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Psychotic symptoms in Chinese adolescent patients with major depressive disorder: prevalence and related endocrine clinical factors

Shiyu Sun[8†], Wei Jin[1†], Tianle Hou[1], Siyu Tong[7], Siyao Zhou[2], Lan Hong[1,3], Keqing Yao[4,5*], Ke Zhao[7*] and Tiansheng Zheng[6*]

Abstract

Objective Major depressive disorder (MDD) is often accompanied by psychotic symptoms. However, few studies have examined the relationship between psychotic symptoms and endocrine factors in adolescent patients with MDD. Therefore, this study aimed to investigate the prevalence and related endocrine clinical factors of psychotic symptoms in Chinese adolescent patients with MDD.

Methods In total, 601 patients (aged 12–18) with MDD were recruited. The Patient Health Questionnaire – 9 items (PHQ – 9) was utilized for assessing depressive symptoms. Psychotic symptoms were assessed through clinical interviews. Prolactin (PRL), thyroid-stimulating hormone (TSH), triiodothyronine (T3), free triiodothyronine (FT3), thyroxine (T4), and free thyroxine (FT4) were also measured.

Results The incidence of psychotic symptoms in adolescent patients with MDD was 22.6%. The findings demonstrated that age, self-harming behavior, PHQ-9 score, FT4, and normalized PRL were independently associated with psychotic symptoms in patients with MDD (All $p < 0.05$).

Conclusions PRL and FT4 levels are more likely to be abnormally elevated in major depressive adolescents with psychotic symptoms. Prolactin and thyroid hormones in patients with MDD should be paid more attention.

Keywords Major depressive disorder, Psychotic symptom, Prevalence, Prolactin, Thyroid hormones

†Shiyu Sun, Wei Jin these authors have contributed equally to this work and share first authorship.

*Correspondence:
Keqing Yao
KQKangning@gmail.com
Ke Zhao
cocozk1986@163.com
Tiansheng Zheng
sky.tsh@163.com
[1]School of Mental Health, Wenzhou Medical University, Wenzhou, China
[2]Zhejiang University, Hangzhou, China
[3]The Third Hospital of Quzhou, Quzhou, China
[4]Shenzhen Mental Health Center, Shenzhen, Guangdong, China
[5]Shenzhen Kangning Hospital, 77 Zhenbi Road, Pingshan District, Shenzhen, Guangdong, China
[6]The Affiliated Kangning Hospital of Wenzhou Medical University Zhejiang Provincial Clinical Research Center for Mental Disorder, Wenzhou, China
[7]Lishui Second People's Hospital, Wenzhou Medical University, Lishui, China
[8]Department of Mental Health, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua, China

Introduction

Major depressive disorder (MDD) is a prevalent mental disorder characterized by significantly diminished interest, depressed mood, and fatigue [1]. Psychotic symptoms, mainly hallucinations and/or delusions, frequently occur in all stages of MDD and are considered the distinct and the most severe subtype of MDD. Previous epidemiological studies have illustrated that 5.3–42% of patients with MDD exhibited psychotic symptoms [2–4]. The prevalence of psychotic symptoms was even higher among hospitalized patients with MDD. Patients with psychotic MDD presented more severe depressive symptoms, higher suicide attempts, worse disease duration, higher recurrence rates, greater social dysfunction, and worse response to depression treatment [2, 5, 6], suggesting that the co-occurrence of MDD and psychotic symptoms predicts poorer clinical outcomes. These psychotic symptoms (delusions and/or hallucinations) appear more commonly in children and adolescents than in adults [7, 8]. Therefore, in order delay the progression of severe illness and reduce the incidence of adverse outcomes, it is necessary to investigate the prevalence of psychotic symptoms in patients with MDD, especially among adolescents.

Hallucinations and delusions are common clinical psychotic symptoms of MDD. However, the mechanism of hallucinations and delusions was unclear. Some previous investigations suggested that psychotic symptoms were closely related to endocrine changes, such as the HPA axes. For example, recent research has focused on hyperprolactinemia in antipsychotic-free patients with first-episode psychosis [9–11]and patients with an at-risk mental state for psychosis [10]. Those finding revealed that compared with the normal control group, the patients diagnosed with first-episode schizophrenia and who have never used any antipsychotic drug have relatively elevated prolactin (PRL) levels. Abnormal level of PRL maybe associated with psychiatric symptoms, thus antipsychotic drugs which may induce increased PRL levels should be carefully selected while treating these patients [10]. It is worth noting that hyperprolactinemia (where serum levels of PRL are higher than the nor mal range) can be caused by many physiological processes which are common in patients with depression, such as psychological distress, sex, stress [12]. Therefore, hyperprolactinemia may be associated with psychiatric symptoms and depressive symptoms. Hyperprolactinemia may result in numerous unfavorable clinical outcomes such as irregular menses or amenorrhea, hypogonadism, subfertility, osteoporosis, and fracture risk [12, 13]. Hence, the consequences cannot be underestimated.

