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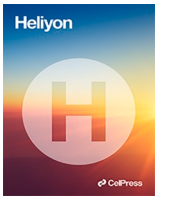

Association between thyroid function and psychotic symptoms in adolescents with major depressive disorder: A large sample sized cross-sectional study in China

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ABSTRACT

Backgrounds: Thyroid function was associated with depression and psychotic symptoms; however, little research has focused on its role in coexisting psychotic symptoms in adolescents with depressive disorder. This study aimed to explore the association between thyroid function and psychotic symptoms among depression adolescents.
Methods: A total of 679 adolescent patients (aged 12–18) diagnosed as depressive disorder were recruited. Their socio-demographic, clinical data and thyroid function parameters were collected. The severity of psychotic symptoms was measured according to the assessment measure in DSM-5. Based on the severity of psychotic symptoms, patients were distributed into psychotic depression (PD) and non-psychotic depression (NPD) subgroups, respectively.
Results: The prevalence rate of PD was 52.7% among adolescents with depressive disorder in this study. PD patients were younger ($p < 0.01$), with more female ($p < 0.001$) and non-Han nationality ($p < 0.01$), and presented serum FT4 level decrease ($p < 0.01$). PD patients displayed a higher rate of abnormal thyroid relevant parameters ($p < 0.05$). 35.2% of PD patients presented at least one abnormal parameter among all five parameters tested (TSH, TT3, FT3, TT4, and FT4), compared to 27.4% among NPD patients. Further logistic regression analysis indicated that increased serum FT4 level was a protective effect of PD with an adjusted odds ratio (OR) of 0.615. We did not find a statistically significant difference in the family history of mental disorders, serum TSH, TT3, FT3, and TT4 levels.
Conclusions: Our results suggested a high prevalence of PD among depression adolescents, associated with younger age, female, non-Han nationality, and decreased serum FT4 level. We recommend that adolescents with depressive disorder regularly screen their serum FT4 levels for better clinical outcomes.

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1. Introduction

Almost 40% of patients experience their first episode of depression before age 20 [1], which is one of adolescents' leading causes of illness and disability [2]. Some depression patients not only experience emotional dysfunction, but also display psychotic symptoms like delusion and hallucination. Those are referred to as psychotic depression (PD) [3]. Prior studies have reported high prevalence rate of PD among major depressive disorder (MDD) patients, ranging from 5.6% to 45% [4–9]. In addition to its high prevalence, PD patients present worse clinical outcomes than non-psychotic depression (NPD) patients [10]. Previous studies suggested PD patients experienced higher mortality rate than NPD patients [11–13].

Hormones in the hypothalamus-pituitary-thyroid (HPT) axis may influence the course of mental disease [14–16]. Patients with thyroid function disorder exhibit a high prevalence of depression [17,18]. Numerous large sample sized studies with participants from different cultural and ethnic backgrounds have demonstrated correlations between thyroid function, including hyper- and hypo-activity of thyroid function, and depression [19–21]. Moreover, thyroid hormone (TH)'s effects on depression were confirmed in animal experiments [22,23].

Researchers suggested that the copresence of psychotic symptomatology in depression is common and is functionally and etiologically highly relevant [24]. TH not only participant in the pathophysiology of depression, but also influence the development of psychotic symptoms. A recent review suggested strong evidence of abnormality in the HPT axis in schizophrenia patients, characterized by psychotic symptoms such as delusion and hallucination [25]. A 1983 review, a 2021 systematic literature review of published case reports [26], along with an Expert Opinion [27] suggest that both hypothyroidism and hyperthyroidism were associated with psychosis [28]. Ozten et al. reported that a Turkish woman exhibited delusional parasitosis after being diagnosed with hyperthyroidism, and the severity of delusion fluctuated depending on her thyroid function during protracted period of follow-up [29]. All those studies suggested both hyper- and hypoactivity of thyroid function may lead to psychotic symptoms.

