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Correlation Between Family Dysfunction and Nonsuicidal Self-Injury in a Sample of Chinese Adolescents: The Mediating Effect of Alexithymia and circRNA_103636

Shaoli Shi[1], Guangyao Li[2], Xiaoli Zhu[2], Lingming Kong[2]

[1]Psychiatry Department, The 5th People's Hospital of Luoyang, Luoyang, Henan Province, 471027, People's Republic of China; [2]Treatment & Prevention Center, No. 904th Hospital, Changzhou, Jiangsu Province, 213003, People's Republic of China

Correspondence: Lingming Kong, Treatment & Prevention Center, No. 904th Hospital, North Peace Road 55, No. 904th Hospital, Changzhou, Jiangsu, 213003, People's Republic of China, Email lingmk123@163.com

Background: Adolescent group may be prone to a variety of behavioral disorders, one of which is nonsuicidal self-injury (NSSI), NSSI intervention is limited for its unknown mechanism, so this study aimed to explore the factors associated with and pathological mechanism underlying NSSI from the perspective of family dysfunction, alexithymia, circRNA_103636 in a sample of Chinese adolescents.

Methods: A total of 200 MDD adolescents with NSSI and 200 healthy controls were enrolled via a convenient sampling method in clinical settings. The Family APGAR Index (APGAR), Toronto Alexithymia Scale (TAS-20), and Adolescent Nonsuicidal Self-injury Assessment Questionnaire (ANSSIAQ) were used for mental assessment of the study group and control group participants. Real-time quantitative reverse transcription PCR (qRT–PCR) was utilized to detect circRNA_103636 expression in peripheral blood mononuclear cells (PBMCs).

Results: There were significant between-group differences of 134 patients (67%) in the study group and 42 patients in the control group (21%) with moderate or severe family dysfunction ($P<0.01$). The APGAR score was lower, and the difficulty identifying feeling (DIF), difficulty describing feeling (DDF) and externally oriented thinking (EOT) scores of the TAS-20 and ΔCt value of circRNA_103636 were greater in the study group than in the control group. NSSI behavior and NSSI function were negatively correlated with the APGAR score and positively correlated with DIF, DDF, and the EOT of TAS-20 and the ΔCt value of circRNA_103636. Multiple regression analysis confirmed that EOT, circRNA_103636 expression, and APGAR were predictors of ANSSIAQ, which could explain 40.5% of the variance. Similarly, the alexithymia and circRNA_103636 expression mediated the correlation between family dysfunction and NSSI in the study group, and these mediating effects accounted for 27.25% and 23.33%, respectively, of the total effect. Taken together, family dysfunction, alexithymia, and circRNA_103636 expression have predictive effects on NSSI and alexithymia, circRNA_103636 expressions are mediators between family dysfunction and NSSI in Chinese adolescent.

Conclusion: Here, we established a new model for NSSI in which exposure to family dysfunction could induce pathological process by modulating personality traits and epigenetic regulators.

Keywords: nonsuicidal self-injury, family dysfunction, alexithymia, circRNA_103636, epigenetics

Introduction

Juvenile is a crucial stage of physical development and personality growth and is considered as a special period of "normative turmoil", "storm and stress", or "oscillations and oppositions" according to the theory of Rousseau–Stanley Hall. These teenagers are prone to a variety of behavioral disorders, one of which is nonsuicidal self-injury (NSSI). NSSI is defined as the intentional damage or destruction to bodily tissues in the form of cutting, burning, scratching, hitting by

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individuals with the intention of not committing suicide, which has a high incidence among countries around the world, NSSI is relatively more common than suicidal ideation and suicide attempts.[1,2] Individuals with NSSI often intentionally injures their tissues and organs with no purpose of suicide, which is unacceptable to the majority of the general public. As a further research field, NSSI was introduced into the diagnostic draft of the Diagnostic and Statistical Manual of Mental Disorders (5th Ed., DSM-5) and may become an independent mental disorder requiring additional attention.

