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Prenatal and postnatal exposure to Tangshan earthquake and *CRHR1* gene polymorphism influence risk of sleep disturbance in adulthood

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Abstract

To determine the effect of earthquake on sleep quality of adults who had experienced Tangshan Earthquake either as infants or fetuses and also investigate whether *CRHR1* polymorphism influenced sleep quality in subjects exposed to seismic stress.

Totally 556 subjects were enrolled in the current study and were divided into 3 groups, those who had experienced Tangshan Earthquake as infants (group I) or fetuses (group II), and those who had not experienced Tangshan Earthquake (group III). Sleep was evaluated using the Pittsburgh Sleep Quality Index (PQSI). Three single nucleotide polymorphisms of the *CRHR1* gene were analyzed.

Fifty two (9.4%) subjects had sleep disturbance, including 17 (9.9%) subjects in group I, 24 (13.4%) subjects in group II, and 11 (5.3%) subjects in group III ($\chi^2 = 7.373$, $P = .025$). Moreover, subjects with *CRHR1* genotype T/T had a significantly lower rate of sleep disturbance (7.8%) than subjects with genotype C/T and C/C (14.7%; $\chi^2 = 4.845$, $P = .028$). Furthermore, subjects with rs7209436 genotype C had an approximately 2-fold increase in the risk of sleep disturbance *versus* those who were not genotype C (OR = 1.978, 95% CI (1.045, 3.744).

Prenatal and postnatal exposure to seismic stress significantly increases subsequent risk of sleep disturbance in adulthood.

Abbreviations: CRH = corticotrophin-releasing hormone, CRHR1 = corticotrophin-releasing hormone receptor 1, HPA = hypothalamus-pituitary–adrenal, PCR = polymerase chain reaction, PSQI = Pittsburgh Sleep Quality Index.

Keywords: *CRHR1*, early childhood stress, long-term effect, polymorphism, sleep disturbance

1. Introduction

Many animal and human studies have shown that major traumatic stress events in the mother during pregnancy can lead to the activation of the hypothalamus-pituitary-adrenal (HPA) axis, resulting higher cortisol levels and glucocorticoid secretion; meanwhile, abnormal maternal hormone levels affect the fetus via placenta homeostasis change.[1–3] The levels of cortisol and adrenaline are increased while the levels of dopamine and serotonin are decreased in women who experience stress during the second and third trimester of gestation. Maternal environmental disorders can also lead to increased levels of cortisol, disturbed sleep patterns, unstable sleep quality and changes in sleep state in newborns.[5] Cortisol response to stress adjustment disorder may be a risk factor for mental health. Studies have found that depression is associated with elevated cortisol levels.[6]

The HPA axis is activated by corticotrophin-releasing hormone (CRH) and modulates the release of stress hormones such as cortisol and hence is a main regulator of the stress response.[8] The CRH receptor 1 (CRHR1), a G-protein coupled CRH I receptor, is intimately involved in the HPA axis and activates the response of the mesencephalic limbic system and the HPA axis to various stress stimuli. *CRHR1* gene polymorphism is also associated with several mental disorders including panic disorder and major depressive disorder.[8] Association of *CRHR1* gene polymorphism with depression has also been examined in the case of traumatic events by numerous investigators, implicating *CRHR1* gene polymorphism in posttrauma psychopathology.[8]

The gene-environment interaction affects the stress response of individuals.[9] Sakamoto et al have recently reported that hippocampal Crhr1 expression was upregulated, which could partially contribute to the activation of CRH-CRHR1 signaling.[10] Lessard and Holman showed that *CRHR1* gene polymorphism moderated the long term health outcomes of

Editor: Massimo Tusconi.

This study was supported by National Science Foundation of China (No. 81271489), Science Technology Research and Development Program of Hebei (No. 09276103D), and National Science Foundation of Hebei (No. H2014206280).

Ethics approval and consent to participate: The study protocol was approved by the Ethics Committee of First Hospital of Hebei Medical University. Informed consent was obtained from all the study subjects before enrollment.

The authors declare that they have no competing interests.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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How to cite this article: Chen YN, An CX, Wang R, Wang L, Song M, Yu LL, Sun FF, Wang XY. Prenatal and postnatal exposure to Tangshan earthquake and CRHR1 gene polymorphism influence risk of sleep disturbance in adulthood. Medicine 2021;100:11(e24565).