Though many previous studies have respectively investigated links between thyroid function and depression and between thyroid function and psychotic symptoms, few studies have focused on TH's association with psychotic symptoms in depression patients. Moreover, existing studies reached no consistent conclusion due to the heterogeneity of subjects -such as age, and ethnicity- and the definition of PD. By exploring thyroid function's association with PD, we may further clarify thyroid's role in the development of psychiatric disease, contributing to early screening and intervention. In addition, the endocrine system presents different features throughout lifetime, and age may be a significant influence in thyroid function's role in depression with psychotic symptoms. Therefore, our study recruited 679 adolescents with depression from seven cities in China. The purposes of this study were to (1) investigate the association between thyroid function and psychotic symptoms in depression adolescents; (2) identify contributors that are significantly associated with psychotic symptoms in adolescents with depression.

2. Methods

2.1. Subjects

From January 2021 to December 2021, this cross-sectional study included 679 patients from 8 different hospitals in seven cities in China, including both outpatient and inpatient departments.

The study inclusion criteria were: (1) age between 12 and 18 years; (2) a diagnosis of depression based on the Diagnostic Interview of the Structured Clinical Interview for DSM-5 (SCID); (3) a score of $\geq$10 on the Patient Health Questionnaire-9 (PHQ-9); (4) with no less than 6 years of education. Exclusion criteria were: (1) having a severe physical disease; (2) prior diagnosis of psychiatric disorders; (3) anamnesis of neurological diseases.

All participants were voluntarily recruited and signed a written informed consent before enrollment. The medical ethics committee at Suzhou Guangji Hospital (2021-012) approved this study.

2.2. Socio-demographic characteristics

Socio-demographic characteristics including age, sex, ethnic group and family history of mental disorders were collected by well-trained researchers.

2.3. Clinical measures

Subjects were interviewed by qualified psychiatrists via the Diagnostic Interview of the Structured Clinical Interview for DSM-5 (SCID-5). Information of patients from outpatient department were collected when admission, while inpatients' were collected within 24 h after hospitalization. Their psychotic symptoms were measured by an interview, by asking each participant about their content and frequency of delusion (delusion of grandeur was excluded) and hallucination in the past 7 days. If their answers were not clear, additional information was obtained by interviewing their family members or friends to draw a conclusion. Based on the collected information, delusion and hallucination were rated according to Clinician-Rated Dimensions of Psychosis Symptom Severity in DSM-5. For the analyses reported here, depression patients rated 0 (both delusion and hallucination were not present) were divided into NPD, while patients rated 1–4 (with any of the two psychotic symptoms equivocal or more severe) were divided into PD group.

2.4. Blood sample

After overnight fasting, participants' blood sample collection was done by study investigators during the morning hours. The hospital laboratory centers were responsible for measuring serum levels of thyroid stimulating hormone (TSH), total triiodothyronine (TT3), free triiodothyronine (FT3), total thyroxine (TT4), and free thyroxine (FT4). According to reference ranges in different hospitals, those five biochemical indicators were divided into decrease, normal, and increase.

2.5. Statistical analysis

Group differences in socio-demographic and clinical characteristics between PD and NPD groups were compared using analysis of variance (ANOVA) for continuous variables, chi-squared test and Fisher's exact test for categorical variables. Continuous variable was expressed as mean ± standard deviation and absolute numbers (percentages) were used to describe those categorical variables. After controlling for demographic and clinical characteristics, a multivariate binary logistic regression analysis was performed, in which psychotic symptoms were used as dependent variable and age, sex, ethnic group, family history of mental disorders, TSH, TT3, FT3, TT4 and FT4 were used as independent variables, to assess the factors associated with PD. In addition, we used Spearman correlation coefficients to examine the correlations between PD and thyroid function. Statistical analysis was computed using SPSS 23, and statistical significance was accepted as $p < 0.05$.

3. Results

3.1. Socio-demographic and clinical characteristics

As shown in Table 1, a total of 679 participants (average age 14.55y) met the inclusion criteria. Among them, 321 (47.3%) met the criteria for NPD and 358 (52.7%) were PD. Compared with NPD, PD patients were younger, with more female, non-Han nationality

Table 1
Socio-demographical and clinical characteristics of the participants.