NSSI has become a prominent global public health concern and a risk factor for future suicidal behavior, depressive disorders, and manic disorders among adolescents.[3–5] An investigation among 7072 Chinese adolescents suggested that 19.4% adolescents reported having ever NSSI over the past 12 months at baseline, and 8.8% reported having ever NSSI at 1-year follow-up and that NSSI was associated with maternal authoritarian parenting style and depressive symptoms.[6] Another study showed that depression played a complete mediating role between suicidal attitudes, frustrated interpersonal needs and NSSI.[7] These results indicate that depression is a predictor of NSSI. In addition, some other study reports have shown that NSSI is correlated with psychoactive substance abuse, bisexual or homosexual preference, gender dysphoria, which can further induce social problems, such as street violence, sexual crime, disease transmission, and drug abuse.[8,9] In one study by Wilkinson et al, NSSI was more prevalent in women aged 16–19 years, and the significant quadratic interaction between age and sex for NSSI incidence and general distress partially mediated the effects of age and sex on NSSI.[4] In recent years, researchers have strongly considered the effect of adverse childhood experience (ACE) on the pathological mechanism of NSSI. Teenagers in middle school with severe and moderate ACEs and abuse/neglect were more likely to commit NSSI than students with mild ACEs were, and adolescent girls had a greater probability of committing NSSI than boys at the same exposed level of ACEs were. Another study in a Japanese nationwide sample showed that 76.1% of methamphetamine users experienced at least one type of ACE before 18 years of age, and females reported more adversities than male controls. The top two ACEs were parental death or divorce and psychological abuse.[10,11] Kindler explored the immunological mechanism underlying the relationship between environmental stress and psychopathological development in female adolescents with NSSI and demonstrated that the absolute leukocyte count and leukocyte/cortisol ratio, which are also associated with childhood maltreatment and depression severity, were greater in the NSSI group than in the healthy control group.[12]

Exploration for the etiology and pathological process of NSSI has become a research focus worldwide, especially for the inseparable relationship between ACEs and NSSI. ACEs, including the loss of family involvement, social support, may impair individuals' emotion experience, emotion expression, emotion regulation, thinking style, and then result in a pragmatic thinking style, social avoidance, dissociation which are the basic features of alexithymia. As a personality trait characterized by difficulties in identifying or describing feelings and externally oriented thinking, alexithymia is often considered a transdiagnostic risk factor for a wide range of psychopathologies, including depression and anxiety.[13] Additionally, people who self-injure exhibit impaired negative emotional response inhibition and superior control over responses to stimuli related to self-injury,[14] that is, the emotion regulation model of NSSI implicates a deficit in controlling their mood and, in particular, in inhibiting unpleasant emotional reactions among people who self-injure. Childhood maltreatment can lead to emotion dysregulation (heightened emotional reactivity, rumination, attentional bias to threats), which can exacerbate and perpetuate poor physical and mental health throughout one's lifespan. Family dysfunction, including lack in family support, parental divorce, psychological maltreatment, and alienation, are considered as the main sources of ACEs; hence, the following hypothesis is proposed: Family dysfunction and alexithymia are related to adolescent NSSI, and alexithymia is the mediator between family dysfunction and NSSI.

In clinical practice, NSSI may exist independently or comorbid with borderline personality disorder (BPD), major depressive disorder (MDD). Some scholars have argued that NSSI, suicidal ideation, suicidal attempt, and suicidal behavior may indicate someone's attitude toward life and coping styles for stressors.[15,16] Recent epigenetic research deeply concern the interaction effects of exposure to environmental risk factors and heredity susceptibility in the development, therapeutic process, relapse of mental disease and multiple epigenetic mechanism (histone modification, DNA methylation, chromatin remodeling, noncoding RNA) have been confirmed by regulating gene transcription or translation, A new circular molecule (circRNA), as one type of noncoding RNA, is reported as a novel regulator in the pathological mechanism of MDD. More and more evidence showed that the circRNA for spatio-temporal specific in tissues and enriching in the brain was involved in various physiological and pathological processes, for example,

