospital, Hefei, Anhui, China

Animal studies indicate that some of the brain structural and functional alterations induced by prenatal stress differ according to offspring sex and depend on the timing of prenatal stress [11]. The presence of periods with specific neurodevelopmental events results in windows of specific vulnerability for adverse influences. Although sex differences have been highlighted in ADHD research primarily because boys are overrepresented in clinical samples, most of the existing studies in humans have not mentioned about whether there are any differences in the effect of prenatal stress on neurobehavioral development in offspring according to the timing of prenatal stress or the gender of offspring. Additionally, a few recent studies have suggested that interpersonal resources such as social support and adaptive coping styles could reduce prenatal stress and alleviate its effects on birth outcome [12], but avoidance coping, also referred to as maladaptive coping, may be applied to stressful events or internal conflicts, often unconsciously. However, little is known about the impact of maternal social support and the coping style during pregnancy on offspring neurobehavioral development.

The aim of the present study was to explore the association between prenatal stress and ADHD symptoms in children aged 48–54 months using a prospective longitudinal sample. A broad measure of common life events was taken as an indicator of PNMS, and social support, the coping style and other multiple confounders were also detected in our study. Based on the findings of previous research [7, 13], we hypothesized that the risk of ADHD symptoms in male offspring whose mothers experienced prenatal stress is higher than that in female offspring. Moreover, we also investigated the timing effect of prenatal stress on ADHD symptoms in offspring.

Methods

Participants

The participants of this prospective study were recruited in the Hefei Maternal and Child Health Hospital between January and September 2008. A total of 2552 pregnant women, of gestational ages from 30 to 34 weeks, willingly participated in the project and completed a structured questionnaire including a Prenatal Life Events Checklist, social support scale and coping style questionnaire. Women with delivery before 32 weeks of gestation ($n = 14$), stillbirth ($n = 11$), birth defect ($n = 12$), 5 min Apgar score below 7 ($n = 27$), pregnancy with assisted reproductive technology ($n = 6$), mental disorder ($n = 2$) or multiple gestations ($n = 48$) were excluded from the study. A total of 2455 eligible participants participated in the follow-up. At 2 months postpartum, information on infant feeding was collected by telephone interview. Between 48 and 54 months postpartum, parents were re-contacted and invited to evaluate their children's behavioral symptoms of ADHD. Finally, we obtained complete data from 1765 (71.9 %) mother–infant pairs. The study was approved by the Ethics Committee of Anhui Medical University (reference number: 2008020), and informed consent was obtained from the participants.

Prenatal stressful life events

A 19-item Prenatal Life Events Checklist [14] designed on the basis of a Life Events Scale [15], which assessed the individuals' perceived stress about adverse negative life events in the first trimester (0–14 weeks), second trimester (15–27 weeks) and third trimester (28–42 weeks),was administered to mothers at the gestational age of 32 weeks. The detailed items were reported in our previous study [14]. Participants were invited to indicate whether the events had occurred during pregnancy using a dichotomous (yes–no) response scale. If the event occurred, they were asked to recall when it occurred, reported as the stage of gestation, and to weigh their perception of its impact on their emotional condition, ranging from no impact (0) to an extreme impact (4). The values in each event were summed up and used to assess the participants' perceptions of stress during the first, second and third trimester. Consistent with our previous study, total scores during the different stages of gestation of 0, 1 and 2 or greater were defined as no stress, modest stress and severe stress, respectively; severe stress has been indicated as a significant predictor of adverse birth outcomes [14]. The two- to four-week test–retest reliability ($n = 200$) of the Prenatal Life Events Checklist was 0.87, which ensured that the assessments of perceived stimulus intensity and the timing of prenatal stress were reliable.

Social support

The Chinese revised edition of the social support scale, which included ten items and was previously validated in healthy populations and clinical samples in China [16], was used to assess social support as a buffer of stress. The scale addresses several dimensions of perceived social support, including emotional support, instrumental support and social integration. For the analysis, a total score is calculated based on all ten items. Higher scores indicate more material and emotional support from the members of one's social network. The scale showed high values of internal consistency (Cronbach's alpha is 0.89), and the test–retest reliability was 0.88. In this study, social support was analyzed both as a continuous variable and as a quartile.

Avoidance coping

The Chinese revised edition of the trait coping style questionnaire (TCSQ), which included ten items giving a total score ranging from 10 to 50 and was previously validated in sample from China [17], assessed avoidance coping to deal with stress. The scale was designed to assess the use of strategies that involved avoiding thinking about a problem, avoiding dealing with a stressor, and avoiding relationships or social activities. For the analysis, global scores were calculated based on all ten items. Higher scores indicated a greater tendency to adopt avoidance coping style to deal with stress. Internal consistency (Cronbach's alpha) of the scales was 0.88, and the test–retest reliability was 0.85. In this study, avoidance coping was analyzed both as a continuous variable and as a quartile.