Variable	NPD (N = 321)	PD (N = 358)	$\chi 2/F$	*P*
Socio-demographic characteristics				
Age, mean ± SD, y	14.75 ± 1.61	14.37 ± 1.57	9.439	<0.01**
Sex			13.501	<0.001***
Male, N (%)	85 (26.5%)	54 (15.1%)		
Female, N (%)	236 (73.5%)	304 (84.9%)		
Ethic group			8.292	<0.01**
Han nationality, N (%)	287 (89.4%)	292 (81.6%)		
Non-Han nationality, N (%)	34 (10.6%)	66 (18.4%)		
Family history of mental disorders			1.226	0.296
Yes, N (%)	19 (5.9%)	29 (8.1%)		
No, N (%)	302 (94.1%)	329 (91.9%)		
Biological indicators				
TSH			0.271	0.891
Decrease, N (%)	5 (1.6%)	5 (1.4%)		
Normal, N (%)	302 (94.1%)	340 (95.0%)		
Increase, N (%)	14 (4.4%)	13 (3.6%)		
TT3			3.762	0.152
Decrease, N (%)	6 (1.9%)	10 (2.8%)		
Normal, N (%)	314 (97.8%)	342 (95.5%)		
Increase, N (%)	1 (0.3%)	6 (1.7%)		
FT3			1.864	0.437
Decrease, N (%)	1 (0.3%)	2 (0.6%)		
Normal, N (%)	310 (96.6%)	338 (94.4%)		
Increase, N (%)	10 (3.1%)	18 (5.0%)		
TT4			1.493	0.622
Decrease, N (%)	25 (7.8%)	26 (7.3%)		
Normal, N (%)	296 (92.2%)	330 (92.2%)		
Increase, N (%)	0 (0.0%)	2 (0.3%)		
FT4			13.845	<0.01**
Decrease, N (%)	18 (5.6%)	51 (14.2%)		
Normal, N (%)	280 (87.2%)	283 (79.1%)		
Increase, N (%)	23 (7.2%)	24 (6.7%)		
TSH, TT3, FT3, TT4, FT4			4.748	<0.05*
All normal	233 (72.6%)	232 (64.8%)		
At least one of them abnormal	88 (27.4%)	126 (35.2%)		

NOTE: psychotic depression (PD); non-psychotic depression (NPD); SD: standard deviation; TSH: thyroid stimulating hormone; TT3: total triiodothyronine; FT3: free triiodothyronine; TT4: total thyroxine; FT4: free thyroxine; TSH: thyroid stimulating hormone; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

people, serum FT4 level decreased and displayed a higher rate of abnormal thyroid relevant parameters (patients experienced abnormal thyroid relevant parameters, but did not meet the diagnostic criteria of specific thyroid function disease). 35.2% of PD patients presented at least one abnormal parameter, compared to 27.4% among NPD patients. No statistically significant difference was observed in family history of mental disorders, serum TSH, TT3, FT3, and TT4 levels.

3.2. Factors associated with PD

Correlation between psychotic symptoms and age ($r = -0.117$, $p < 0.01$), sex ($r = 0.141$, $p < 0.001$), ethic group ($r = 0.111$, $p < 0.01$) and serum FT4 level ($r = -0.112$, $p < 0.01$) were significant in depression adolescents in this study (Table 2). Multivariate binary logistic regression showed that age (OR = 0.902; 95%CI:0.817–0.996), ethic group (OR = 1.729; 95%CI:1.087–2.751), sex (OR = 1.711; 95%CI:1.146–2.550) and serum FT4 levels (OR = 0.615; 95%CI:0.413–0.916) were associated with PD (Table 3).

4. Discussion

Our study revealed that the prevalence of PD in this large-sized adolescent depression sample was 52.7%. Compared with NPD, PD patients were younger, with more female, non-Han nationality people, serum FT4 level decreased and displayed a higher rate of abnormal thyroid relevant parameters. We did not find statistically significant difference in family history of mental disorders, serum TSH, TT3, FT3 and TT4 levels. Further logistic regression analysis showed that younger age, female, non-Han nationality and lower serum FT4 level were associated with PD, suggesting that these parameters may be important risk factors associated with PD.