circRNA could concentrate in mammalian brain and nerve cell lines, most of which were up-regulated during nerve cell genesis and more significantly enriched in synapses than their linear transcripts, circRNAs produced by key disease-related loca were also involved in human disease processes.[17–21] Due to its special structure, circRNA, not only for its stability but also for the specific expression in the cell and plasma (including blood and saliva), can be served as a new potential marker for diagnosis.[22–25] one case–control study verified that expression level of has_circRNA_002143, has_circRNA_103636, has_circRNA_100679, has_circRNA_102802, has_circRNA_104953 in peripheral blood mononuclear cells (PBMCs) of MDD patients significantly downregulated and only expression level of has_circRNA_103636 upregulated after 8-week antidepressant treatment, it was argued that altered expression of has_circRNA_103636 in PBMCs is a potential biomarker for the diagnosis and treatment of MDD.[26] Moreover, there is a long tradition of examining cognitive processes as potential precursors of risk in suicide research accompanied by recent developments in NSSI research. Some previous studies have shown that self-injurious thoughts and behaviors are strongly associated with executive function, attention, memory, impulsivity, and intelligence, which can be predicted by the expression level of hsa_circRNA_103636 in PBMCs.[27,28] In recent years, investigations about the pathophysiology and potential biomarkers of neuropsychiatric disease have increasingly relied upon blood-based expression profiling of noncoding RNAs for gene expression was similar in whole blood and alterations in peripheral blood may mirror pathological processes in the brain.[29–31] Based on the common comorbidity of NSSI and MDD and empirical data about the impact of hsa_circRNA_103636 on disorders of cognition, behavior and emotion, this study proposed another hypothesis: has_circRNA_103636 may be aberrantly expressed in the NSSI group and mediate the relationship between family dysfunction and NSSI.

In summary, exploring the pathological process of human behavioral disorder from the perspective of epigenetics is a hot research topic in recent years, nevertheless, little is known about how the environmental stressors finally induce behavioral disorder, therefore, this study aimed to explore the etiology and pathological mechanism of NSSI in a way of family dysfunction, alexithymia, hsa_circRNA_103636 for providing a scientific basis for NSSI intervention and prevention in adolescents. The hsa_circRNA_103636 expression level in PBMCs was tested by Real-time quantitative reverse transcription PCR (qRT–PCR), and the psychological scales were employed for assessment of family dysfunction, alexithymia and NSSI.

Material and Methods

Participants

Study group. From Jan. 2020 to Oct. 2022, 200 adolescents aged 15 to 17 years, 112 males and 88 females were enrolled in clinical settings. The inclusion criteria were as follows: All the participants were the first visitors for clinical counseling and intervention and met the diagnostic criteria for nonsuicidal self-injury recommended in the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5).[5] Individuals who were in good health without physical disability, major physical disease or severe mental disorder history were also included. Patients who were orphans or whose parents were divorced, who were left-behind children or who had a diagnosis of chronic physical disease were excluded.

Control group. 200 adolescents with no history of major physical diseases or mental disorders, 102 males and 98 females aged 14 to 17 years, were enrolled in the healthy control group. Participants who were in good condition and had psychosocial functioning without obvious adjustment disorders, learning difficulties, interpersonal difficulties, bereavement, divorced parents, and left-behind experience were recruited.

The Clinical Trial Registration Number is ChiCTR-OOC-16007994.

Clinical Measures

In this study, Family APGAR Index, Toronto Alexithymia Scale, Adolescent Nonsuicidal Self-injury Assessment Questionnaire, with good psychometric property and common application in Chinese sample, were used for the assessment of family dysfunction, alexithymia and NISS.

Family APGAR Index (APGAR). The APGAR, which includes 5 dimensions—adaptation, partnership, growth, affection and resolve, is widely utilized in clinical research for evaluating family dysfunction. The APGAR is evaluated on a 3-point scale ranging from “0~2”, with a higher score indicating better family functioning and total scores ranging

from 7~10, 4~6, and 0~3 indicating good family dysfunction, moderate impairment, and severe impairment, respectively.[32] The Cronbach's α of the APGAR in this study was 0.846.

Toronto Alexithymia Scale (TAS-20). The TAS-20 comprises 20 items and is classified into three factors: difficulty identifying feeling (DIF), difficulty describing feeling (DDF), and externally oriented thinking (EOT). The scale is scored from 1 to 5, and a higher score indicates more severe alexithymia.[33] The Cronbach's α of the TAS-20 in this study was 0.714.

Adolescent Nonsuicidal Self-injury Assessment Questionnaire (ANSSIAQ). The 31 items of the ANSSIAQ were assigned to two dimensions: the behavior questionnaire (eg, NSSI behavior with and without obvious tissue damage) and the functional questionnaire (eg, selfish social interaction, negative self-reinforcement and emotional expression). The ANSSIAQ is a 5-point scale ranging from 0 ~ 4. The higher the score is, the more serious the NSSI.[34] The Cronbach's α of the ANSSIAQ in the present study was 0.766.