Received: 9 September 2020 / Received in final form: 30 November 2020 / Accepted: 11 January 2021

http://dx.doi.org/10.1097/MD.0000000000024565

persons who had experienced childhood stress.[8] Blomeyer et al found that adolescents homozygous for the C allele of rs1876831 of *CRHR1* gene were more prone to heavy alcohol use following repeated episodes of stress.[8] In addition, prenatal stress has long-term effects on pregnancy outcomes and sleep duration and structure of newborns.[4] Maternal stress in the second and third trimester of pregnancy could lead to increased plasma cortisol levels, sleep pattern disorder, unstable sleep quality and changes in sleep state in newborns.[8] The offspring of pregnant women with high plasma cortisol level had a higher ratio of sleep disorder including reduced deep sleep duration, sleep structure disorder and more frequent physical activities and crying.[7] CRH regulates sleep-awakening and affects sleep by mediating the action of CRHR1; furthermore, CRHR1 antagonist could alleviate sleep disorders related to stress.[8]

Increasing evidence from preclinical and clinical studies indicates that maternal psychosocial stress during pregnancy adversely affects child and adult health outcomes.[11,12]*CRHR1* polymorphism has been shown to be associated with longitudinal trajectory of trauma symptoms over time in pediatric victims.[8,13] However, little literature is available on the effect of *CRHR1* polymorphism on sleep quality of adults who experienced a stressful event during the fetal period or infancy. Tangshan Earthquake struck the city of Tangshan, Hebei province, China on July 28, 1976 with a magnitude of 7.8 and killed approximately a quarter million people and severely injured 160.000 persons.[14] In the current cross-sectional study, we sought to determine the effect of earthquake on the sleep quality of adults who had experienced Tangshan Earthquake either as infants or fetuses and also investigate whether earthquake exposure and *CRHR1* polymorphism interacted with each other in modulating sleep.

2. Methods

2.1. Subjects

The study protocol was approved by the ethics committee of the First Affiliated Hospital of Hebei Medical University, Shijiazhuang, Hebei, China (No. 2014005). Written informed consent was provided by all the study participants.

The study included workers of Hebei Tangshan Kailuan Mining Group. We surveyed a total of 9 mining areas, 3 communities and 5 subsidiary units. The current study was carried out between January February and December June 2014 and enrolled subjects who were born between July 29, 1975 and April 28, 1976 and had experienced Tangshan Earthquake as infants, or between July 29, 1976 and April 28, 1977 and who had experienced Tangshan Earthquake as fetuses, or between July 29, 1977 and April 28, 1978 and who did not experience Tangshan Earthquake. We included those who had resided in Tangshan since birth and who understood the content of the rating scales and were cooperative with the study. Furthermore, only subjects whose genomic DNA was available for *CRHR1* genotyping were included. We excluded persons who had somatic diseases that interfered with their sleep. We further excluded pregnant or lactating women, persons with active infection, hypertension, epilepsy or convulsions, diabetes, thyroid disease, alcohol use, or a history of trauma other than earthquakes. We also excluded persons with a recent and past diagnosis of mental illness such as schizophrenia, depression, anxiety, and bipolar disorder or neurological diseases such as brain tumor and peripheral neuropathy and other diseases affecting cognitive function. Persons with incomplete data or who did not understand instructions or were not cooperative were also excluded. Persons whose mothers had infection, epilepsy or convulsion, hypertension, diabetes, a history of medication, drinking, or other traumatic events except earthquake were excluded.

2.2. Genotyping

Five ml peripheral blood was obtained from each subject after an overnight fast. Genomic DNA (10 ng) was extracted using a commercially available centrifugal adsorption column that specifically binds DNA (Tiangen Biotech, Beijing, China) as instructed by the manufacturer. The Chinese Han population typing data was downloaded from the HapMap database (http://www.hapmap.org) and selected according to the principle of minimum allele frequency >0.05 and linkage disequilibrium coefficient (r^2) > 0.8. Three single nucleotide polymorphisms, rs110402, rs242924, and rs242924, on the *CRHR1* gene were selected and analyzed by fluorescence quantitative polymerase chain reaction (PCR) using the PCR ABI 7500 system as instructed by the manufacturer (Applied Biosystems). The primers for *CRHR1* were designed using Primer5.0. Quality control included a proportional examination of allele typing, Hardy-Weinberg test. Duplicate genotyping was performed on approximately 5% of the population for quality control.

2.3. General evaluation

The study participants were asked to complete a questionnaire that elicited data on sociodemographic variables including name, age, date of birth, sex, years of education, ethnicity, occupation, marital status, family monthly income, smoking history, and drinking history, pregnancy history including experiences by the mothers during the earthquake, birth history, previous history of the subjects and their family history. Furthermore, mental illness was evaluated using Structured Clinical Interview for DSM-IV-TR Axis I Disorders-Patient Edition. The whole study subjects were investigated by one-on-one interviews. All the investigators had completed standardized training for the study and the concordance rate among the investigators was 93%.