Meanwhile, the thyroid hormone was also believed to share a close relationship with psychiatric symptoms. Clinically relevant hyperthyroidism might manifest in people with psychotic symptoms, whereas hypothyroidism may cause mood symptoms that resemble negative symptoms of schizophrenia [14, 15]. Do people with MDD, who also have psychotic symptoms such as hallucinations and delusions, have similar mechanisms of psychotic symptoms resembling schizophrenia and involve similar abnormal level of endocrine levels?

The onset of psychotic symptoms in children or adolescents with depression or anxiety disorders may indicate a more severe course of an illness or more clinically important behavior, such as the possibility of suicidal thoughts or self-harm [5, 16, 17]. As we all know, adolescence is a period of rapid development, both physically and mentally. In this special period, thyroid hormones and PRL are crucial for early neurocognitive development and growth and development in childhood and adolescence [18, 19]. Simultaneously, adolescents are surrounded by many psychological stress problems, such as academic pressure, peer bullying, and parental relations [20, 21]. Studies have revealed that psychotic depression at the age of 12 is associated with poorer educational, occupational, and social outcomes at the age of 16–20 [22]. This means that adolescents with depression and psychiatric symptoms have more difficulty returning to society. Given the differences in age at onset and the incidence of psychotic symptoms, psychotic symptoms may play a different role in depression in adolescents than in adults [23]. Thyroid hormones and PRL are crucial for neurocognitive development and growth in early childhood and adolescence [18, 19]. However, the effects of psychotic symptoms on depressive symptom outcomes in adolescents have not been well studied, especially in the endocrine direction.

In conclusion, adolescent patients with MDD having psychotic symptoms face more difficulty achieving ideal treatment outcomes and may have more severe adverse outcomes. More importantly, they may have endocrine disorders similarly to schizophrenia. This hidden and undetected clinical condition can be quite dangerous, especially for adolescents who are undergoing necessary physical and mental development [18, 19, 24]. To reduce the incidence of adverse outcomes, it is crucial to investigate the relationship between psychotic symptoms and endocrine factors in patients with MDD, especially among adolescents. Therefore, this study will take Chinese adolescent patients as subjects to explore the incidence of psychotic symptoms in MDD and the related influencing factors.

This study hypothesized that significant differences were present in PRL and thyroid hormone between psychotic MDD and non-psychotic MDD groups. Moreover, PRL, thyroid hormone, and self-harming behavior were risk factors for psychotic symptoms of patients with MDD.

Methods

Subjects

This national multi-center and cross-sectional study was based on a cohort study of Chinese adolescent depression (CADC). The study proposal was approved by the Institutional Review Board (IRB) of the Shenzhen Kangning Hospital (IRB:2020-k021-02). The data was collected from January to December 2021. A total of 601 inpatients were recruited from the inpatient department of cooperative hospitals. The inclusion criteria of this study are as follows: (1) patients belonging to age group: 12–18 years; (2) patients meeting the criteria of the fifth edition of the Diagnostic and Statistical Manual (DSM-5) for MDD; (3) patients achieving the score of PHQ-9≥10; (4) the patients must have never received psychotropic medications (e.g., risperidone, paliperidone, among others) (5) years of education≥five years; (6) patients must be right-handed; and (7) Each participant obtained informed consent from their legal guardian before approving to participate in the study. Participants and their legal guardians received a full study description and voluntarily signed written informed consent. The exclusion criteria were as follows: (1) patients having complications from severe somatic diseases, infectious diseases, or immune system diseases, or have a previous history of the thyroid-related disease; (2) patients with brain trauma, epilepsy, or other known severe nervous system diseases or brain organic diseases; (3) patients having a previous history of severe mental disorders such as schizophrenia or mental retardation. After receiving informed consent for enrollment, all participants underwent comprehensive interview assessments conducted by two experienced psychiatrists. These assessments covered clinical diagnosis, the presence of psychotic symptoms, and details regarding the content and frequency of such symptoms. Prior to the study, all research team members at each center underwent identical training and passed a consistency test. Clinical diagnoses were made based on the observations and evaluations conducted during these assessments.