qRT–PCR Test for hsa_circRNA_103636 Expression Level in PBMC

PBMCs were first isolated from elbow vein blood of participants in the NSSI and control groups. Then, complementary DNA (cDNA) was synthesized by using a TaqMan microRNA Reverse Transcription Kit, and a circRNA fluorescence probe was synthesized by Invitrogen. qRT–PCR was performed with a TaqMan reagent kit. All the operations were carried out strictly in accordance with the instructions provided by the kit suppliers. With β-actin serving as a normalization control, the relative circRNA expression level was calculated by applying the formula $2^{-\Delta\Delta Ct}$ ($\Delta Ct=Ct_{cirRNA}-Ct_{\beta\text{-actin}}$). The higher the Ct value of a circRNA is, the lower the expression level.[26]

Statistical Analysis

SPSS20.0 was used for statistical processing. Descriptive statistical analysis, chi-square tests and t tests were performed to confirm the status quo of family functioning in the study group. Pearson correlation and multiple-regression analyses were used to investigate the associations between family dysfunction, alexithymia, and circRNA_103636 and NSSI in adolescents.

Results

Between-group comparison of the incidence of family dysfunction

According to the cutoff point of the APGAR,[32],134 patients (67%) in the study group had moderate or severe family function disorders, while 42 patients (21%) were in the control group, and there was a significant between-group difference ($\chi 2=42.94$, $P<0.01$).

Comparison of family function, alexithymia and ΔCt value of circRNA_103636 between the study and control group

The results of the independent sample *t* test showed that the APGAR score was lower and the DIF, DDF, EOT and ΔCt value of circRNA_103636 were greater in the NSSI group than their controls (P=0.000) (Table 1).

Correlation analysis of NSSI with family functioning, alexithymia, and the ΔCt value of circRNA_103636 in the study group

Table 1 Comparison of Family Function and Alexithymia Between Study Group and Control group ($\overline{X} \pm s$)

Factors	Study group (n=200)	Control group (n=200)	*t*	*P*
APGAR	5.14±2.59	7.73±1.42	−12.38	0.000
DIF	11.05±2.69	10.07±1.80	4.28	0.000
DDF	8.56±3.37	7.43±1.79	4.17	0.000
EOT	12.63±3.30	11.28±2.29	4.77	0.000
circRNA_103636	14.91±3.38	14.11±3.30	2.40	0.017

Pearson correlation analysis suggested that NSSI behavior and NSSI function were negatively correlated with the APGAR score and positively correlated with DIF, DDF, the EOT of the TAS-20 and the ΔCt value of circRNA_103636 (P<0.01) (Table 2).

Stepwise regression analysis for factors associated with NSSI in the study group

Stepwise regression analysis was conducted for factors associated with NSSI, and the results showed that EOT, circRNA_103636 expression, and APGAR had predictive effects on the ANSSIAQ score, which could explain 40.5% of the total variance in the ANSSIAQ score (P<0.01) (Table 3).

Mediating effect analysis of alexithymia and circRNA_103636 expression between family function and NSSI in the study group

Following the procedure of the mediating effect test proposed by Wen,[35] hierarchical regression analysis was employed to test the mediating effect of alexithymia and circRNA_103636 expression between family function and NSSI. The following three steps of regression analysis were performed: Step 1. The APGAR score was used as the independent variable, and the total ANSSIAQ score was used as the dependent variable. Step 2 The APGAR score was used as an independent variable, and the total TAS-20 score and circRNA_103636 were used as dependent variables. Step 3 APGAR and TAS-20, APGAR and circRNA_103636 expression were used as independent variables, and the total ANSSIAQ score was used as the dependent variable. The results showed that the APGAR score had a significant predictive effect on the total ANSSIAQ score (P=0.001), and alexithymia and circRNA_103636 expression partially mediated the associations between family function and NSSI and explained 27.25% and 23.33%, respectively, of the total effect (Table 4 and Table 5).

Table 2 Correlation Analysis of NSSI and Family Function, Alexithymia in Study Group (r)

Factors	APGAR	DIF	DDF	EOT	circRNA_103636
NSSI Behavior	−0.368**	0.492**	0.495**	0.597**	0.405**
NSSI Function	−0.355**	0.354**	0.369**	0.453**	0.443**

Notes: **P<0.05.