ADHD symptoms in offspring

The children's behavioral symptoms of ADHD were assessed using the parent version of the Conners' Hyperactivity Index [18], which has been widely used in epidemiological and clinical studies [19–21] and has previously been validated in preschooled children in China [22, 23]. This index comprises ten items rated on a four-point scale (from 0 = not at all to 3 = very much). The internal consistency (Cronbach's alpha) of the scales was 0.84, and the reliability was 0.89. The items were summed with higher scores reflecting higher levels of behavioral symptoms of ADHD. In addition, a score of >15 was used to identify those above the clinically significant cutoff of symptoms [18].

Confounding factors

Information on essential potential confounders, including maternal sociodemographic characteristics, prepregnancy lifestyle, prepregnancy body mass index (BMI), complications with pregnancy, pregnancy and birth outcomes and infant-feeding patterns, was prospectively collected from medical records or interviews. Maternal sociodemographic characteristics included age, education (≤9 and >9 years of completed schooling) and household income (<2000, 2000–4000 and more than 4000 Yuan/RMB Yuan/month). Prepregnancy lifestyle characteristics included maternal alcohol consumption and paternal smoking and alcohol consumption up to 6 months before pregnancy. The prepregnancy BMI was calculated based on the height routinely measured at the clinical visit, and the prepregnancy weight obtained at the interview. Complications with pregnancy included diabetes mellitus, hypertension, heart failure, glandula thyreoidea disease, intrahepatic cholestasis of pregnancy and moderate and severe anemia. Pregnancy and birth outcomes included the delivery mode, infant sex, birth weight and gestational age at birth. Preterm births (births with a gestational age <37 completed weeks) were calculated from the gestational age (incompleted weeks) based on the difference between the date of the last menstrual period and the date of delivery. Low birthweight was defined as an infant weighing less than 2500 g, and fetal macrosomia was defined as a fetus or infant weighing more than 4000 g. In the telephone interview at 2 months postpartum, participants were asked about how they had been feeding their infants, including predominantly breast-feeding or breast-feeding and bottle-feeding. The definitions of infant-feeding patterns refer to the criteria that define selected infant-feeding practices of the WHO and UNICEF [24].

Statistical analysis

Crude odd ratios (ORs) and 95 % confidence intervals (CIs) were generated for associations of maternal sociodemographic characteristics and birth outcomes with ADHD symptoms in the offspring using Chi-square tests (Table 1). Interrelationships between predictors (prenatal SLEs during different stages of pregnancy, maternal social support and avoidance coping) and ADHD symptoms in the offspring were assessed using Pearson's correlations (Table 2). Multiple linear regression models were performed to calculate the regression coefficient of each predictor of ADHD symptoms in the offspring (Table 3). Multiple logistic regression models were used to test whether each predictor was independently associated with an increased risk of clinically significant behavioral symptoms of ADHD (Table 4). We adjusted for the following factors that have been suggested to be potentially associated with prenatal stress or neurodevelopment: maternal age, education, income, prepregnancy BMI, complications of pregnancy, smoking, alcohol consumption, mode of delivery, gestational weeks, birth weight and infant-feeding patterns. To identify the unique contribution of prenatal SLEs in each trimester, the occurrences of SLEs at other time point were controlled for. To test for possible sex-specific effects, the data were stratified by the sex of the infants. Sensitivity analyses were performed by adjusting for propensity scores [25]. Additionally, the effects of interactions of prenatal SLEs during different stages of pregnancy, social support and coping styles on ADHD symptoms in the offspring were tested using hierarchical logistic regression models. A sample size of 800 is robust enough to detect an effect size of 0.05 with 90 % power and 95 % confidence. All analyses were two-tailed, and $P < 0.05$ was considered significant. SPSS version 10.0 was used to perform the analyses.

Table 1 Sociodemographic characteristics for study population according to ADHD symptoms in 48- to 54-month-old child