In our present study, the prevalence of PD in adolescent depression patients was 52.7%. Hitherto, prior studies have reached inconsistent prevalence rate of PD among MDD patients, ranging from 5.6% to 45% [4–9]. The primary reason for the discrepancy of different studies may result from the different definitions and group divisions of PD and NPD. In our study, only depression patients presented neither hallucination nor delusion were defined as NPD, while with either or both of the suspicious psychotic symptoms were characterized as PD, which may lead to a higher prevalence rate of PD than in studies with stricter inclusion criteria of PD. While employing a similar definition of PD, our result comes close to a study conducted among Canadian adolescents with depression, whose PD prevalence rate was 45% [5]. A systematic review demonstrated PD prevalence rate of 42% among MDD inpatients [4], much higher than 19% in outpatients. This may suggest that the severity of depression, since inpatients' illness states are normally more severe than outpatients', could influence prevalence of PD. This may partly account for the high prevalence rate in our study, as the participants included in our study not only met the diagnostic criteria of DSM-5, but also with PHQ-9 scores $\geq$10 [30], implying their more severe depression. In addition, age heterogeneity of participants enrolled may partly account for the higher prevalence rate in our study. However, studies focused on PD adolescents were fairly rare. Adolescents may present a higher risk of experiencing PD than the general population [24].

In our present study, PD and NPD presented different socio-demographic characteristics regarding age, sex and ethnic group. Our present study suggest that PD patients were younger, which is consistent with several prior studies [4,9,24]. Besides, our study suggested female a risk factor for PD, which is consistent with several previous studies. For instance, Johnson et al., Qi et al. and Ohayon, and Schatzberg reported a higher prevalence of PD among female depression patients through large sample sized study in the United States, China and Europe, respectively [9,31,32]. The sex difference may result from different insular region in male and female [33] and their endocrine system with sexual distinction. However, there are still discrepancies. For instance, Wigman et al. found that male is associated with PD [24], suggesting further exploration in this area. In our study, non-Han nationality served as a risk factor for PD compared to Han nationality. Several studies have corroborated different disease distributions among various ethnic groups [34,35]. As people of different ethnic groups are various in terms of genes, cultural backgrounds, diets, etc., all of these may influence the development of PD. Moreover, family history of mental disorder was not an influential factor of PD in our present study. A 2018 systematic review revealed that previous studies disagreed on the influences of family history of different psychiatric illnesses on PD

Table 2
Correlation analysis between psychotic symptoms, TSH, T3, FT3, T4 and FT4 in adolescent depression patients.

Variable	Psychotic symptoms	Age	Sex	Ethic group	Family history of mental disorders	TSH	TT3	FT3	TT4	FT4
Psychotic symptoms	1	−0.117	0.141	0.111	0.042	−0.012	0.012	0.040	0.019	−0.112
Age	0.002**	1	−0.193	−0.092	−0.030	−0.030	−0.028	−0.062	0.042	0.089
Sex	0.000***	0.000***	1	0.118	0.026	0.040	0.023	−0.085	0.053	−0.128
Ethic group	0.004**	0.017*	0.002**	1	−0.082	0.026	−0.152	0.027	−0.074	−0.098
Family history of mental disorders	0.269	0.441	0.499	0.032*	1	−0.005	0.051	0.006	−0.075	0.036
TSH	0.747	0.432	0.302	0.494	0.887	1	0.042	−0.019	−0.063	−0.114
TT3	0.764	0.469	0.550	0.000***	0.183	0.273	1	0.088	0.220	0.053
FT3	0.299	0.108	0.028*	0.490	0.873	0.627	0.022*	1	0.097	0.048
TT4	0.614	0.279	0.164	0.055	0.050*	0.101	0.000**	0.012*	1	0.152
FT4	0.004**	0.020*	0.001**	0.011*	0.351	0.003**	0.168	0.212	0.000***	1

NOTE: *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Table 3
Multivariate binary logistic regression for factors associated with psychotic symptoms in depression.