Table 3 Step-Wise Regression Analysis for Associated Factors of NSSI in Study Group

Dependent variable	Independent variable	Regression coefficient	Standard error	t	*P*	R^2
ANSSIAQ	EOT	1.858	0.275	6.752	0.000	0.405
	circRNA_103636	1.175	0.270	4.347	0.000	
	APGAR	−1.369	0.340	−4.022	0.000	

Table 4 Mediating Effect Analysis of Alexithymia Between Family Function and NSSI in Study Group

Steps	Dependent variable	Independent variable	Standard error	Beta	t	*P*
Step1	ANSSIAQ	APGAR	0.394	−0.368	−5.58	0.000
Step2	TAS-20	APGAR	0.078	−0.230	−3.32	0.001
Step3	ANSSIAQ	APGAR	0.361	−0.268	−4.43	0.000
		TAS-20	0.108	0.436	7.19	0.000

Table 5 Mediating Effect Analysis of circRNA_103636 Between Family Function and NSSI in Study Group

Steps	Dependent variable	Independent variable	Standard error	Beta	t	*P*
Step1	ANSSIAQ	APGAR	0.394	−2.195	−5.577	0.000
Step2	circRNA_103636	APGAR	0.090	−0.301	−3.337	0.001
Step3	ANSSIAQ	APGAR	0.374	−1.684	−4.508	0.000
		circRNA_103636	0.287	1.701	5.932	0.000

Abbreviations: NSSI, nonsuicidal self-injury; ACE, adverse childhood experience; PBMCs, peripheral blood mononuclear cells; APGAR, Family APGAR Index; TAS-20, Toronto Alexithymia Scale; DIF, difficulty identifying feeling; DDF, difficulty describing feeling; EOT, externally oriented thinking; ANSSIAQ, Adolescent Nonsuicidal Self-injury Assessment Questionnaire; qRT–PCR, Real-time quantitative reverse transcription PCR.

Discussion

A meta-analysis conducted by Han found that the NSSI incidence was 27.4% in middle school students in mainland China.[36] Previous studies have shown that, before NSSI commitment, adolescents often experience strong negative emotions, and the NSSI motivation is mostly to regulate, manage or express emotion. It is believed that NSSI is strongly associated with suicidal ideation, impulsivity and suicidal behavior under certain conditions.[37,38] This study explored the risk factors and pathological mechanism of NSSI from the aspects of family function, personality traits of alexithymia and epigenetic regulators of circRNA_103636.

First, the present study revealed that the incidences of moderate and severe family dysfunction (134 patients, 67%) and the DIF, DDF, and EOT scores were significantly greater, the APGAR score was lower in the NSSI group than in the healthy control group (42 patients, 21%). Pearson correlation and multiple-regression analyses for factors associated with NSSI suggested that APGAR score, DIF, DDF, and EOT had significant predictive effects on the total score on the ANSSIAQ, which could explain 37.4% of the variance. All these results indicate that there is more family dysfunction in the NSSI group than in the control group and that family function and alexithymia are predictors of adolescent NSSI. Family function is regarded as an interaction process of physical, affective and psychological activities among family members, through which the family as a whole communicates with other people and manipulates the social environment to solve life problems. Family function is closely related to personality modulation and social development and can further affect social adaptation, interpersonal strategies, stress coping styles, self-care, psychological resilience, gross motor function, activity, and participation, etc.[39–43] As a result, adolescents usually have difficulty adapting to social conditions characterized by low group status, lack of group belonging and lack of social support, and may become the target of campus bullying. In this adverse case, NSSI may become an extreme way for adolescents to gain affection concerns, seek peers' help, and increase self-identity and group acceptance. In addition, previous studies have suggested that family function, as a predictor of adolescent mental resilience and impulsivity, plays an intermediary role in family function and suicidal attitudes in middle school students.[44,45] These results indicate that poor family functioning can lead to difficulty in recovering from body function damage and stress-associated negative emotions and worsening emotional and behavioral impulsivity. NSSI is more likely to occur under these conditions. Alexithymia, as a personality trait, is described as an individual characteristic associated with defects, incompetence or insufficiency in emotion processing. The percentage of adolescents with alexithymia is approximately 7.3%~23.6%, and individuals with high alexithymia have more defects in emotional experience and emotional expression and are often unable to adopt effective coping strategies. These individuals tend to adopt psychological defense mechanisms related to maladaptation (eg, repression, regression, denial, etc). Several studies have shown that alexithymia can impair empathy ability, increasing the difficulty of accurately inferring the inner psychological process and content of others, communicating with other people and executing emotion reasoning; therefore, people with alexithymia usually fail to develop effective interpersonal relationships and establish social support systems. Affection repression and lack of social support may accompany adolescents' self-injurious behaviors.[14,15,46–49]