2.4. Pittsburgh sleep quality index (PQSI)

Sleep was evaluated using the Pittsburgh Sleep Quality Index (PQSI), which has been validated in Chinese subjects.[15] The PSQI has the following domains, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction over the last month. Scoring of the answers in each domain is based on a 0 to 3 scale, whereby 3 reflects the negative extreme on the Likert Scale and the range of the global sum is 0 to 21. A PSQI score of 7 and above was defined as sleep disturbance.

2.5. Statistical analysis

Data were input into Epidata 3.1 database, and analyzed using the SPSS 21.0 software (SPSS Inc., Chicago, IL). One-way analysis of variance was used to compare age of the fetal exposure group and the infant exposure group and the control group. Sleep quality (PSQI score) was used as the dependent variable, and

gender, ethnicity, years of education, marital status, family monthly income, occupation, smoking and drinking history, the presence of early earthquake stress and insomnia, *CRHR1* gene polymorphism phenotype were used as independent variables for univariate logistic regression analysis. All significant factors ($P < .05$) in univariate analysis were entered into the unconditioned logistic multivariable regression analysis model, and the LR backward method was applied. $P < .05$ represented statistically significant difference.

3. Results

3.1. Sociodemographic and baseline characteristics of the study population

Totally 1534 subjects were screened for eligibility. One hundred twenty eight subjects were excluded because they refused to provide consent. Using random sampling method, 210 people were selected from the infantile exposure group, the fetal exposure group and the control group respectively for the detection of *CRHR1* gene polymorphism. Twenty one cases with incomplete general data, 12 cases with infection during pregnancy or other stressful events, and 5 cases with missing PSQI scores were excluded. A total of 592 subjects met the inclusion criteria. *CRHR1* gene polymorphism was detected by PCR, including rs110402, rs242924, and rs7209436 in 69, 555, and 552 cases, respectively. Finally, 556 subjects were included in the statistical analysis. They included 172 subjects who had experienced the earthquake as fetuses, 172 subjects who experienced the earthquake as infants and 205 subjects who did not experience the earthquake. The majority (84.7%) of the subjects were male. The 3 groups were comparable in sociodemographic and baseline variables ($P > .05$) except age ($\chi^2/F = 698.644$, $P = .000$) (Table 1).

3.2. PQSI

The mean total PQSI score was 3.48 ± 2.62 for the study population and was comparable among the 3 groups ($P > .05$) (Table 2). Fifty two (9.4%) subjects had sleep disturbance (PSQI score ≥ 7), including 17 subjects (9.9%) in the infant exposure group, 24 subjects (13.4%) in the fetal exposure group, and 11 subjects (5.3%) in the non-exposure group ($\chi^2 = 7.373$, $P = .025$ among the 3 groups and $P = .005$ between the fetal exposure group and non-exposure group) (Table 2).

The 3 groups were comparable in PSQI component scores I, and IV to VII ($P > .05$) (Table 3). Meanwhile, the fetal exposure group had a significantly higher score in sleep latency (component

Table 1

Sociodemographic and baseline characteristics of the study population.

	Fetal exposure	Infant exposure	No exposure	χ^2/F	P
N	179	172	205		
Sex, n (%)				0.645	.353
Male	157 (87.7)	145 (84.3)	169 (82.4)		
Mean age ± SD, years	38.60 ± 0.50	39.5 ± 0.5	37.6 ± 0.5	698.644	.000*
Ethnicities, n (%)				2.341	.310
Han Chinese	177 (98.9)	170 (98.8)	199 (97.1)		
Minorities	2 (1.1)	2 (1.2)	6 (2.9)		
Years of education, n (%)				6.828	.145
< 6	1 (0.6)	3 (1.7)	5 (2.4)		
6–12	137 (76.5)	134 (77.9)	140 (68.3)		
>12	41 (22.9)	35 (20.4)	60 (29.3)		
Marital status, n (%)	1 (0.6)	1 (0.6)	2 (1.0)	4.289	.368
Single	171 (95.5)	163 (94.8)	186 (90.7)		
Married	7 (3.9)	8 (4.7)	17 (8.3)		
Divorced, remarried and widowed					
Monthly family income, Yuan, n (%)				3.961	.682
<1000	5 (2.8)	2 (1.2)	8 (3.9)		
~ 2000	49 (27.4)	43 (25.0)	60 (29.3)		
~ 5000	116 (64.8)	117 (68.0)	126 (61.5)		
>5000	9 (5.0)	10 (5.8)	11 (5.4)		
Profession, n (%)				0.938	.919
Manual labor	153 (85.5)	147 (85.5)	171 (83.4)		
Office workers	12 (6.7)	9 (5.2)	14 (6.8)		
Others	14 (7.8)	16 (9.3)	20 (9.8)		
Smoking history, n (%)				2.593	.628
Current smoker	85 (47.5)	79 (45.9)	107 (52.2)		
Former smokers	18 (10.1)	13 (7.3)	17 (8.3)		
Non-smokers	76 (42.5)	80 (46.5)	81 (39.5)		
Drinking history				4.363	.628
Frequent drinkers	28 (15.6)	21 (12.2)	35 (17.1)		
Former drinkers	6 (3.4)	3 (1.7)	7 (3.4)		
Occasional drinkers	82 (45.8)	92 (53.5)	93 (45.4)		
Non-drinkers	63 (35.2)	56 (32.6)	70 (34.2)		

