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Adverse childhood experiences and chronic pain in adolescent patients with depressive disorder: the mediating role of circadian rhythm disruption

Yumeng Jing[1], Li Tan[1] and Yanrong Wang[2*]

Abstract

Background There is growing evidence that adolescent patients with depressive disorder often experience somatic pain symptoms, but the evidence is inconclusive, and the underlying mechanisms are less known.

Methods From October 2023 to October 2024,a cross-sectional study of the participants were recruited 256 participants from the Mental Health Clinic of the General Hospital of Ningxia Medical University. Using Chinese version of Revised Adverse Childhood Experience Questionnaire, Adolescent Biological Rhythm Disorder Evaluation Questionnaire and the Numeric Rating Scale for Pain. Statistical analysis was performed using Pearson correlation and mediation analysis.

Results A total of 256 participants were enrolled in our study with a mean age of 15.65 ± 2.04 years. The majority of them were women (72.3%). Adverse childhood experiences and circadian rhythm disruption were significantly positively correlated with chronic pain. The mediation analysis showed that the circadian rhythm disruption of adolescent depressive disorder played a partial mediating role in adverse childhood experiences and chronic pain, and the mediating effect accounted for 25.51% of the total effect.

Conclusion In adolescents with depressive disorder, adverse childhood experiences could positively predict chronic pain, and circadian rhythms disruption had a partial mediating effect on adverse childhood experiences and chronic pain. Future research should expand the sample size and adopt longitudinal designs, and further exploring the mechanism of circadian rhythms disruption in adverse childhood experiences and chronic pain.

Keywords Depressive disorder, Adverse childhood experiences, Circadian rhythm disruption, Chronic pain, Mediation analysis

*Correspondence:
Yanrong Wang
ronger-2006@163.com
[1]Ningxia Medical University, Yinchuan 750004, China
[2]Mental Health Center, General Hospital of Ningxia Medical University, Yinchuan 750004, China

Introduction

Depressive disorder has become a mental health problem that seriously affects the physical and mental health and social function of adolescents.It is typified by a persistently depressed or low mood, and is frequently accompanied by diverse degrees of cognitive and behavioral alterations [1].According to a systematic review and meta-analysis of the prevalence of depressive disorder among adolescents worldwide, the annual prevalence of depressive disorder among adolescents aged 10–19 years is 8% [2], while the prevalence rate in China is 3% [3].Studies have shown that depressive disorder is one of the causes of morbidity and disability in adolescents aged 10–19 years [4], and tends to have its onset in adolescence [5].So it can be crucial for studying this group. Adolescent patients with depression are often accompanied by somatic pain symptoms, and chronic pain in childhood and adolescence has been shown to heighten risk for in adults [6].

Chronic pain is an unpleasant sensory and emotional experience associated with, or similar to, actual or potential tissue damage, persisting beyond three months [7]. Studies have shown that about 50% of patients with chronic pain have depressive disorders [8]. The meta-analysis suggested that 1 in 8 youth with chronic pain meet criteria for depressive disorder, adolescents with chronic pain have more severe depression symptoms compared with controls [9]. Depressive disorder and chronic pain is bidirectional, depressive disorder is a positive predictor of chronic pain development, and chronic pain increases the risk of depression, and the two overlap in the anatomical region of the brain [10]. A longitudinal study of pain and depression in Chinese adolescents showed that frequent headaches and other non-specific pain were significantly associated with an increased risk of depressive symptoms one year later [11].