Variable	β	Odds Ratio	95% Confidence Interval		P
			Lower	Upper	
Age	−0.104	0.902	0.817	0.996	<0.05*
Sex	0.537	1.711	1.146	2.550	<0.01**
Ethic group	0.548	1.729	1.087	2.751	<0.05*
Family history of mental disorders	0.416	1.515	0.817	2.809	0.187
TSH increase	−0.269	0.764	0.392	1.489	0.429
TT3 increase	0.167	1.181	0.487	2.865	0.712
FT3 increase	0.423	1.526	0.708	3.289	0.281
TT4 increase	0.264	1.302	0.707	2.396	0.397
FT4 increase	−0.486	0.615	0.413	0.916	<0.05*

NOTE: *p < 0.05; **p < 0.01.

[4], which may result from inconsistent levels and methods of mental family history collection in various studies.

In our study, serum TT3 and TT4 levels presented no statistically significant difference between PD and NPD patients. This may be account for the different clinical significance between free and total TH. More than 99% of TH molecules are tightly bound to the carrier proteins, thyroid binding globulin (TBG), transthyretin and albumin. At the same time, only a tiny percentage circulates as free hormones, which act on target tissues by binding onto thyroid receptors in the nuclei of target cells [36]. Thienpont et al. suggested that the biological effect and supply of TH to the cells are governed by the non-protein-bound part [37]. Therefore, TT4 and TT3 levels may be less accurate in reflecting thyroid function than FT4 and FT3 level.

It is worth noting that in this study, we found that increased FT4 level was negatively correlated with adolescence PD. Though many studies explored TH's association with psychotic symptoms [25,28,29,38,39], few were conducted among PD patients. Existing researches elucidated association between hypothyroidism and more frequency of coexisting psychotic phenomenology in depression [40,41], consistent with our study. As we have discussed above, free TH play as the active form, presenting stronger affinity to TH receptor and more accurate reflection of thyroid function. TH could influence PD in several ways. First, fluctuation of TH can influence regional cerebral glucose metabolism [42] and glioendocrine system [43], leading to changes in brain function. Second, TH affects catecholaminergic system and brain serotonin (5-HT) system [44], both of which are significant to the development of psychotic symptoms. Third, an enhanced secretion of cortisol led by a hyperactive HPT axis in PD patients may lead to thyroid dysfunction [45]. However, no statistically significant difference was observed in FT3, which also belongs to free TH. This may result from the FT3's different distribution and biological characteristics from FT4's. In some tissues, such as the brain, FT3 acts locally. However, in our study, we only collected serum FT3 level rather than brain FT3 level. Thus, serum FT3 levels may not reflect the actual amount of intracellular FT3 in the brain, which strongly correlates with psychological pathology [46]. Moreover, FT3 presented a shorter half-life than FT4, which may lead to less testing stability.

In our present study, serum TSH level presented no statistically significant difference between two subgroups. However, correlations between psychotic symptoms and TSH were delivered by previous studies [7,47–51]. Several reasons may account for the discrepancy. Firstly, the distinctive condition of our participants' dopamine system and its influences towards pituitaty gland may explain our results [52]. Subjects in those studies above only experienced psychosis rather than both psychotic symptoms and depression as in our study. Dopamine neurotransmission is significantly related to psychotic symptoms like delusion and hallucination [53]. Patients with those two symptoms may present dopaminergic hyperactivity, affecting the pituitary gland and leading to reduced TSH [52]. In contrast, depression patients usually display deficits in the dopaminergic system [54]. Participants in our study experienced depressive disorder. While presenting psychotic symptoms, their dopamine system activity may be offset mutually, resulting in less influence on TSH. Secondly, delusion and hallucination are common psychotic symptoms in schizophrenia. A community-based retrospective study with a matched-control design found that prior to the diagnosis of schizophrenia, there was no statistically significant difference in the distribution of TSH levels between patients and healthy controls. However, after diagnosis of schizophrenia and antipsychotic treatment, the same subjects were found to be at increased risk for decreased TSH, suggesting it may be related to the antipsychotic treatment [55]. In our study, though information on previous antipsychotic treatment was not collected, participants had no prior diagnosis of mental disorders, implying a small probability of previous antipsychotic treatment. Thus, their thyroid function may be closer to that of drug naïve patients whose distribution of TSH level displayed no statistically significant difference regardless of having psychotic symptoms or not. However, Peng et al. demonstrated higher TSH level in PD than NPD in patients with first-episode and drug-naïve major depressive disorder [7]. This may result from the third reason that participants involved in our study were adolescents aged 12–18, who may present distinctive characteristics in the HPT axis with adults, suggesting long-term thyroid function monitoring through adulthood. Fourthly, according to a meta-analysis demonstrated that TSH had weaker clinical significance than FT3 and FT4 [56]. Though no correlations were observed between PD and TSH in our study, TSH is strongly associated with poor clinical outcomes in MDD patients, such as suicide attempt [15]. Some hallucination and delusion, such as suicide order, insulting comments and delusion of persecution, may aggravate depression and potential suicide attempt. Thus, further monitoring of TSH in PD patients is significant for long-term prognosis.