* compare among the 3 groups.

Table 2

PSQI scores of the study population.

	Fetal exposure	Infant exposure	Non-exposure	χ^2	*P*
N	179	172	205		
PSQI scores, n (%)					
Mean total scores	3.78 ± 2.96	3.48 ± 2.62	3.21 ± 2.28	2.245	.107
<7	155 (86.6)	155 (90.1)	194 (94.6)	7.373	.025*,†
≥7	24 (13.4)	17 (9.9)	11 (5.3)		

* compare among the 3 groups.

† Fetal exposure vs the control group; $ $\chi^2 = 0.728$ and $P = .695$ among the 3 trimester groups. PSQI = Pittsburgh Sleep Quality Index.

Table 3

PSQI component scores of the study population.

	Fetal exposure	Infant exposure	Non-exposure	*F*	*P*
N	179	172	205		
PSQI component scores					
I (subjective sleep quality)	1 (0, 3)	1 (0, 3)	1 (0, 3)	0.631	.372
II (sleep latency)	1 ((0, 3)	1 (0, 3))	1 (0, 3)	5.626	.048*,‡
III (sleep duration)	1 (0, 3)	1 (0, 3)	1 (0, 3)	10.533	.005*,†,‡
IV (habitual sleep efficiency)	1 (0, 3)	1 (0, 3)	1 (0, 3)	0.082	.959
V (sleep disturbances)	1 (0, 3)	1 (0, 3)	1 (0, 3)	0.368	.833
VI (use of sleep medication)	1 (0, 3)	1 (0, 3)	1 (0, 3)	0.844	.657
VII (daytime dysfunction over the last month)	1 (0, 3)	1 (0, 3)	1 (0, 3)	3.489	.175

* compare among the 3 groups.

† Infancy exposure vs no exposure.

‡ fetal exposure vs no exposure.

PSQI = Pittsburgh Sleep Quality Index.

II) than the infant exposure group and the non-exposure group ($F = 4.456$, $P = .012$). Furthermore, the infant exposure group had a significantly higher score in sleep duration (component III) than the fetal exposure group and the non-exposure group ($F = 4.831$, $P = .008$). The fetal exposure group also had a significantly higher score in sleep duration than the non-exposure group.

Our subgroup analysis further revealed that 12.5% of the subjects who experienced the earthquake in the 1st trimester had sleep disturbance vs 13.3% of those who had experienced the earthquake in the 2nd trimester and 17.9% of those who experienced the earthquake during 3rd trimester (Table 4). No statistically significant difference was observed in the rate of sleep disturbance among the 3 groups ($P > .05$).

3.3. CRHR1 gene polymorphism and sleep disturbance

CRHR1 rs110402 was detected in 69 subjects. Fifty (72.5%) subjects had genotype T/T while 19 (27.5%) subjects had genotype C/T and C/C. There was no statistically significant difference in the rate of sleep disturbance between subjects with genotype T/T (6.1%) and those with genotype C/T and C/C ($P > .05$). *CRHR1* rs242924 was detected in 555 subjects. Four hundred sixty two (83.2%) subjects had genotype A/A while 93 (16.8%) subjects had genotype A/C and C/C. Subjects with genotype A/A had a significantly lower rate of sleep disturbance (6.1%) than subjects with genotype A/C and C/C (14.0%; $P = .008$). Furthermore, *CRHR1* rs7209436 was detected in 552 subjects. Four hundred fifty (81.5%) subjects had genotype T/T;

Table 4

***CRHR1* genotypes and PSQI scores.**

Genotype	No. of subjects	PSQI score, n (%)		χ^2	*P*
		≥7	<7		
rs110402					
without C	50	6 (12.0)	44 (88.0)	0.029	.864
with C	19	2 (10.5)	17 (89.5)		
rs242924		28 (6.1)	434 (93.9)		
without C	462	13 (14.9)	80 (86.0)	7.094	.008
with C	93				
rs7209436					
without C	450	35 (7.8)	415 (92.2)	4.845	.028
with C	102	15 (14.7)	87 (85.3)		

CRHR1 = corticotrophin-releasing hormone receptor 1, PSQI = Pittsburgh Sleep Quality Index.