Demographic characteristics

The following demographic and clinical data of all patients were collected in this study: sex, age, years of education, and self-harming behavior. Self-harm was defined as the deliberate act of injuring one's own body, such as intentionally cutting the skin, hitting oneself, or biting. If participants self-reported engaging in self-harming behavior in the past year, and the frequency of such incidents was five or more, researchers identified the participant as having self-harm behavior. Otherwise, it be considered non-existent.

Clinical measurements

In this study, depressive symptoms were evaluated by the Patient Health Questionnaire – 9 items (PHQ – 9) [25], which has nine items and one function of general evaluation. The PHQ – 9 is recognized as an effective tool for assessing the depressive status of adolescents [26, 27]. PHQ-9≥10 is often used as the dividing point of major depression [28].

Psychotic symptoms were assessed through interviews by two experienced psychiatrists where each participant was questioned about the content and frequency of delusions (excluding delusions of grandeur) and hallucinations experienced in the past 7 days. In cases where responses were ambiguous, supplementary information was gathered from interviews with their family members or friends to reach a conclusion. Each item is rated on a five-point Likert scale: 0=never, 1=occur occasionally or suspiciously, 2=definitely present (with emotional background), 3=definitely present (without emotional background), 4=accompanied by hallucinations. To reduce false positive rates and ensure consistency in the study, patients were included in the psychotic symptoms group only if one of the symptoms, such as hallucinations or delusions, was clearly present (a score of 2 or more for any of these was considered positive).

Measurement of PRL and thyroid hormones

Fasting blood samples were collected at the sub-center between 6 a.m. and 8 a.m., centrifuged and stored in a -80℃ refrigerator. Finally, all blood samples were mailed to the headquarters of Shenzhen Mental Health Center. PRL, thyrotropin (TSH), triiodothyronine (T3), free triiodothyronine (FT3), thyroxine (T4) and free thyroxine (FT4) were determined in the headquarters.

Statistical analysis

The incidence of psychotic symptoms in patients with MDD was expressed as a proportion (percentage). The normal distribution of data was examined by the Shapiro-Wilk test. The t test and χ^2 test were used to compare demographic and clinical variables, which were normally distributed between psychotic MDD and non-psychotic MDD groups. Continuous variables of normal distribution are expressed as mean±standard deviation (M±SD). The ordered rank variables of non-normal distribution were described by median (lower quartile, upper quartile) and compared with the Mann-Whitney U test. PRL values analyzed on a continuous variable were first log-transformed (to accommodate positive skew) and then normalized for men and women separately based on the log-transformed reference ranges for healthy men and women. For this assay, the normal PRL range is 63.6–318mIU/L for males and 84.8–487.6mIU/L for females [29]. The means and SDs of the log-transformed

Table 1 Demographic and clinical variables in psychotic MDD group and non-psychotic MDD group

Characteristics	MDD without psychotic symptoms (*n* = 465, 77.4%)	MDD with psychotic symptoms (*n* = 136, 22.6%)	t/χ^2	*P*-Value
Age (years), M (SD)	14.77(0.08)	14.20(0.13)	3.923	< 0.001
Sex, (n, %)			1.602	0.206[a]
Female	382(82.2)	118(86.8)		
Male	83(17.8)	18(13.2)		
Education(years), M (SD)	9.10(0.08)	8.64(0.13)	2.801	0.005
Self-harming behavior, (n, %)			9.277	0.002[a]
No	136(29.2)	22(16.2)		
Yes	329(70.8)	114(83.8)		
PHQ-9 score, M (SD)	18.80(0.23)	21.16(0.38)	−5.035	< 0.001
TSH (mIU/L), M (SD)	2.12(0.10)	2.18(0.23)	−0.267	0.790
T3 (mIU/L), M (SD)	1.51(0.02)	1.69(0.03)	−4.123	< 0.001
FT3 (pmol/L), M (SD)	4.62(0.07)	5.01(0.07)	−4.091	< 0.001
T4 (pmol/L), M (SD)	73.96(1.57)	86.01(1.72)	−5.183	< 0.001
FT4 (pmol/L), M (SD)	10.73(0.23)	13.48(0.26)	−7.935	< 0.001
PRL (mIU/L), M (SD)	601.20 (26.98)	713.22 (46.84)	−2.002	0.045
PRL normalized, M (SD)	1.35(0.14)	2.23(0.17)	−3.992	< 0.001