Sociodemographic characteristics	$N = 1765$	Clinically significant ADHD symptoms[a]			
	N (%)	%	OR	95 % CI	*P* value
Maternal age					
20–24 years	256 (14.5)	11.3	1.0 [reference]		
25–29 years	1034 (58.6)	13.9	1.27	0.83–1.94	0.28
Above 30 years	475 (26.9)	11.2	0.98	0.61–1.59	0.95
Maternal school education					
≤9 years	298 (16.9)	12.1	0.92	0.63–1.35	0.68
>9 years	1467 (83.1)	13.0	1.0 [reference]		
Maternal income					
<2000 Yuan/RMB	281 (15.9)	13.2	1.10	0.75–1.62	0.62
2000–4000 Yuan/RMB	1290 (73.1)	12.1	1.0 [reference]		
>4000 Yuan/RMB	194 (11.0)	17.0	1.49	0.99–2.25	0.057
Prepregnancy BMI					
Underweight	411 (23.3)	12.2	0.92	0.66–1.29	0.63
Normal	1222 (69.2)	13.1	1.0 [reference]		
Overweight or obesity	132 (7.5)	12.1	0.92	0.53–1.58	0.75
Complication of pregnancy[b]					
No	1473 (83.5)	12.4	1.0 [reference]		
Yes	292 (16.5)	14.7	1.22	0.85–1.74	0.28
Maternal alcohol consumption up to 6 months before pregnancy					
None	1493 (84.6)	12.5	1.0 [reference]		
Any	272 (15.4)	14.3	1.17	0.81–1.70	0.41
Paternal smoking up to 6 months before pregnancy					
None	975 (55.2)	12.1	1.0 [reference]		
1–5 cigarettes daily	388 (22.0)	11.3	0.93	0.64–1.34	0.70
Above 6 cigarettes daily	402 (22.8)	15.9	1.38	0.99–1.91	0.058
Paternal alcohol consumption up to 6 months before pregnancy					
None	329 (18.6)	13.7	1.16	0.82-1.67	0.41
Once a week or less	1211 (68.6)	12.0	1.0 [reference]		
Several times a week or more	225 (12.7)	16.0	1.40	0.94–2.08	0.096
Gender of infant					
Male	951 (53.9)	12.5	0.95	0.71–1.25	0.69
Female	814 (46.1)	13.1	1.0 [reference]		
Mode of delivery					
Vaginal delivery	663 (37.6)	12.7	1.0 [reference]		
Cesarean section	1102 (62.4)	12.9	1.02	0.76–1.36	0.90
Gestational weeks					
Full term	1660 (94.1)	12.8	1.0 [reference]		
Premature	105 (5.9)	12.4	0.96	0.53–1.75	0.89
Birth weight					
<2500 g	50 (2.8)	12.0	0.91	0.38–2.17	0.84
2500–3999 g	1563 (88.6)	13.0	1.0 [reference]		
≥4000 g	152 (8.6)	11.2	0.84	0.50–1.43	0.53
Infant-feeding patterns at 2 months postpartum					
Predominant breast-feeding	1048 (59.4)	12.1	1.0 [reference]		
Breast-feeding	525 (29.7)	13.1	1.10	0.80–1.50	0.56
Bottle-feeding	192 (10.9)	15.6	1.34	0.87–2.07	0.18

OR odd ratio, *CI* confidence intervals

[a] The clinically significant ADHD symptoms were defined as the scores of ADHD symptoms assessed by the Conners' Hyperactivity Index—parent version more than 15

[b] Complications with pregnancy included diabetes mellitus, hypertension, heart failure, glandula thyreoidea disease, intrahepatic cholestasis of pregnancy, moderate and severe anemia

Results

Characteristics of the study population

Attrition analyses show the mean values of years of education in non-participants were significantly lower than that in participants at follow-up (12.89 ± 2.98 vs 13.45 ± 2.64 years, $P < 0.05$). For all other sociodemographic characteristics, the non-participants did not differ from the participants. The characteristics of the study population as well as the associations between sociodemographic characteristics and ADHD symptoms in the offspring are presented in Table 1. There were 226 children (12.8 %) above the clinically significant cutoff for ADHD. No significant difference between males and females for the prevalence of ADHD symptoms was observed.

Correlation between predictors and ADHD symptoms in offspring

Table 2 shows the univariate correlation of prenatal SLEs during different stages of pregnancy, social support and avoidance coping with ADHD symptoms measured as continuous variables. The mean value of ADHD symptom scores in boys and girls was 10.23 (range from 0 to 28, SD = 4.11) and 10.09 (range from 0 to 26, SD = 4.20), respectively. For males, ADHD symptoms were positively correlated with prenatal SLEs in the second trimester ($r = 0.09$, $P = 0.004$) and with avoidance coping ($r = 0.17$, $P < 0.001$) but negatively correlated with social support ($r = -0.10$, $P = 0.002$). For females, ADHD symptoms were only positively correlated with prenatal SLEs in the third trimester ($r = 0.08$, $P = 0.025$). In addition, prenatal

Table 2 Pearson's correlation of prenatal life events stress, social support, avoidance coping with ADHD symptoms as continuous variables in 48- to 54-month-old child