Table 5

Univariate analysis of risks of sleep quality.

	No. of subjects	PSQI scores, n (%)		χ^2	*P*
		≥7	<7		
rs7209436				4.845	.028
without C	450	35 (7.8)	415 (92.2)		
with C	102	15 (14.7)	87 (85.3)		
Frequent drinking (>2 times /week)				4.052	.040
No	469	41 (8.7)	428 (91.3)		
Yes	87	14 (16.1)	73 (83.9)		

102 (18.5%) subjects had genotype C/T and C/C. Subjects with genotype T/T had a significantly lower rate of sleep disturbance (7.8%) than subjects with genotype C/T and C/C (14.7%; $\chi^2 = 4.845$, $P = .028$).

3.4. Comparison of correlation between CRHR1 locus phenotype and individual PSQI score

CRHR1 rs110402 was detected in 69 subjects. Fifty (72.5%) subjects had genotype T/T, while 19 (27.5%) subjects had genotype C/T and C/C. There was no statistically significant difference in the rate of sleep disturbance between subjects with genotype T/T (6.1%) and those with genotype C/T and C/C ($P > .05$). *CRHR1* rs242924 was detected in 555 subjects. Four hundred sixty two (83.2%) subjects had genotype A/A while 93 (16.8%) subjects had genotype A/C and C/C. Subjects with genotype A/A had a significantly lower rate of sleep disturbance (6.1%) than subjects with genotype A/C and C/C (14.0%; $P = .008$). Furthermore, *CRHR1* rs7209436 was detected in 552 subjects. Four hundred fifty (81.5%) subjects had genotype T/T; 102 (18.5%) subjects had genotype C/T and C/C. Subjects with genotype T/T had a significantly lower rate of sleep disturbance (7.8%) than subjects with genotype C/T and C/C (14.7%; $\chi^2 = 4.845$, $P = .028$).

3.5. Independent risks of sleep disturbance

Our univariate analysis showed that rs7209436, rs242924 and frequent drinking (>2 times/week) were significantly different among subjects with and without sleep disturbance (Table 5). These significant variables were fed into multivariable logistic regression analysis. We found that persons who were exposed to the seismic stress had a more than 2-fold increase in the risk of sleep disturbance vs those who were not exposed to the event (OR = 2.081, 95% CI 1.070–4.064) (Table 6). Furthermore, subjects with rs7209436 genotype C had an approximately 2-fold increase in the risk of sleep disturbance vs those who were not genotype C (OR = 1.978, 95% CI (1.045–3.744). Frequent drinking (>2 times per week) was not a significant risk of sleep disturbance vs less frequent drinkers (OR = 1.883, 95% CI 0.950–3.373) (Table 6).

4. Discussion

There is growing evidence that human pathological behaviors may be originated from the interaction among genetic factors and antenatal and postnatal environmental factors. Early stress is a reliable predictor of abnormal sleep patterns and, at the same time, affects the circadian rhythm and steady state regulation.[8] Substantial evidence from animal studies suggests that sleep disturbance is associated with early stress. In pregnant mothers who are exposed to stress, both the HPA axis and the circadian rhythm of their babies will be disrupted.[1] Many symptoms associated with sleep disorders are partially attributed to psychosocial factors, but in most subjects, the origin of sleep problems still remains unclear.[16] Our study explored the possible link between abnormal sleep quality and early stress, *CRHR1* gene polymorphism and other risk factors using a cohort of subjects who had experienced Tangshan Earthquake as fetuses or infants vs those who did not experience the traumatic event.

Our study showed that infants and fetuses who were exposed to the earthquake had a significantly higher rate of sleep disturbance in adulthood than those who were not, suggesting that experiencing earthquake stress in infancy or the fetal period adversely affects sleep quality in adulthood. Prenatal and postnatal periods are the most critical and sensitive periods during the development of an individual.[17] Evidence from

Table 6

Logistic regression analysis of risks of sleep disturbance.