Note: PHQ-9 = Patient Health Questionnaire-9; [a] Chi-square test for categorical variables

Table 2 Prolactin normalized in MDD with psychotic symptoms and without psychotic symptoms

	MDD with psychotic symptoms		MDD without psychotic symptoms	
	Men (*n* = 18)	Women (*n* = 118)	Men (*n* = 83)	Women (*n* = 382)
Prolactin normalized				
Mean ± SD.	1.57 ± 0.85	1.57 ± 0.29	-1.07 ± 0.46	−0.53 ± 0.20
Median	2.67	2.31	−0.79	−0.93
Range	−6.08–5.26	−11.70–5.82	−8.43–5.46	−9.30–6.83

SD, standard deviation

normative samples for men and women were calculated by taking the means of log-transformed upper and lower bounds of the reference ranges and dividing the differences between log-transformed upper and lower bounds of the reference ranges by 3.92, respectively. Thus, the normal sex difference in PRL observed in healthy individuals was partially removed from the continuous PRL measurement before inclusion in the models [30].

Binary logistic regression analyses (forward stepwise method) were conducted for risks related to adolescent MDD patients with psychotic symptoms, together with odds ratios (OR) and 95% confidence intervals (CIs), after controlling for the related variables. All statistical analyses were performed by SPSS version 26.0. A two-tailed *p*-value less than 0.05 was considered statistically significant.

Results

Demographic and clinical characteristics of patients with psychotic MDD and non-psychotic MDD

Table 1 shows that the percentage of the psychotic MDD study sample was 22.6% (136/601). More women (23.6%, 118 of 500) had psychotic symptoms compared to men (17.8%, 18 of 101). Significant differences were observed with respect to age ($p<0.001$), education ($p=0.005$), and PHQ-9 score ($p<0.001$) between psychotic MDD and non-psychotic MDD. The incidence of self-harming behavior in the psychotic MDD group (83.8%) was higher than that in the non-psychotic MDD group (70.8%). Additionally, there was no significant difference in TSH levels between patients with MDD who had comorbid psychotic symptoms and those who did not ($p>0.05$) (Table 1). However, TSH levels were slightly higher in the patients of the psychotic MDD group. The serum levels of FT3, FT3, T4, and FT4 in the psychotic MDD group were significantly higher than those in the non-psychotic MDD group (all $p<0.001$).

The analysis of PRL as a continuous variable (PRL normalized by sex) revealed that that PRL levels were significantly higher in patients having both MDD and psychotic symptoms than in those without psychotic symptoms ($p<0.001$). Table 2 depicts the mean and standard deviation of the normalized PRL values by group (patient/control) and sex (male/female).

Factors associated with psychotic symptoms of MDD

The binary logistic regression model was used to determine the relevant factors for psychotic symptoms in

patients with MDD. The results demonstrated that age (OR=0.820; 95%CI: 0.715–0.942), self-harming behavior (OR=1.986; 95%CI: 1.157–3.410), PHQ-9 score (OR=1.103; 95%CI: 1.053–1.157), normalized PRL (OR=1.220; 95%CI: 1.108–1.343), and FT4 (OR=1.215; 95%CI: 1.145–1.289) were independently associated with psychotic symptoms of MDD (Table 3).

Discussion

This is a large sample based clinical study to investigate the incidence of psychotic symptoms in Chinese patients (aged 12–18) with MDD, and to explore the association of psychotic symptoms with endocrine factors such as PRL and thyroid hormone. This cross-sectional study found that the prevalence of psychotic symptoms in patients with MDD was 22.6%. Normalized PRL and FT4, self-harming behaviors, and depressive symptoms might be the risk factors for psychotic symptoms in patients with MDD. This is basically consistent with our hypothesis.

Combined with previous epidemiological studies, there are some differences in the reported incidence of depression with psychotic symptoms. This may be due to factors such as the age range of participants, the severity of depression, and the method of assessment. First, adolescents with depression seem to be more likely to develop psychotic symptoms [8]. The prevalence of psychotic symptoms among MDD adolescents in this study was 22.6%, which is higher than among Chinese adults with major depression [31]. Second, the incidence of psychotic depression was much higher in the sample of patients with MDD. In a European study of patients who met the criteria for MDD, 18.5% also met the criteria for an episode of major depressive disorder with psychotic features [32]. By contrast, Xin et al. study found that the prevalence of psychotic features in depressed patients was about 9.2%, and it did not place a specific limit on the severity of depression [33]. Other previous studies have also reported that patients with psychotic symptoms have more severe depressive symptoms [34]. In addition, a previous study of MDD adolescents in China reported an incidence of up to 52% of psychotic symptoms. Their relatively broad definition of psychotic symptoms may be the main reason why the results are significantly higher than in other studies [35]. In summary, patients with MDD seem to have more psychotic symptoms, which should cause more clinical attention.