Scores of predictors	Range	Mean score (SD)		ADHD symptoms scores[a]		
		Males	Females	All	Males	Females
Maternal life events stress						
In the first trimester	0–7	0.20 (0.65)	0.21 (0.65)	0.03	0.03	0.03
In the second trimester	0–8	0.13 (0.53)	0.14 (0.56)	0.05*	0.09**	<−0.01
In the third trimester	0–8	0.10 (0.40)	0.12 (0.60)	0.06**	0.05	0.08*
Social support	18–54	38.06 (5.21)	37.54 (5.16)	−0.08**	−0.10**	−0.06
Avoidance coping	10–50	25.79 (8.85)	26.71 (9.08)	0.11**	0.17***	0.05

SD standard deviation

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

[a] The scores of ADHD symptoms were assessed by the Conners' Hyperactivity Index—parent version

Table 3 Associations of maternal life events stress during pregnancy, social support and avoidance coping with ADHD symptoms as continuous variables in 48- to 54-month-old child in multiple regression models

Scores of predictors	Male, β (95 % CI)		Female, β (95 % CI)	
	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]
Maternal life events stress				
In the first trimester	0.19 (−0.22, 0.59)	−0.04 (−0.45, 0.37)	0.18 (−0.26, 0.62)	0.07 (−0.38, 0.52)
In the second trimester	0.72 (0.23, 1.21)*	0.55 (0.06, 1.05)*	−0.02 (−0.54, 0.50)	−0.07 (−60, 0.45)
In the third trimester	0.48 (−0.17, 1.14)	0.39 (−0.27, 1.05)	0.55 (0.07, 1.03)*	0.51 (0.02, 0.99)*
Social support	−0.08 (−0.13, −0.03)*	−0.06 (−0.11, −0.02)*	−0.05 (−0.10, 0.01)	−0.04 (−0.10, 0.02
Avoidance coping	0.08 (0.05, 0.11)***	0.07 (0.04, 0.10)***	0.02 (−0.01, 0.06)	0.02 (−0.1, 0.05)

CI confidence interval

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

[a] Model 1 is crude estimate of maternal life events stress during different stages of pregnancy, social support and avoidance coping on ADHD symptoms in offspring

[b] Model 2 is adjusted for maternal age, education, income, prepregnancy BMI, complication of pregnancy, maternal alcohol consumption, paternal smoking and consumption up to 6 months before pregnancy, mode of delivery, gestational weeks, birth weight, infant-feeding patterns and occurrence of life events at other time point

SLEs in the second trimester were weakly positively correlated with stress in the third trimester ($r = 0.09$, $P < 0.001$) and avoidance coping ($r = 0.07$, $P < 0.001$) in the whole sample.

Linear relationship between predictors and ADHD symptoms in offspring

Table 3 presents the results of the multiple linear regression analyses examining the associations between predictors and ADHD symptoms in the offspring measured as continuous variables. After adjusting for all of the confounding variables, prenatal SLEs in second trimester, maternal social support and avoidance coping independently contributed to the variance in ADHD symptoms in male. However, prenatal SLEs in the third trimester were independently positively correlated with ADHD symptoms in females.

Odds ratios of predictors for clinically significant ADHD symptoms in offspring

As shown in Table 4, boys whose mothers experienced severe SLEs in the second trimester had a significantly increased risk (OR = 2.41, 95 % CI: 1.03–5.66, $P = 0.041$) of clinically significant ADHD symptoms comparing with boys in the reference group. Boys whose mother were in the highest quartile of avoidance coping (OR = 2.64, 95 % CI: 1.39–5.00, $P = 0.002$) or in the lowest quartile of social support (OR = 1.92, 95 % CI: 1.08–3.41, $P = 0.022$) had the highest risk of clinically significant ADHD symptoms

Table 4 Risk ratio for maternal life events stress during pregnancy, social support and avoidance coping on clinically significant ADHD symptoms in 48- to 54-month-old child