Independent variables	*B*	S.E.	Wals	df	*P*	OR	95% CI
Seismic stress							1.070~4.064
No	0.744	0.392	3.919	1	.028	1	
Yes						2.081	
rs7209436							1.045~3.744
without C	0.682	0.326	4.390	1	.036	1	
with C						1.978	
Frequent drinking (>2 times /week)							0.950~3.733
No							
Yes	0.633	0.349	3.285	1	.07	1	
						1.883	

preclinical studies indicates that the brain is particularly sensitive to remodeling by environmental factors: adverse early-life experiences, such as stress exposure or suboptimal maternal care, can have long-lasting negative consequences leading to "early-life programming" of individual health and diseases.[8]

Although there are limited studies on possible mechanisms of the potential relationship between stress events during pregnancy and disease risk, there is evidence that impaired negative feedback control of glucocorticoid on the HPA axis can alter the neurotransmission of glutamate and reduce the formation of hippocampal nerves in both prenatal and postnatal stress mice.[18] According to a study in mice and nonhuman primates by Flinn et al, the offspring who experience stress early in life tend to exhibit high HPA axis activities and at the same time show enhanced and prolonged HPA response to stress.[19] It will reduce the feedback inhibition of CRH, and at the same time extend plasma glucocorticoid effects on stress reaction.[20] In prenatal stress mice, CRH level is higher in the amygdala while glucocorticoid receptor and the mineralocorticoid receptor (MR) level is low in the hippocampus.[21] High stress reaction in its essence is considered to improve viability of adaptive prediction, and prepare for the particular range of acquired unpredictable environment stress behavior and neuroendocrine responses after enhancement, may reflect the individual more alert to environmental threats, even needed to adapt to the time is very long, it will also help the individual survival[22] although many experienced stress event no disease states, but chronic stress may be one of those susceptibility crowd cause this susceptibility might, in turn, depends on the activity of HPA axis continues to increase, which in turn will increase the susceptibility of offspring of various stress related diseases. In addition, the epigenetic process may be disturbed during the fetal and infant period due to seismic exposure.

The mothers of these exposed participants in our study experienced major stress in their pregnancy, and also many aftershocks, loss of loved ones, poor living conditions and scant psychological support during and after the traumatic event, all negatively impacting on brain development, health condition and disease generation in the offspring. There is evidence that early life stress is associated with various health problems in later life, such as increased stress response,[18] abnormal sleep quality such as abnormal wakefulness, and circadian rhythm disorder, mental disorders and behavioral disorders.[8] This study showed that the 3 groups differed significantly in component II (sleep latency) and component III (sleep duration) scores. Compared with the non-exposure group, the fetal exposure group had longer sleep latency, but shorter sleep duration. Davidson et al[19] found that postpartum stress experience was related to an individual's response to stress events in adulthood, and can lead to a variety of negative health outcomes in adulthood, including increased reactivity to stress and sleep disorder.[23] Emerging evidence from both animals and humans indicate that apart from environmental contributors to the development of insomnia, prenatal stress may also contribute to a predisposition for insomnia in humans.[24] Exposure to prenatal restraint stress heightened the responsiveness of the HPA axis to stress. Prolonged restraint stress can induce decreased feedback inhibition of CHR by increasing circulating glucocorticoids. In a rat prenatal stress model, sleep–wake cycle modification led to alterations in circulating glucocorticoids; rats had increased glucocorticoid after stress, as well was frequent awakening and circadian rhythm disorder, with prolonged sleep latency and shortened sleep duration.[8] Grammatopoulos et al[25] hypothesized that, in addition to glucocorticoids, other factors may be involved in the long-term effects of prenatal stress on sleep. As CRH is involved in the regulation of physiological waking by promoting it under both baseline conditions and stress conditions, CRH may act in inducing an increase in the activity of noradrenergic neurons in the locus coeruleus.[26] Thus, permanent neurochemical changes in the activity of the noradrenergic systems may participate in sleep modifications in prenatally stressed rats. Prenatal life experiences are thus associated with persistent changes in both modulation of the activity and the response of the HPA axis to stress with a tendency towards hyperactivity.[8] These conclusions may suggest that experiencing stress during pregnancy can lead to over-stress response in adults, which has a tendency to lead to sleep disorders.[8] Grammatopoulo et al[25] found that the 3rd trimester is a critical period for stress factors to affect fetal development. Maternal exposure to stressful events during late pregnancy would increase anxiety and depression-like behavior in their offspring, which are often associated with the appearance of sleep disorders. It suggest that both the gestational weeks of exposure to stress events and the age level of individuals exposed to stress events during the fetal period are important factors related to sleep disorders and mental illness.[27]