Previous studies have shown that adverse childhood experiences can lead to chronic pain. Adverse childhood experiences (ACEs) are defined as exposure to potentially traumatic experiences before 18 years of age that could have long-lasting effects on health and well-being [12], such as emotional neglect, physical abuse and parental divorce, which may affect children's growth and are closely related to the occurrence of adolescent depression [13]. Experiences of ACEs increased the risk for depressive symptoms, the more the number of ACEs, the higher the incidence and severity of depressive symptoms [14]. The relevance of ACEs related to suicidal behaviors across multiple populations.As described in a systematic review and meta-analysis has shown that exposure to ACEs increases the risk of suicide behaviors in patients with affective disorders [15]. Similarly, another study showed that ACEs strongly increased the likelihood of suicidal behavior in patients with schizophrenia spectrum disorders [16]. Notably, meta-analyses showed that participants who experienced ACEs are around twice as likely to present chronic pain during adulthood [17]. Nelson recently introduced a novel conceptual framework for understanding the effects of ACEs on the development of childhood chronic pain, based on the biopsychosocial model of chronic pain [18].

ACEs may affect the circadian rhythm by reshaping the stress response pattern of the Hypothalamic - Pituitary - Adrenal axis(HPA axis). Circadian rhythm is a 24-hour periodic physiological behavior pattern regulated by the biological clock. By integrating key functions such as sleep-awakening, feeding, and body temperature, life can adapt to the Earth 's alternating day and night environment [19], which can also affect the occurrence and development of depressive disorders. Adolescent circadian rhythm disruption have been become a global public health problem [20], a study of more than 90,000 participants showed that circadian rhythm disruption has a worse mental experience and is associated with depressive disorders [21], the severity of symptoms follows a diurnal with an improvement in the evening hours [22]. ACEs and chronotype have been suggested to be connected through emotional imbalance [23]. Other work has corroborated these findings, reporting that a group of young women with higher ACE scores were more likely to be evening chronotypes compared to those with lower ACE scores [24]. There was a dose-response gradient between ACEs scores and sleep duration, reporting ≥ four ACEs had 3.10 and 2.13 times the risk for short-sleep and long-sleep duration compared to respondents reporting no ACEs in elderly populations [25]. Results of the logistic regression model evaluating the impacts of ACEs on insomnia indicated that students who reported only ACEs had 2.47 times the odds of receiving an insomnia diagnosis in the past year compared with students who reported no ACEs [26]. Therefore, there is association between ACEs and sleep duration and sleep rhythm. Circadian rhythm disruption play an important role in maintaining normal sleep-wake cycle, so ACEs may affect circadian rhythm disruption.

In addition, emerging evidence also suggests that chronic pain is regulated by circadian rhythm with puberty-associated chronic pain exacerbation mechanistically linked to delayed sleep-wake cycles [27]. Insomnia as a robust predictor of changes in chronic pain, which has a significant influence on chronic pain [28]. The suprachiasmatic nucleus secretes substances such as dopamine and cytokines to synchronize the circadian clocks in peripheral tissues and participate in the regulation of chronic pain [29]. A longitudinal study of 2676 adolescents showed that the late sleep phase at the baseline level also indicated an increase in chronic pain [30]. With the increase of the severity of depression, there is

a more obvious circadian rhythm disruption, which is aggravated with repeated depressive episodes [31]. These investigations imply the correlation between ACEs and circadian rhythm disruption and chronic pain.

In summary, ACEs and circadian rhythm disruption can have an impact on chronic pain, and circadian rhythm disruption can be affected by ACEs, Therefore, we propose a hypothesis that in patients with adolescent depressive disorder, chronic pain is related to ACEs and circadian rhythm disruption, which may be that ACEs lead to pain in patients through circadian rhythm disruption. This demonstrates a pathway from ACEs to chronic above and beyond ACEs' impact on circadian rhythm disruption. In clinical practice, cognitive behavioral therapy can improve negative thinking, so as to help individuals exposed to ACEs correct wrong cognition and form effective coping styles. However, this study takes into account that ACEs, as a traumatic event experienced in childhood [32], have a long-term persistent and irreversible impact on individuals, and the effect of psychological intervention is not significant. Therefore, the degree of chronic pain can be reduced alleviated by intervening the circadian rhythm disruption as an intermediary variable. Common methods for improving circadian rhythms include light therapy, sleep health education, time therapy, melatonin and hypnotic drug therapy [33]. Thus, the purpose of this study is to describe and analyze the mechanism of action between ACEs, circadian rhythm disruption and chronic pain in adolescent patients through the mediation analysis.