Prenatal exposure	*N* (%)	Male ($n = 951$)			Female ($n = 814$)		
		N (%)	Crude OR (95 % CI)	Adjusted OR (95 % CI)[a]	*N* (%)	Crude OR (95 % CI)	Adjusted OR (95 % CI)[a]
Maternal life events stress							
In the first trimester							
0	1540 (87.3)	101 (12.1)	1.0 [reference]	1.0 [reference]	91 (12.9)	1.0 [reference]	1.0 [reference]
1	139 (7.9)	11 (14.1)	1.19 (0.61–2.32)	1.02 (0.48–2.12)	10 (16.4)	1.33 (0.65–2.71)	1.19 (0.56–2.53)
≥2	86 (4.9)	7 (17.1)	1.49 (0.64–3.45)	1.30 (0.57–3.00)	6 (13.3)	1.04 (0.43–2.53)	1.01 (0.41–2.49)
In the second trimester							
0	1618 (91.7)	104 (11.9)	1.0 [reference]	1.0 [reference]	96 (12.9)	1.0 [reference]	1.0 [reference]
1	86 (4.9)	7 (14.6)	1.26 (0.55–2.88)	1.18 (0.51–2.72)	6 (15.8)	1.27 (0.52–3.12)	1.19 (0.47–3.01)
≥2	61 (3.5)	8 (25.0)	2.46 (1.08–5.62)*	2.41 (1.03–5.66)*	5 (17.2)	1.41 (0.53–3.79)	1.33 (0.47–3.83)
In the third trimester							
0	1650 (93.5)	109 (12.2)	1.0 [reference]	1.0 [reference]	101 (13.3)	1.0 [reference]	1.0 [reference]
1	81 (4.6)	7 (15.9)	1.36 (0.59–3.12)	1.25 (0.52–2.99)	4 (10.8)	0.79 (0.27–2.28)	0.74 (0.26–2.12)
≥2	34 (1.9)	3 (18.8)	1.66 (0.46–5.90)	1.54 (0.39–5.98)	2 (11.1)	0.81 (0.18–3.59)	0.72 (0.16–3.23)
Social support							
Quartile 1 (lowest)	356 (20.2)	34 (18.7)	2.26 (1.32–3.88)*	1.92 (1.08–3.41)*	23 (13.2)	1.02 (0.57–1.83)	0.94 (0.50–1.74)
Quartile 2	374 (21.2)	25 (12.5)	1.41 (0.79–2.49)	1.24 (0.68–2.26)	19 (10.9)	0.82 (0.45–1.51)	0.76 (0.40–1.45)
Quartile 3	500 (28.3)	32 (12.1)	1.35 (0.79–2.32)	1.32 (0.75–2.31)	35 (14.9)	1.17 (0.69–1.98)	1.14 (0.66–1.98)
Quartile 4 (highest)	535 (30.3)	28 (9.2)	1.0 [reference]	1.0 [reference]	30 (13.0)	1.0 [reference]	1.0 [reference]
Avoidance coping							
Quartile 1 (lowest)	465 (26.3)	16 (6.6)	1.0 [reference]	1.0 [reference]	26 (11.7)	1.0 [reference]	1.0 [reference]
Quartile 2	394 (22.3)	24 (10.6)	1.68 (0.87–3.25)	1.60 (0.81–3.16)	16 (9.6)	0.80 (0.41–1.54)	0.85 (0.43–1.68)
Quartile 3	473 (26.8)	38 (15.5)	2.60 (1.41–4.81)**	2.50 (1.32–4.75)**	34 (14.9)	1.32 (0.76–2.28)	1.46 (0.81–2.63)
Quartile 4 (highest)	433 (24.5)	41 (17.4)	2.98 (1.62–5.48)**	2.64 (1.39–5.00)**	31 (15.7)	1.41 (0.80–2.47)	1.59 (0.87–2.89)

The clinically significant ADHD symptoms were defined as the scores of ADHD symptoms assessed by the Conners' Hyperactivity Index—parent version more than 15

OR odd ratio, *CI* confidence interval

* $P < 0.05$, ** $P < 0.01$

[a] Adjustment for maternal age, education, income, pre-pregnancy BMI, complication of pregnancy, maternal alcohol consumption, paternal smoking and alcohol consumption up to 6 months before pregnancy, mode of delivery, gestational weeks, birth weight, infant-feeding patterns and occurrence of life events at other time point

compared with boys in the reference group, respectively. However, no significant effect of maternal exposure to prenatal SLEs during pregnancy, social support and avoidance coping on clinically significant ADHD symptoms was observed in female offspring.

Sensitivity analyses and interaction effects

We conducted the sensitivity analyses by adjusting for propensity scores using as continuous variables or categorical variables with four levels and found that the associations between prenatal stress in the second trimester and ADHD symptoms in the male offspring remained significant ($\beta = 0.56$, 95 % CI: 0.07–1.05, $P = 0.025$; OR = 2.38, 95 % CI: 1.01–5.62, $P = 0.048$). Additionally, significant interaction effects of prenatal SLEs, social support and coping style on ADHD symptoms were found in males. There was a significant association between prenatal SLEs in the second trimester and the risk (OR = 3.31, 95 % CI: 1.13–9.70, $P = 0.029$) of clinically significant ADHD symptoms in male among mothers with higher avoidance coping scores (greater than the 50th percentile), but not among mothers with lower avoidance coping scores (less than the 50th percentile). Similarly, there was a significant association between prenatal SLEs in the second trimester and the risk (OR = 4.39, 95 % CI: 1.05–18.31, $P = 0.042$) of clinically significant ADHD symptoms in male among mothers with lower social support scores (less than the 50th percentile), but not among mothers with higher social support scores (more than the 50th percentile).