Our study also showed that individuals with *CRHR1* gene rs242924 and rs7209436 C genotype carriers had a significantly higher rate of sleep disturbance than those without C genotype while no significant difference was observed among *CRHR1* gene rs110402 genotypes. Some studies have indicated that the effects of CRH on sleep–wake control are mediated through CRHR1; specific CRHR1 antagonist can increase non-REM sleep in mice during recovery from sleep deprivation, suggesting that brain CRH is involved in non-REM sleep regulation through CRHR1.[8] However, CRHR1 antagonist restores impaired sleep patterns only if CRH stimulation occurs under pathophysiological conditions, such as severe acute or chronic stress, rather than under normal circumstances.[28] It has been shown that REM sleep is a fragile state and receives a more dominant influence than non-REM sleep when CRH is excessively produced in a particular part of the brain in mice after sleep deprivation.[29] These results underscore potential effects of central CRH on sleep through CRHR1. Gregory et al suggest that CRHR1 variation could modulate reactivity to stress, and that altered CRHR1 function would be associated with stress-related psychopathology, particularly anxiety, and depressive disorders. Many complex mental diseases, including depression and anxiety disorders, can be initiated by inadequate adaptation to stress.[21] Sleep disorder can be a clinical manifestation of both anxiety and depression: some patients begin with difficulty falling asleep, poor quality of sleep, lack of sense of sleep and other symptoms, which may explain the potential relationship between the different phenotypes of genetic polymorphisms of *CRHR1* and sleep disturbance in this study.

Our study found that alcohol consumption, as a risk factor for abnormal sleep quality, also affected sleep in various ways. The study of Ebrahim et al showed that alcohol consumption temporarily increased sleepiness, but later led to frequently waking up in the night and early morning.[30] People who drink too much often drink alcohol before going to bed to improve sleep. Many moderate drinkers also drink before bed if they suffer from insomnia,[31] and the result is a vicious cycle of insomnia and decreased sleep quality, increasing dependence on alcohol.

This study has several limitations. Information on exposure to earthquake stress was obtained through face-to-face interview

and based on recall, which may not be accurate and cause bias. In addition, confounding variables influencing the growth of the participants with sleep disturbance could not be distinguished. Sleep quality is affected by multidimensional factors, and these miscellaneous situations were not fully accounted for in the analysis. The blood samples of subjects who experienced early stress will be further investigated for indicators related to sleep issues in the future as we continue to seek to explore the correlation between early stress, gene polymorphism expression of *CRHR1* and various sleep phases such as sleep latency time and sleep duration. Overall, fetal or infant exposure to seismic stress leads to a significant increase in the rate of sleep disturbance in adulthood.

5. Conclusion

Prenatal and postnatal exposure to seismic stress significantly increases subsequent risk of sleep disturbance in adulthood. Furthermore, *CRHR1* gene polymorphisms affect the development of sleep disturbance and subjects with *CRHR1* rs7209436 genotype C is ata significantly greater risk of sleep disturbance vs those who are not genotype C. Our findings suggest that there is a complex interaction between early stressful events and genetic factors in determining the development of sleep disturbance in subsequent adult life.

Author contributions

YNC and CXA contributed to the conception and design of the study; RW, LW, MS, LLY and FFS performed the experiments, collected and analyzed data; YNC, CXA, XYW wrote the manuscript; All authors reviewed and approved the final version of the manuscript.