Materials and methods

Study design

A total of 256 Chinese adolescent participants with depressive disorder were enrolled in this cross-sectional study. The participants were recruited from the Mental Health Clinic of the General Hospital of Ningxia Medical University, which was conducted collected from 2023 to 2024. Clinical psychiatrists were responsible for patient recruitment and scale assessment, The participants with depressive disorders in Ningxia, China, aged between 10 and 19 years old. The research adopted the method of questionnaire survey, selected patients who met the diagnostic criteria of ICD-10 and evaluated by two psychiatrists holding the title of attending physician or above. During the study, all patients signed an informed consent form after a detailed explanation by the investigators. This study was reviewed and approved by the Ethics Committee of the General Hospital of Ningxia Medical University (approval number: 2023-G164) and was conducted in accordance with the Helsinki Declaration. Informed consent from all participants and their parents.

Data collection

The questionnaire was divided into two sections: sociodemographic characteristics and psychological health. The sociodemographic data included a list of variables generally associated with psychological distress in younger populations, including age, gender, education, income, residence status, class ranking, and others. The mental health questionnaire comprised the Childhood Adverse Experience Scale, the Adolescent Biological Rhythm Disorder Evaluation Questionnaire and the Numeric Rating Scale for Pain.

Measures

Adverse childhood experiences were measured using the Chinese version of Revised Adverse Childhood Experience Questionnaire(ACEQ-R), which is concise and easy to understand, and has good feasibility. It is a comprehensive tool for studying adverse childhood experiences before the age of 18, including 14 items such as physical abuse, emotional abuse, sexual abuse, emotional neglect, physical neglect, and parental separation/divorce. Each of the above items represents one ACE. The scale measured whether the subjects had the above adverse experiences and did not appear as'0'points. It is counted as '1'. The ACEQ-R total score of the individual was obtained by accumulating the scores of 14 items in the scale. The higher the total score, the more types of adverse experiences experienced [34].

Circadian rhythm was measured using the Adolescent Biological Rhythm Disorder Evaluation Questionnaire, including four dimensions of electronic product use, sleep rhythm, diet rhythm, and activity rhythm were determined, with a total of 29 items. The questionnaire developed in this study was based on Likert 's 5-level scoring criteria for the project. The options were evaluated according to'1–5 points ',with higher scores indicating better more severe biological rhythm disorder. Its Cronbach's alpha coefficient was 0.87, with good internal consistency [35].

Finally, the intensity of chronic pain was measured through the Numeric Rating Scale for Pain (NRS Pain), where 0 points indicated no chronic pain and 10 points indicated the most severe possible chronic pain. Among them,1–3 mild chronic pain (chronic pain does not affect sleep), 4–6 moderate chronic pain, 7–9 severe chronic pain (unable to fall asleep or wake up in sleep), 10 severe chronic pain [36].

Statistical analysis

SPSS version 27 was used for statistical description of the data. Descriptive statistics summarized the sociodemographic characteristics, presented as mean ± standard deviation (M ± SD) for continuous variables or percentages (%) for categorical variables.Harman's single-factor