Discussion

This is the first prospective longitudinal study to simultaneously examine the sex-specific and time-dependent effects of PNMS on the early behavioral development of ADHD symptoms. The study showed that boys whose mother experienced perceived severe SLEs during the second trimester but not the first or third trimester were over two times more likely to have clinically significant behavioral symptoms of ADHD after adjusting for extensive confounding factors. However, no significantly increased risk of ADHD symptoms was observed in girls whose mothers experienced prenatal severe SLEs.

Our findings suggest that boys are more vulnerable than girls and more likely to display ADHD symptoms in later life when their mother experienced prenatal SLEs, which is in line with those from two previous clinical studies [8, 26]. However, there is a lack of data concerning the biological plausibility. We speculate that the sex-specific effect on neurodevelopment maybe due to differences between male and female fetuses on the vulnerability of the dopamine transmitter system [27], the binding ability of the 5-HT1A receptor in the ventral hippocampus [28], the hypothalamic–pituitary–adrenocortical axis [29] and the neurotrophic effect of estrogen [30]. However, there is also another possibility that the brain development of both males and females is influenced by prenatal stress but that they respond in different ways [11, 28]. PNMS may result in different behavioral/emotional problems in girls, and this needs to be examined in future studies.

Previous studies have suggested that the effect of PNMS on neurodevelopment may vary according to the timing of exposure [6, 31]. However, human studies designed to investigate the gestational time window when stress exposure produces the greatest impact on the risk of ADHD symptoms are limited [8, 26]. The findings of this study suggest that the middle or the second half of pregnancy is a particularly sensitive period for the effects of PNMS on the development of ADHD symptoms in offspring. This is in line with the finding that pregnancy anxiety at 19 weeks of gestation was associated with gray matter volume reductions in the prefrontal cortex of offspring [31] and that maternal exposure to natural disasters or anxiety during the second half of pregnancy is related to neurobehavioral development in offspring [6, 32]. The time-dependent effect might be attributed to the fact that different brain regions have a unique timetable for development, indicating specific periods of neural vulnerability [33].

To date, the roles of maternal social support and coping styles in fetal in trauterine development and late development in childhood remain incompletely understood. Multiple types of social support from different sources may encourage mothers to adopt healthier lifestyles, reduce their stress levels and pursue better prenatal care [34]. Coping efforts may influence birth outcomes by serving to minimize or prevent negative emotional, behavioral, cognitive and physiological responses to stressors [35]. Previous studies indicated that a lack of social support, avoidant coping styles and poor coping skills might result in adverse effects on pregnancy outcomes and infant development [36, 37]. Our findings show that maternal lower social support and higher avoidance coping may be independently related to the later development of ADHD symptoms and may moderate the association between prenatal SLEs and ADHD symptoms in male offspring. Future studies should explore the neurobiological factors associated with the contribution of maternal social support and coping styles to fetal development.

The prospectively collected data, the large sample and the statistical adjustment for a large number of covariates are clear strengths of this study. The perceived stimulus intensity was used as analysis indicators rather than counts of life events to better estimate the quantity of stimulants of stressful life events. An earlier assessment of ADHD

symptoms might reduce the confounding of the postnatal environment on the associations between prenatal factors and late neurobehavioral development.

However, some limitations of this study should also be acknowledged. First, sample attrition bias and recall bias were inevitable in this longitudinal follow-up study. Second, for the stratification by the sex of the offspring and the stages of gestation in Table 4, the sample size in the subgroups is relatively small, resulting in limited statistical power. The association between prenatal stress in the second trimester and ADHD symptoms in male was not significant in the context of the conservative Bonferroni correction, in which the level of significance was 0.05/12. Therefore, findings in this study should be cautiously interpreted and further prospective studies with large sample sizes should be conducted to validate our results. Third, assessment of the child's behavioral symptoms of ADHD was based on parental report. However, mothers with elevated perceived stress, lower social support or higher avoidance coping might experience higher levels of difficulties and have biased negative representations of their children, which may lead to measurement bias. Fourth, the absence of data on heritable factors, postnatal stress and environmental factors could be viewed as a major limitation. Thus, we could not exclude the potential contributions of these essential confounding factors to the increased risk of ADHD symptoms in offspring aged 48–54 months; this may result in residual confounding in this study. Missing data on prenatal stress after 32 weeks also might slightly contribute to the lack of effects in the third trimester. Finally, earlier assessment raises a disadvantage that some children in this age range did not display significant behavioral symptoms of ADHD, which may partly contribute to the reason why there was no male predominance in the prevalence of ADHD symptoms in this study. Further studies on the long-term effects of prenatal stress on ADHD in offspring are needed. Additionally, although the correlations between the prenatal SLEs, avoidance coping, social support and ADHD symptoms are significant, the intensities of the dose–response relationship are very small and should be considered as weak correlations.