To the best of our knowledge, our study is the first to explore association between thyroid function and psychotic symptoms in depression adolescents in China. Effects of hormones in the HPT axis have long been perceived significant in psychiatric fields. Since the endocrine system in adolescents presented different features from the general population, our study focusing on this particular age

group might offer a more exact clinical outcome. Besides, with the increasing testing precision [57], TH could be detected more accurately. Thus evidence of association between TH and psychotic symptoms in depressive disorder would apply to clinical practice with a technical basis. Moreover, as our study was conducted in various Chinese provinces that share different diet habits, ethnic group backgrounds, economic development levels, and climates, our findings could be valuable and with less limitation of extension among adolescents in China.

Several limitations should be noted in this study. Firstly, there have reached no consensus on definition of PD among prior studies. Our study applied DSM-5, which is a universally acknowledged rating standard in the field of psychiatry research, for the rating of psychotic symptoms. This may lead to discrepancy in definition of PD with some prior studies, leading to a relevant higher prevalence. A generally accepted distribution should be explored in future studies. Secondly, several confounding factors critical to a comprehensive reflection of thyroid function, such as thyroid function before the onset of depressive disorder, serum anti-thyroglobulin (TgAb) and thyroid peroxidases antibody (TPOAb) level were not collected, expecting prospective study in the future. Thirdly, although all patients enrolled met the diagnostic of depressive disorder, there is a possibility to include diseases other than depressive disorder, such as bipolar disorder and schizophrenia, which can manifest as depression in certain disease stages. Fourthly, though participants had no prior diagnosis of mental disorders, implying a small probability of previous antipsychotic treatment. However, information on previous antipsychotic treatment, which may influence thyroid function [55], was not collected. Fifthly, our study was a multicenter study conducted in different hospitals applying different testing methods with inconsistent reference ranges. Therefore, while statictical analysis, we divided the clinical data into three groups according to their reference range, causing a loss of information as the numeric variable carries more information than the rank variable. It is suggested that future multicenter studies apply identical testing methods for better statistical analysis and more accurate clinical evidence. Sixthly, as a cross-sectional study, its effectiveness in explaining the causal effects of thyroid function towards psychotic symptoms in adolescent depressive disorder is limited. Finally, our research results should be considered preliminary due to a lack of a healthy control group, needing future studies to confirm and replicate.

5. Conclusion

In conclusion, our results showed that psychotic symptoms are common among adolescents with depression. PD patients were more likely to be younger, female, non-Han nationality, with decreased serum FT4 level and experience abnormal thyroid function relevant parameters than NPD patients. We recommend that adolescents with depressive disorder regularly screen their serum FT4 levels and actively treat thyroid dysfunction for better clinical outcomes.

Author contribution statement

Xiangdong Du; Yongjie Zhou: Conceived and designed the experiments; Wrote the paper.

Ruchang Yang: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Feng Zhu: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Yan Yue: Conceived and designed the experiments; Performed the experiments; Contributed reagents, materials, analysis tools or data.

Xinchuan Lu; Xueli Zhao; Xuna Yang: Performed the experiments.

Ping Zhu: Analyzed and interpreted the data.

Zhe Li: Contributed reagents, materials, analysis tools or data.

Data availability statement

Data will be made available on request.

Additional information

No additional information is available for this paper.

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Declaration of competing interest

None.

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