Table 1 Socio-demographic characteristics

Variable		Cases(*N*)	*N*(%)/M(SD)
Age/years	-	256	15.65(2.04)
Gender	Male	71	27.7%
	Female	185	72.3%
Single child	yes	74	28.9%
	no	182	71.1%
residence	urban	228	89.1%
	rural	28	10.9%
Family situation	nuclear family	174	68.0%
	divorced single-parent families	44	17.2%
	reconstituted family	28	10.9%
	extended family	10	3.9%
Father's education level	junior high school and below	142	55.5%
	technical secondary school or high school	48	18.8%
	junior college or undergraduate	65	25.4%
	graduate student	1	0.40%
Mother's education level	junior high school and below	141	55.1%
	technical secondary school or high school	38	14.8%
	junior college or undergraduate	75	29.3%
	graduate student	2	0.80%
Class leaders	yes	65	25.4%
	no	191	74.6%
Class ranking	below average	118	46.1%
	average	55	21.5%
	above average	83	32.4%

test potential common method bias in the questionnaire data. Pearson correlation analysis examined the relationships between adverse childhood experiences, circadian rhythm disruption and chronic pain. The double check was entered into Excel, and the statistical software SPSS27.0 PROCESS v4.1 plug-in was used to analyze the mediating effect, and the Bootstrap method was used to test the mediating effect model.The statistical significance of the mediation analysis was analyzed using the bootstrap method, using 5000 bootstrap samples analyzed with a 95% confidence interval.Sex and age were included as covariates in the mediation analysis.A P value <0.05 was considered statistically significant (double-sided).

Results

Common method biases analyses

Harman single factor method was used to test the common method deviation of the questionnaire content. The results show that the number of common factors with eigenvalues greater than 1 is 14, and the variance interpretation rate of the first common factor is 17.318% (< 40% critical value), indicating that there is no serious common method bias problem in this study.

Table 2 Analysis of relationship

Variable	Adverse childhood experiences	Circadian rhythm disruption	Chronic pain
Adverse childhood experiences	**1**		
Circadian rhythm disruption	**.368****	**1**	
Chronic pain	**.262****	**0.244****	**1**

**$p<0.01$

Patient characteristics

The cross-sectional study involved 256 adolescent patients with depressive disorder, aged between 10 and 19 years, with an average age of (15.66 ± 2.04) years. Participants comprised 71 males (27.7%) and 185 females (72.3%), accounting for a large proportion of females. Most of the adolescent patients were non-only children, with a detection rate of 72.3%.For education distribution, 142 individuals had junior high school or below, accounting for 55.4% of the total number. It appears that the education level of parents of adolescent patients is mostly concentrated in junior high school or below. In population living, urban residents accounted for 89.1%, and rural residents accounted for 10.9%.Among them, most of the adolescent patients involved in this study did not serve as class cadres, accounting for 74.6%. Their academic performance was primarily in the middle and lower ranges, accounting for 46.1%. Baseline demographics are described in Table 1.

The correlation between adverse childhood experiences, circadian rhythm disruption and chronic pain

The average scores of childhood adverse experiences, circadian rhythm disruption and chronic pain in 256 adolescent patients with depressive disorder were (3.62 ± 2.15) points, (101.26 ± 18.04) points and (2.77 ± 2.54) points. respectively.The results of the Pearson correlation analysis showed that the ACEs of the respondents were significantly positively related with circadian rhythm disruption and chronic pain ($r = 0.368$, $p < 0.01$;$r = 0.262$,$p < 0.01$). Addtionally, chronic pain and circadian rhythm disruption were significantly related ($r = 0.244$, $p < 0.01$).The specific results are presented in Table 2.

Mediating effect analysis

To explore the internal mechanism of the significant positive impact of ACEs on chronic pain, the circadian rhythm disruption was further introduced into the structural equation model as an intermediary variable in the study. The Model 4 in the SPSS macro program Process v4.1 conducted the mediation analysis. According to the Bootstrap method provided by Hayes, the mediating role