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References

[1] Talge NM, Neal C, Glover V. Antenatal maternal stress and long-term effects on child neurodevelopment: how and why? J Child Psychol Psychiatry 2007;48:245–61.
[2] O'Donnell K, O'Connor TG, Glover V. Prenatal stress and neurodevelopment of the child: focus on the HPA axis and role of the placenta. Dev Neurosci 2009;31:285–92.
[3] Strahm AM, Bagne AG, Rued HA, et al. Prenatal traumatic stress and offspring hair cortisol concentration: a nine year follow up to the Red River flood pregnancy study. Psychoneuroendocrinology 2020;113: 104579.
[4] de Weerth C, Zijl RH, Buitelaar JK. Development of cortisol circadian rhythm in infancy. Early Hum Dev 2003;73:39–52.
[5] Palagini L, Drake CL, Gehrman P, et al. Early-life origin of adult insomnia: does prenatal-early-life stress play a role? Sleep Med 2015; 16:446–56.
[6] Chopra KK, Ravindran A, Kennedy SH, et al. Sex differences in hormonal responses to a social stressor in chronic major depression. Psychoneuroendocrinology 2009;34:1235–41.
[7] Field T, Diego M, Hernandez-Reif M, et al. Sleep disturbances in depressed pregnant women and their newborns. Infant Behav Dev 2007; 30:127–33.
[8] Claes SJ. Corticotropin-releasing hormone (CRH) in psychiatry: from stress to psychopathology. Ann Med 2004;36:50–61.
[9] Foley P, Kirschbaum C. Human hypothalamus-pituitary-adrenal axis responses to acute psychosocial stress in laboratory settings. Neurosci Biobehav Rev 2010;35:91–6.
[10] Sakamoto K, Higo-Yamamoto S, Egi Y, et al. Memory dysfunction and anxiety-like behavior in a mouse model of chronic sleep disorders. Biochemical Biophysical Res Communications 2020;529:175–9.
[11] MacKinnon N, Kingsbury M, Mahedy L, et al. The association between prenatal stress and externalizing symptoms in childhood: evidence from the avon longitudinal study of parents and children. Biological Psychiat 2018;83:100–8.
[12] Simcock G, Cobham VE, Laplante DP, et al. A cross-lagged panel analysis of children's sleep, attention, and mood in a prenatally stressed cohort: The QF2011 Queensland flood study. J Affect Disord 2019;255: 96–104.
[13] Polanczyk G, Caspi A, Williams B, et al. Protective effect of CRHR1 gene variants on the development of adult depression following childhood maltreatment: replication and extension. Arch Gen Psychiatry 2009;66: 978–85.
[14] Sheng ZY. Medical support in the Tangshan earthquake: a review of the management of mass casualties and certain major injuries. J Trauma 1987;27:1130–5.
[15] Tsai PS, Wang SY, Wang MY, et al. Psychometric evaluation of the Chinese version of the Pittsburgh Sleep Quality Index (CPSQI) in primary insomnia and control subjects. Qual Life Res 2005;14:1943–52.
[16] Anstead M. Pediatric sleep disorders: new developments and evolving understanding. Curr Opin Pulm Med 2000;6:501–6.
[17] Maccari S, Krugers HJ, Morley-Fletcher S, et al. The consequences of early-life adversity: neurobiological, behavioural and epigenetic adaptations. J Neuroendocrinol 2014;26:707–23.
[18] Heim C, Binder EB. Current research trends in early life stress and depression: review of human studies on sensitive periods, gene-environment interactions, and epigenetics. Exp Neurol 2012;233:102–11.
[19] Davidson RJ, McEwen BS. Social influences on neuroplasticity: stress and interventions to promote well-being. Nat Neurosci 2012;15:689–95.
[20] Loman MM, Gunnar MR, Early Experience S, et al. Early experience and the development of stress reactivity and regulation in children. Neurosci Biobehav Rev 2010;34:867–76.
[21] Gregory AM, Caspi A, Moffitt TE, et al. Family conflict in childhood: a predictor of later insomnia. Sleep 2006;29:1063–7.
[22] Nevarez MD, Rifas-Shiman SL, Kleinman KP, et al. Associations of early life risk factors with infant sleep duration. Acad Pediatr 2010;10:187–93.
[23] Weinstock M, Poltyrev T, Schorer-Apelbaum D, et al. Effect of prenatal stress on plasma corticosterone and catecholamines in response to footshock in rats. Physiol Behav 1998;64:439–44.
[24] Munro A, Griffiths AB. Some psychiatric non-sequelae of childhood bereavement. Br J Psychiatry 1969;115:305–11.
[25] Grammatopoulos DK, Chrousos GP. Functional characteristics of CRH receptors and potential clinical applications of CRH-receptor antagonists. Trends Endocrinol Metab 2002;13:436–44.
[26] Marinesco S, Bonnet C, Cespuglio R. Influence of stress duration on the sleep rebound induced by immobilization in the rat: a possible role for corticosterone. Neuroscience 1999;92:921–33.
[27] de Kloet ER, Joels M, Holsboer F. Stress and the brain: from adaptation to disease. Nat Rev Neurosci 2005;6:463–75.
[28] Yang CK. Concise guide to evaluation and management of sleep disorders. Seoul: Hana Medical Publishers; 2001.
[29] Staner L. Comorbidity of insomnia and depression. Sleep Med Rev 2010;14:35–46.
[30] Ebrahim IO, Shapiro CM, Williams AJ, et al. Alcohol and sleep I: effects on normal sleep. Alcohol Clin Exp Res 2013;37:539–49.
[31] Park SY, Oh MK, Lee BS, et al. The effects of alcohol on quality of sleep. Korean J Fam Med 2015;36:294–9.