Conclusion

The epidemiological evidence in this prospective follow-up study suggests that early behavioral development in male offspring may be more vulnerable to PNMS than that in female offspring and that the middle or the second half of pregnancy may be a critical window during which PNMS has a greater influence on fetal brain and ADHD symptom development. This study also raises the possibility of interventions for neurobehavioral development in offspring by providing social support and resilience training to mothers during pregnancy. These findings support intervention research or animal study to further identify the causality underlying these associations.

Acknowledgments The authors are grateful to the children and the families who participated in this study. This work was supported by National Natural Science Foundation of China (81472991, 81330068, 81373012), National Training Programs of Innovation and Entrepreneurship for Undergraduates (201310366038), Key Project Foundation for the Talents by Educational Commission of Anhui Province (2013SQRL020ZD) and Program for the Innovative Talents of Anhui Medical University.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Spencer TJ, Biederman J, Wilens TE, Faraone SV (2002) Overview and neurobiology of attention-deficit/hyperactivity disorder. J Clin Psychiatry 63(Suppl 12):3–9
2. Hudziak JJ, Derks EM, Althoff RR, Rettew DC, Boomsma DI (2005) The genetic and environmental contributions to attention deficit hyperactivity disorder as measured by the Conners' Rating Scales-Revised. Am J Psychiatry 162(9):1614–1620. doi:10.1176/appi.ajp.162.9.1614
3. Owens JA (2005) The ADHD and sleep conundrum: a review. J Dev Behav Pediatr 26(4):312–322
4. Boyle CA, Boulet S, Schieve LA, Cohen RA, Blumberg SJ, Yeargin-Allsopp M, Visser S, Kogan MD (2011) Trends in the prevalence of developmental disabilities in US children, 1997–2008. Pediatrics 127(6):1034–1042. doi:10.1542/peds.2010-2989
5. Laplante DP, Barr RG, Brunet A, Galbaud du Fort G, Meaney ML, Saucier JF, Zelazo PR, King S (2004) Stress during pregnancy affects general intellectual and language functioning in human toddlers. Pediatr Res 56(3):400–410
6. Kinney DK, Miller AM, Crowley DJ, Huang E, Gerber E (2008) Autism prevalence following prenatal exposure to hurricanes and tropical storms in Louisiana. J Autism Dev Disord 38(3):481–488. doi:10.1007/s10803-007-0414-0
7. Khashan AS, McNamee R, Henriksen TB, Pedersen MG, Kenny LC, Abel KM, Mortensen PB (2011) Risk of affective disorders following prenatal exposure to severe life events: a Danish population-based cohort study. J Psychiatr Res 45(7):879–885. doi:10.1016/j.jpsychires.2010.12.005
8. Li J, Olsen J, Vestergaard M, Obel C (2010) Attention-deficit/hyperactivity disorder in the offspring following prenatal maternal bereavement: a nationwide follow-up study in Denmark. Eur Child Adolesc Psychiatry 19(10):747–753. doi:10.1007/s00787-010-0113-9
9. Motlagh MG, Katsovich L, Thompson N, Lin H, Kim YS, Scahill L, Lombroso PJ, King RA, Peterson BS, Leckman JF (2010) Severe psychosocial stress and heavy cigarette smoking during pregnancy: an examination of the pre- and perinatal risk factors associated with ADHD and Tourette syndrome. Eur Child Adolesc Psychiatry 19(10):755–764. doi:10.1007/s00787-010-0115-7
10. Ronald A, Pennell CE, Whitehouse AJ (2010) Prenatal maternal stress associated with ADHD and autistic traits in early childhood. Front Psychol 1:223. doi:10.3389/fpsyg.2010.00223
11. Weinstock M (2007) Gender differences in the effects of prenatal stress on brain development and behaviour. Neurochem Res 32(10):1730–1740. doi:10.1007/s11064-007-9339-4