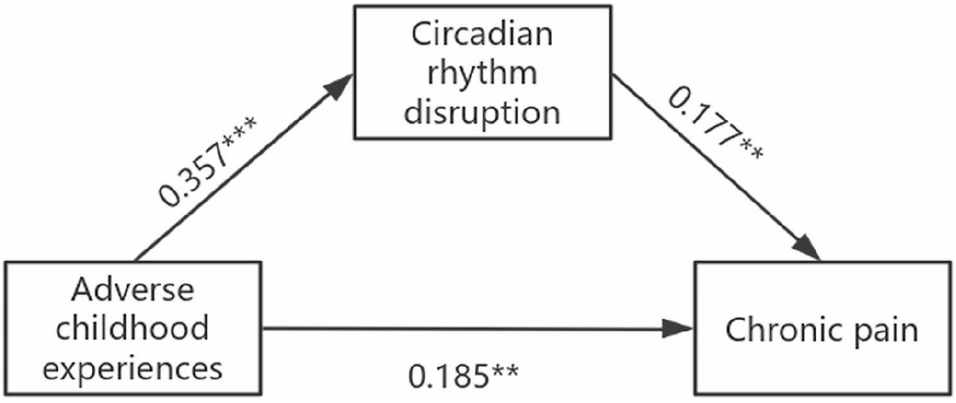

Fig. 1 The path relationship between circadian rhythm disruption in adverse childhood experience and chronic pain

Table 3 Mediation effect test table

	model fit indices			coefficient significance		
	R	R2	F	β	t	*p*
Adverse childhood experiences→circadian rhythm disruption	0.405	0.164	16.505	0.357	6.099	< 0.001
Adverse childhood experiences→chronic pain	0.274	0.075	6,790	0.248	4.026	< 0.001
Adverse childhood experiences→circadian rhythm disruption→chronic pain	0.318	0.101	7.05	0.185	2.835	0.005
				0.177	2.706	0.007

Table 4 Total effect, direct effect and mediating effect decomposition table

	Effect size	Se	LLCI	ULCI	Effective dose
Totol effect	0.294	0.073	0.150	0.438	
Direct effect	0.219	0.077	0.067	0.371	74.49%
Mediating effect	0.075	0.031	0.019	0.139	25.51%

of circadian rhythm disruption in ACEs and chronic pain was verified. In patients with adolescent depressive disorder, we used ACEs as independent variables, chronic pain as a dependent variable, circadian rhythm disruption as mediating variable, and gender and age as covariates. The results showed that ACEs significantly positively predicted circadian rhythm disruption (β = 0.357, t = 6.099, $p < 0.001$) and chronic pain(β = 0.185, t = 2.835, $p = 0.005$). Circadian rhythm disruption can positively predict chronic pain (β = 0.177, t = 2.706, $p = 0.007$). The path coefficient between ACEs and chronic pain in circadian rhythm disruption is shown in Fig. 1 and Table 3.

Mediating effect test

According to Table 4, The bootstrap test results revealed that the direct effect of the direct effect of ACEs on chronic pain of the 95% CI ranged between 0.067 and 0.371, and the interval did not contain 0.The Bootstrap test results of the mediating effect of circadian rhythm disruption between ACEs and chronic pain of the 95% CI ranged between 0.019 and 0.139, and the interval did not contain 0. The results suggested that both direct effect and mediating effect were statistically significant, indicating that the partial mediating effect model was established. It shows that adverse childhood experiences can not only have a direct effect on chronic pain, but also have a mediating effect on chronic pain through the variable of circadian rhythm disruption. The direct effect and mediating effect respectively accounted for 74.49% and 25.51% of the total effect.

Discussion

The results of this study found that the ratio of male to female in adolescents with depressive disorder was 1: 2.6,and similar to the results of Wang et al. [37]. The results of this study show that the highest education of parents of adolescent patients is mostly junior high school and below, suggesting that parents'education may be related to adolescent depression. We consider that parents'low education may be lacking in children 's education methods, which may lead to personality defects and eventually depression. This study also found that the detection rate of non-only children is slightly higher than that of the only child group, which may be due to the lack of attention to children caused by parents'energy dispersion or excessive family burden.