Patients with MDD and psychotic symptoms were more likely to report an earlier age of illness onset and have lower educational attainment than those without psychotic symptoms [2, 36]. This result is basically consistent with the findings of this study.

This study showed that the psychotic MDD group had a higher PRL level (PRL normalized by sex) than the non-psychotic MDD group. Although little evidence has been reported on PRL levels in patients with MDD and psychotic symptoms, the finding is agreed with previous research works that documented the positive correlations between PRL levels and psychiatric symptoms in adult patients with MDD and other prominent psychoses [37–40]. For instance, Asmahan Elgellaie's study on adult patients with MDD reported that the plasma PRL was associated with psychiatric symptoms, such as psychoticism, paranoid ideation, and hostility [40]. Furthermore, some studies were inconsistent with the finding of this study. An investigation of 18 inpatients with delusional depression and 22 with non-delusional depression found no difference in PRL levels between the two groups [41]. However, their sample size was small and similar results are rarely reported. Patients with MDD and psychotic symptoms have higher levels of PRL, especially adolescents, which may be caused by a series of physiological and psychological factors. Hormonal fluctuations during adolescence often cause higher stress levels in adolescents. Many authors have argued that enhanced PRL secretion in early psychosis may be secondary to the increased stress reactivity at the onset of psychosis [42, 43]. Stress activates the HPA axis, thereby stimulating the pituitary gland to release stress hormones such as ACTH [44, 45]. In contrast, PRL release is also enhanced in response to stressors against the damage caused by stress and inhibiting the HPA axis reactivity as a protective role [46, 47]. Different from drug-induced hyperprolactinemia, Riecher-Rössler et al. have suggested that increased levels of PRL could directly enhance dopamine

Table 3 Logistic regression analyses for factors related to psychotic symptoms in patients with MDD [a]

Variables	B	Waldχ^2	OR (95%CI)	*P*-value
Age	–0.198	7.944	0.820(0.715–0.942)	0.005
Self-harming behavior				
No	-	-	reference	-
Yes	0.686	6.190	1.986(1.157–3.410)	0.013
PHQ-9	0.098	16.775	1.103(1.053–1.157)	< 0.001
FT4	0.195	41.456	1.215(1.145–1.289)	< 0.001
PRL normalized	0.199	16.355	1.220(1.108–1.343)	< 0.001

[a] Variables in the model: (Age, Education, Suicide attempt, PHQ-9, normalized PRL, T3, FT3, T4, FT4)

Note: OR=odds ratio; CI=confidence interval

release by the feedback loop, thus triggering psychotic symptoms in patients [48, 49]. This result may explain why this study found that increased PRL was a risk factor for psychotic symptoms. However, some authors have suggested that no causal link may exist between PRL and the onset of psychiatric symptoms. Hyperprolactinemia could be just a simple stress-related phenomenon, and other stress-related hormones really play an essential role [42, 50]. Although the physiological importance of stress-induced PRL in psychotic depression remains unclear, considering the inflammation responses and cognitive impairment caused by hyperprolactinemia [51–53], more attention should be directed toward the side effects such as hyperprolactinemia in antidepressant–antipsychotic combinations therapies.

In this study, patients with MDD and psychotic symptoms had higher levels of T3, FT3, T4, and FT4 compared to those without psychotic symptoms. In addition, there was no significant difference in TSH levels between the two groups, which was inconsistent with previous studies [54]. Differences in thyroid levels at different ages may have contributed to the differences in inconsistent outcomes [55–57].There was no statistically significant difference between serum TT3 and TT4 levels in Chinese adult depression samples, and TSH level was considered to an independent risk factor for psychotic symptoms [31]. Based on hypotheses of previous research, TSH levels may increase the severity of psychotic symptoms and the risk of suicide in MDD through underlying mechanisms [58, 59], but our study did not verify this result (a positive correlation between TSH levels and psychotic symptoms). It is worth noting that a systematic review of thyroid hormones suggested that thyroid hormone levels, especially FT4 levels, seemed to correlate more strongly with clinical parameters than TSH levels [60]. This is basically consistent with our findings.