12. Lobel M, Hamilton JG, Cannella DT (2008) Psychosocial perspectives on pregnancy: prenatal maternal stress and coping. Soc Pers Psychol Compass 2(4):1600–1623
13. Suenaga T, Yukie M, Gao S, Nakahara D (2012) Sex-specific effects of prenatal stress on neuronal development in the medial prefrontal cortex and the hippocampus. Neuroreport 23(7):430–435. doi:10.1097/WNR.0b013e3283529805
14. Zhu P, Tao F, Hao J, Sun Y, Jiang X (2010) Prenatal life events stress: implications for preterm birth and infant birthweight. Am J Obstet Gynecol 203(1):34.e31–34.e38. doi:10.1016/j.ajog.2010.02.023
15. Yang DS, Zhang YL (1990) Behavioral medicine. Hunan Normal University Press, Chagsha
16. Xiao SY (1994) Theoretical principle and application of social support scale. J Clin Psychiatry 4:98–100
17. Jiang QJ, Zhu YH (1999) Further explorations for a coping style questionnaire. Chin J Behav Med 8(3):167–169
18. Conners CK, Barkley RA (1985) Rating scales and checklists for child psychopharmacology. Psychopharmacol Bull 21(4):809–843
19. Heinonen K, Raikkonen K, Pesonen AK, Andersson S, Kajantie E, Eriksson JG, Vartia T, Wolke D, Lano A (2011) Trajectories of growth and symptoms of attention-deficit/hyperactivity disorder in children: a longitudinal study. BMC Pediatr 11:84. doi:10.1186/1471-2431-11-84
20. Conners CK, Casat CD, Gualtieri CT, Weller E, Reader M, Reiss A, Weller RA, Khayrallah M, Ascher J (1996) Bupropion hydrochloride in attention deficit disorder with hyperactivity. J Am Acad Child Adolesc Psychiatry 35(10):1314–1321. doi:10.1097/00004583-199610000-00018
21. zheng W (2010) Epidemiological investigation and treatment effect of attention deficit hyperactivity disorder in child. Chin J Child Health Care 18(04):329–321
22. Ou P, Cheng X, Qian QF (2001) Diagnostic value of Conners' Hyperactivity Index in attention deficit hyperactivity disorder. Chin J Child Health Care 9(03):201–203
23. Zhang F, Wang J, Yin LQ (2003) Application of Conners' Hyperactivity Index in diagnosis of attention deficit hyperactivity disorder. Chin J Behav Med Sci 12(06):627–630
24. Daelmans B, Dewey K, Arimond M (2009) New and updated indicators for assessing infant and young child feeding. Food Nutr Bull 30(2 Suppl):S256–S262
25. Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Stürmer T (2006) Variable selection for propensity score models. Am J Epidemiol 163(12):1149–1156
26. Rodriguez A, Bohlin G (2005) Are maternal smoking and stress during pregnancy related to ADHD symptoms in children? J Child Psychol Psychiatry 46(3):246–254. doi:10.1111/j.1469-7610.2004.00359.x
27. Berger-Sweeney J, Hohmann CF (1997) Behavioral consequences of abnormal cortical development: insights into developmental disabilities. Behav Brain Res 86(2):121–142. doi:10.1016/S0166-4328(96)02251-6
28. Van den Hove DL, Lauder JM, Scheepens A, Prickaerts J, Blanco CE, Steinbusch HW (2006) Prenatal stress in the rat alters 5-HT1A receptor binding in the ventral hippocampus. Brain res 1090(1):29–34. doi:10.1016/j.brainres.2006.03.057
29. Garcia-Caceres C, Lagunas N, Calmarza-Font I, Azcoitia I, Diz-Chaves Y, Garcia-Segura LM, Baquedano E, Frago LM, Argente J, Chowen JA (2010) Gender differences in the long-term effects of chronic prenatal stress on the HPA axis and hypothalamic structure in rats. Psychoneuroendocrinology 35(10):1525–1535. doi:10.1016/j.psyneuen.2010.05.006
30. Grigoriadis S, Seeman MV (2002) The role of estrogen in schizophrenia: implications for schizophrenia practice guidelines for women. Can J Psychiatry 47(5):437–442
31. Buss C, Davis EP, Muftuler LT, Head K, Sandman CA (2010) High pregnancy anxiety during mid-gestation is associated with decreased gray matter density in 6 to 9-year-old children. Psychoneuroendocrinology 35(1):141–153. doi:10.1016/j.psyneuen.2009.07.010
32. Van den Bergh BR, Marcoen A (2004) High antenatal maternal anxiety is related to ADHD symptoms, externalizing problems, and anxiety in 8- and 9-year-olds. Child Dev 75(4):1085–1097
33. Rice D, Barone S Jr (2000) Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. Environ Health Perspect 108(Suppl 3):511–533
34. Feldman PJ, Dunkel-Schetter C, Sandman CA, Wadhwa PD (2000) Maternal social support predicts birth weight and fetal growth in human pregnancy. Psychosom Med 62(5):715–725
35. Guardino CM, Dunkel Schetter C (2013) Coping during pregnancy: a systematic review and recommendations. Health Psychol Rev 8(1):70–94. doi:10.1080/17437199.2012.752659
36. Elsenbruch S, Benson S, Rucke M, Rose M, Dudenhausen J, Pincus-Knackstedt MK, Klapp BF, Arck PC (2007) Social support during pregnancy: effects on maternal depressive symptoms, smoking and pregnancy outcome. Hum Reprod Oxf Engl 22(3):869–877. doi:10.1093/humrep/del432
37. Dole N, Savitz DA, Siega-Riz AM, Hertz-Picciotto I, McMahon MJ, Buekens P (2004) Psychosocial factors and preterm birth among African American and White women in central North Carolina. Am J Public Health 94(8):1358–1365. doi:10.2105/AJPH.94.8.1358