There is a certain relationship between depressive disorder and adverse childhood experiences, circadian rhythm disruption, and chronic pain. In this study, the score of participants'adverse childhood experiences was (3.62 ± 2.15) points, indicating that at least two adverse events were experienced in adolescents with depressive disorders. Adverse childhood experience is a high risk factor for depressive disorder. Adversity experiences in childhood can double the risk of depression, and DNA

methylation has become a potential way to explain the link between adversity and depression [38]. The score of circadian rhythm disruption was (101.26 ± 18.04) points, which was at a high level, indicating that circadian rhythm disruption was common in adolescents with depressive disorder. Adolescents are in the phase of awakening consciousness, facing academic pressure, peer pressure and social pressure. Under long-term stress, circadian rhythm disruption can occur and may act as a trigger for depressive disorder. Studies have shown that circadian rhythm disruption is an important pathophysiological way to cause depressive disorder [39], and the severity of depressive disorder is significantly positively correlated with circadian rhythm disruption [40]. The score of chronic pain was (2.77 ± 2.54) points, indicating that there was a certain degree of pain in the participants. Chronic pain is one of the symptoms of depressive disorder on clinical. The adrenergic and noradrenergic systems play a key role in both of them, which is an important biochemical basis for their co-existence [41].

The results of the correlation analysis of the study showed that there was a correlation between childhood adverse experiences, circadian rhythms disruption and chronic pain. Studies have shown that adverse childhood experiences are one of the root causes of chronic pain. Experiencing adverse childhood experiences can lead to dysfunctional threat detection, fear processing, and reward/counter-reward mechanisms, and ultimately lead to abnormal chronic pain perception in the body [42]. Reducing adverse childhood experiences would likely prevent cases of chronic pain in adulthood [43]. What's more, the occurrence of pain is affected by circadian rhythm, reaching a peak in the evening or night [44]. Circadian rhythms disruption can exacerbate chronic pain behavior, and chronic pain can in turn affect circadian rhythms [45]. It has been reported that the HPA axis is over-activated in adolescents who have experienced adverse childhood experiences, which leads to circadian rhythm disruption by regulating the HPA axis [46]. In contrast, chronic pain may change the circadian rhythm of the basic activity of the locus coeruleus by regulating [47]. In summary, there is an interactive and interrelated complex network among childhood adverse experiences, circadian rhythms disruption and chronic pain in adolescent patients with depressive disorder. The analysis that sought to better understand provided a new perspective for the exploration of chronic pain in adolescent depressive disorders.

The current study revealed the partial mediating role of circadian rhythm disruption in the relation between ACEs and chronic pain in adolescents with depressive disorder. Specifically, circadian rhythms disruption could not only directly affect chronic pain, but also affect chronic pain through circadian rhythms disruption. The prospective evidence indicates that bullying victimization in youth is more likely to lead to negative reported pain experiences [48]. A human study have shown that adverse childhood experiences are associated with more severe chronic pain levels, a dose-response association was observed between the cumulative number of ACEs and reports of chronic pain in 10-year-old children, suggesting that embodiment of ACEs starts as early as childhood [49]. Some ACEs are more closely related to possible chronic pain, and children with low economic status and mental illness in family members are more likely to have chronic pain [50]. We speculate that it may be the impairment of pain perception and processing ability of individuals with ACEs [51], which reduces the response threshold to pain. However, Some scholars believe that circadian rhythms can affect chronic pain systems, the rhythmicity of pain may be regulated by the central biological clock [52]. Microdialysis studies have shown that the extracellular glutamate concentration in the neostriatum is circadian, Nonetheless glutamate is an important neurotransmitter in the primary transmission of nociceptive information [53]. A review has shown that circadian rhythm disorders can directly lead to sleep fragmentation and slow wave sleep reduction, while sleep deprivation enlarges pain perception by reducing the cognitive control of pain in the prefrontal cortex and enhancing the emotional processing of pain in the amygdala [13].