On the other hand, the ΔCt value of circRNA_103636 was greater in the NSSI group than in the control group, and NSSI behavior and NSSI function were positively correlated with the ΔCt value of circRNA_103636, which indicates that the circRNA_103636 expression level is also a predictor of NSSI. CircRNAs, single-stranded RNA transcripts with a closed loop structure, exhibit abundant expression, dynamic expression, backsplicing events, and spatiotemporal regulation in the human brain. Several previous studies have proposed that circRNAs play special roles in numerous neurological functions, such as neurotransmitter-associated tasks, neural cell maturation, and synapse functions.[50] Aberrant expression of circRNAs may induce brain dysfunction and structural alterations. It was found that adolescents with NSSI had significant alterations in cognitive EEG components associated with emotional processing during negative emotional face stimulation, particularly in EEG components of inhibitory control, and that there was a lateralization effect on emotional processing in the brain. Another study showed that external emotional regulation, significantly associated with decreased putamen volume, represented the main function of NSSI engagement.[51,52] The aforementioned pathological brain process may be the result of aberrant circRNA expression.

The test of the mediating effect of alexithymia between family function and NSSI in the NSSI group showed that the APGAR score could significantly predict the total ANSSIAQ score and that alexithymia partially mediated the association between family function and NSSI; moreover, the mediating effect could explain 27.25% of the total effect. These results indicate that family function can directly predict NSSI and indirectly predict it through alexithymia in adolescents. Previous studies in this field have shown that alexithymia, related to childhood trauma experience (eg, emotion abuse and neglect), can increase the difficulty of identifying feelings and externally oriented thinking. Repeated trauma exposure and family dysfunction in childhood may ultimately increase emotion regulation deficits by activating the hypothalamic–pituitary–adrenal axis and reversing the structural development process of the hippocampus and amygdala.[53–55] Emotion regulation deficits are often a core feature of alexithymia. The present study confirms the hypothesis that poor family functioning increases the risk of NSSI by inducing alexithymia.

The mediating effect test also showed that circRNA_103636 mediates the relationship between family function and NSSI, which means that family function may affect NSSI by altering the circRNA_103636 expression level. Family function, on the one hand, is usually considered a moderator between perceived stress and psychotic-like experiences; on the other hand, family dysfunction is a stressor.[56–59] Chronic unpredictable mild stress could downregulate the expression level of hippocampal circSYNDIG1, as a novel circRNA, circSYNDIG1 binding to miR-344–5p could attenuate depressive- and anxiety-like behaviors in mice. The severity of depressive symptoms was verified to be the only independent factor connected to both NSSI and suicide,[60,61] thus, long-term chronic stress associated with family functioning may change circRNA_103636 expression and further induce NSSI.

Several limitations need to be noted. One limitation of the present study is that it is a cross-sectional study from which we cannot determine the causal relationships among variables. Future studies with larger samples and longitudinal designs could provide more robust evidence and address these limitations. Another limitation is that the sample size is relatively small, which may have made the results susceptible to type II errors. However, these limitations are offset by several strengths. To the best of our knowledge, this is the first study exploring NSSI pathology from the perspective of exposure to family stressors, aberrantly expressed circRNA_103636, and alexithymia. These findings adequately verify the hypothesis about gene–environment interactions in the pathological process of human behavioral disorders; therefore, the results of this study could provide a link between risk factor exposure and epigenetic regulators or maladaptive personality traits and facilitate a deeper understanding of the pathophysiology of NSSI. As an initial study on the correlation between family function, alexithymia, epigenetic regulators (circRNAs) and NSSI in a group sampled from clinical settings, these findings highlight the urgent need to improve family function and develop health personality traits for the prevention or intervention of NSSI in adolescent populations. Finally, the results of this study combined with the existing literatures may not support the independence of NSSI from MDD for their shared pathological mechanisms.[26–28]

Conclusion

In summary, this study revealed that family function, alexithymia, and circRNA_103636 are predictors of NSSI in adolescents and that alexithymia and circRNA_103636 are mediating variables between family function and NSSI.

The present study established a new model for NSSI in which exposure to family dysfunction could induce pathological process related to NSSI by modulating personality traits and epigenetic regulators in an adolescent sample.

Ethics Approval and Informed Consent

The study was approved by the Ethical Review Committee for medical research in No. 904 Hospital (Approval number: 2019-2019-6-4) and conducted in accordance with the Declaration of Helsinki. All participants and their parents or Legal guardians provided written informed consent prior to enrollment.

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Disclosure

The authors report no conflicts of interest in this work.

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