To date, only a limited number of studies explored the association between thyroid dysfunction and psychotic symptoms in patients with MDD, and the findings from these studies have been inconsistent. A recent Chinese study conducted in patients with MDD and psychotic symptoms found higher levels of T3 in female [61]. Yang et al. found increased FT4 level was negatively correlated with adolescence psychotic symptoms [35]. The inconsistencies in results could be attributed to variations in inclusion and exclusion criteria, methods of calculating thyroid hormone levels, and other related data across studies. The unique role of altered hormone levels during adolescence in adolescent-onset depression should be noted [62–64]. This study found that increased FT4 levels were independent risk factors for psychotic symptoms in patients with MDD. This result may be attributed to the fact that the thyroid hormone can promote the growth of dopamine neurons and increase dopamine synthesis [65–67], leading to psychotic symptoms such as hallucinations and delusions. In summary, the thyroid hormone may be a potential biological indicator to distinguish between non-psychotic MDD and psychotic MDD. The correlation between thyroid hormones and psychotic symptoms remains controversial. Future literature should further examine the possible relationship between thyroid levels and the development of psychotic symptoms in patients with MDD.

Several limitations are present in this study. First, psychotic symptoms should be assessed using a proprietary scale. In addition to examining the presence of hallucinations or delusions, additional psychopathological characteristics such as grandiosity, hostility, or excitement should be further explored in the future, which may imply different dimensions beyond psychotic depression (e.g., mixed properties). It was an important limitation that the Short Psychiatric Rating Scale (BPRS), the Psychiatric Depression Assessment Scale (PDAS) and the Hamilton Depression Scale (HAMD) were not be used in this study. In subsequent studies, we will be more rigorous and use more professional scales simultaneously to further improve accuracy and reduce limitations. Therefore, this study's findings should be considered preliminary because they need to be confirmed in other studies before making any definitive conclusions. Second, this study does not prohibit the use of antidepressants. The subjects in this study were patients with MDD, and the researchers did not prevent them from using antidepressants from the perspective of severe disease course and life safety, which may have affected this study's results. A long-term follow-up of patients with MDD should be conducted in the future. Third, the samples were the inpatients. Hence, this study's findings cannot be extended to other patients in different settings, such as outpatients and community patients. Finally, stress may be involved in endocrine disorders and psychiatric symptoms in patients with MDD and psychotic symptoms. Future studies should also assess individual perceived stress levels using, for example, the perceived stress scale [68].

In conclusion, this study found psychotic symptoms in approximately two out of ten patients with MDD, implying that psychotic symptoms are relatively common among patients with MDD in the adolescent population, especially among the youngest and less educated. More importantly, this study demonstrated that the levels of normalized PRL and FT4, self-harming behaviors, and depressive symptoms might be the risk factors for patients with MDD and psychotic symptoms. It is suggested that clinicians should pay more attention to the psychotic symptoms, thyroid function and PRL level in patients with MDD.

Abbreviations

MDD	Major depressive disorder
PHQ-9	Patient Health Questionnaire-9
PRL	Prolactin
TSH	Thyroid-stimulating hormone
T3	Triiodothyronine
FT3	Free triiodothyronine
T4	Thyroxine
FT4	Free thyroxine
CADC	A cohort study of Chinese adolescent depression
IRB	The study proposal was approved by the Institutional Review Board
OR	Odds ratio
CI	Confidence interval
SD	Standard deviation
CIs	Confidence intervals

Supplementary Information

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Supplementary Material 1

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Author contributions

SYS and WJ led the study design, and were the major contributor in writing the manuscript. KQY, KZ, TSZ, conceived the idea for the study. SYS, WJ, TLH, SYT, SYZ and LH analyzed and interpreted the patient data, and all co-authors critically revised the manuscript. All the authors approved the final version of the manuscript.

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Data availability

The data used and analyzed during the study are available from the corresponding author if the request is reasonable.

Declarations

Ethics approval and consent to participate

The study protocol was reviewed and approved by the Institutional Review Board (IRB) of the Shenzhen Kangning Hospital (IRB:2020-k021-02) before the research was carried out. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 200. Each participant obtained informed consent from their legal guardian before approving to participate in the study. Participants and their legal guardians received a full study description and voluntarily signed written informed consent.

Consent for publication

Not applicable.

Conflict of interest

The authors report no conflicts of interest in this work.

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