In individuals with adolescent depressive disorder, in view of the fact that ACEs, as an event that has occurred, have high stability and are difficult to change directly through intervention, the findings of this study suggest that by improving the potential mediating factor of circadian rhythm disruption, it provides a feasible intervention target and practical path for relieving chronic pain. Since this study is a cross-sectional study, only investigates the relationship between ACEs and chronic pain of adolescent patients at one point in time, the results of the study reflect the relationship, rather than a clear causal relationship.So the present study not dynamically investigating the relationship between the two variables, we cannot rule out the possibility of reverse causality [54].

The results showed that the direct effect of ACE on chronic pain was 74.49%, and the mediating effect was 25.51%, indicating that there was a significant correlation between ACEs and chronic pain. About 20% of the effects were indirectly achieved through the mediating variable of circadian rhythms disruption, and its mediating effect played a role that could not be ignored. This result is consistent with the study of Zhao, whose bio-psychosocial model showed that psychological factors (such as neuroticism) and circadian rhythms together explain more than 60% of ACEs-chronic pain association [55], showed that ACEs will directly affect the degree of chronic pain in patients, and circadian rhythms disruption also plays

an indirect role in it. We believe that patients with circadian rhythm disruption tend to aggravate the impact of adverse childhood experiences on chronic pain. A study has shown that circadian rhythms can regulate pain by regulating opioid resistance [56]. We speculate that in the presence of adverse childhood experiences of adolescents, long-term in a chronic state of stress, sleep disorders will occur and thus undermine the body 's circadian rhythm, emotional problems and negative thinking resulting in excessive attention to the body to amplify pain signals.

This study is the first to explore the partial mediating role of circadian rhythm disruption in the relationship between ACEs and chronic pain among adolescent patients with depressive disorder. ACEs and circadian rhythm disorders can positively predict chronic pain. Based on the chronic pain caused by ACEs, circadian rhythm disruption further enhances the sensitivity to chronic pain and increases the degree of chronic pain. Therefore, regulating circadian rhythm may help to alleviate the severity of chronic pain and improve the prognosis for adolescent patients with depressive disorder.

Nonetheless, the limitation of this study may include the following aspects. First, this study comes from a cross-sectional study, and its causal relationship argument strength is insufficient. In the future, longitudinal studies are needed to track the time changes of ACEs patients from adolescence to adulthood. Second, the biological mechanism is unknown. In the future, it is necessary to verify the role of specific circadian rhythms disruption in ACEs and chronic pain through animal models to further refine the mechanism. Third, the sample of study is relatively small, and all individuals were recruited from a single site in Ningxia, China, which may limit the generalizability of our findings to other populations or regions. Thus a prospective study with large samples is warranted in the future.

Conclusion

Our study shows that there is a significant correlation among adverse childhood experiences, circadian rhythm disorders and chronic pain in adolescent patients with depressive disorder. Among them, circadian rhythms disruption play a partial mediating role in ACEs and chronic pain. Future research should expand the sample size and adopt longitudinal designs, and further explore the mechanism of circadian rhythms disruption in ACEs and chronic pain.

Abbreviations

ACEs	Adverse childhood experiences
ACEQ-R	Adverse Childhood Experience Questionnaire
NRS Pain	Numeric Pain Rating Scale Numeric Rating Scale for Pain

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None.

Authors' contributions

Yumeng Jing: Investigation, methodology, formal analysis, data curation, conceptualization, writing – review & editing, writing-original draft. Li Tan: Investigation, conceptualization, validation， writing-review & editing.Yanrong Wang: Supervision, project administration, conceptualization, writing – review & editing, funding.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The Ethics Committee of Ningxia Medical Universityrants the approval to carry out this study(2023-G164).Informed consent was obtained from all study participants and their parents.The study adhered to the Declaration of Helsinki.

Consent for publication

Study participants gave their verbal consent for publishing their data in this paper.

Competing interests

The authors declare no competing interests.

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