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Relationship between thyroid-stimulating hormone and blood lipids in patients with first-episode depression

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Abstract

Background Previous studies demonstrated thyroid stimulating hormone (TSH) plays an important role in regulating lipid metabolism, but the relationship between the two is controversial. Meanwhile, it has not been reported in a population with major depressive disorder (MDD).

Methods We divided 1718 first-episode and drug naïve patients with MDD into a TSH abnormal group (TSH-AB) and a TSH normal group (TSH-NOR). The participants in the two groups were assessed by the Hamilton Depression Rating Scale (HAMD), Hamilton Anxiety Rating Scale (HAMA) and the positive subscale of Positive and Negative Syndrome Scale. The patients' blood was tested for TSH, free T3, free T4, fasting blood glucose, lipid indexes and body mass index was recorded.

Results The participants in the TSH-AB group had significantly higher HAMD scores, HAMA scores and total scores of positive symptoms, as well as higher incidence of suicide attempts than those in the TSH-NOR group, accompanied by significantly higher thyroglobulin antibodies, thyroid peroxidase antibodies, fasting blood glucose values, total cholesterol (TC), triglycerides (TG) and low-density lipoprotein cholesterol (LDL-C) levels compared with those of TSH-NOR patients. However, the high-density lipoprotein cholesterol (HDL-C) of TSH-AB patients was lower than those of TSH-NOR patients. TSH values were positively correlated with TC, TG, and LDL-C values, and negatively correlated with HDL-C value.

Conclusion TSH was highly correlated with abnormal lipid metabolism in patients with MDD. The specific molecular mechanism of the relationship between TSH, lipid metabolism and the development of depression needs to be further in-depth investigation.

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Keywords Major depressive disorder, Suicide attempts, TSH, Lipid metabolism

Introduction

Lipids are a major component of the brain, accounting for approximately 60% of dry weight. **A cross-sectional study in Turkey found a higher prevalence of metabolic syndrome among patients with first-episode psychosis and schizophrenia** [1], **in which Plasma apelin and resistin levels were significantly higher than those in controls, that may be associated with certain central nervous system (CNS) pathologies, including the severity of psychiatric disorders** [2]. Lipids are involved in functions such as neurogenesis and synapse formation, and their metabolism is critical for myelin formation, synaptic plasticity and receptor function in the CNS. Previous studies suggested that lipid oxidative stress is associated with major depressive disorder (MDD) related inflammatory responses or immune activation. A previous meta-analysis showed that lipid peroxidation was more severe in patients with MDD compared to controls, and that the more pronounced the depressive symptoms, the more severe the lipid peroxidation in patients [3]. Antidepressant treatment is associated with a reduction of the lipid peroxidation in patients with MDD [3]. At the same time, it had been shown that lipid oxidative stress enhances acid phosphatase activity and increases the release of IL-1β and IL-6, which in turn promotes the development of depression [4, 5]. In addition, overactivated acid sphingomyelinase can increase ceramide levels, which directly or indirectly affects the hypothalamic-pituitary-adrenal (HPA) axis, leading to its dysregulation and affecting the development of depression [6, 7]. Increased activity of acidic sphingomyelinase in the hippocampus can also promote ceramide production, reduce neurogenesis, neuronal maturation and neuronal survival, and promote the occurrence and development of depression [4]. These previous studies have shown a close relationship between lipid metabolism and the occurrence and development of depression. As lipids can cross the blood-brain barrier and lipid disturbances associated with oxidative stress and inflammation in the brain that can be reflected in other matrices, such as plasma. Therefore, we can correlate them by studying lipid changes in peripheral blood.

Thyroid-stimulating hormone (TSH) plays an important role in the regulation of lipid metabolism [8]. Studies have shown that TSH correlates with lipids in healthy adults, and in patients with schizophrenia, but the relationship between the two is controversial. A previous study, recruiting 3664 Chinese participants with normal thyroid function (TSH: 0.27–5.5 mIU/L), found that TSH was independently correlated with lipids and was significantly positively correlated with total cholesterol (TC) and triglyceride (TG), after controlling free triiodothyronine (FT3), free thyroxine (FT4), total T3, total T4, and non-thyroidal factors [9]. Another cross-sectional study, based on the Chinese national population with normal thyroid function, found that TC was negatively correlated with TSH levels in individuals with normal TSH levels (0.3–4.2 mIU/L) [10]. A previous study involving 20,192 participants who participated in routine health tests showed that TSH concentration was weakly and positively correlated with blood TC, TG, and high-density lipoprotein cholesterol (HDL-C), but not with low-density lipoprotein cholesterol (LDL-C) [11].

Despite numerous studies on TSH concentration levels and lipid metabolism, the relationship between the two is still unclear. However, the study on TSH and lipid metabolism in patients with MDD has not been reported. This study aims to assess the relationship between TSH and lipid metabolism in patients with MDD through a large sample of patients with MDD, and provide a scientific basis for an in-depth understanding of the relationship between the onset of MDD and lipid metabolism.

Methods

Participants

We recruited 1718 patients (aged 18–60 years, 34.2% male, 65.8% female) from September 2016 to December 2018 in the Department of Psychiatry of the First Clinical Medical College of Shanxi Medical University, Shanxi, China. All of them were recruited in the outpatient clinic. All of them fulfilled the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) diagnostic criteria for depression, as shown in Table 1. Patients included in the study fulfilled the following inclusion criteria: met the diagnostic criteria for MDD of the Structured Clinical Interview for DSM-IV (SCID) conducted by a professional clinical psychiatrist; all of them had a Hamilton Depression Scale (HAMD-17 items) score of 24 or above, and was the first-episode depression; were at the age of 18 to 60 years old; the duration of the depression equal to or less than 24 months; the clinical symptoms could be present with anxiety and psychotic symptoms that did not meet the criteria for a diagnosis of anxiety disorder and/or schizophrenia; without any antidepressants or antipsychotics treatment; without any thyroxine or medication treatment that affects thyroid function. None of the recruited patients knew whether they had thyroid abnormalities or dyslipidaemia prior to the consultation. Patients were screened for thyroid-related markers and blood biochemistry at the initial visit.

Table 1 Demographics, clinical characteristics, and peripheral blood biochemical markers between the TSH-NOR and TSH-AB groups

Characteristics	TSH-NOR	TSH-AB	T-test/ Chi-square *p* value
Gender (M/W)	230/444 (0.518)	358/686 (0.522)	$p < 0.0001$
	Mean ± SD	**Mean ± SD**	
Onset Age	20.249 ± 2.364	35.44 ± 12.28	$P = 0.007$
Marital status (S/M)	218/456 (0.478)	284/760(0.374)	$p < 0.0001$
BMI (kg/m^2)	23.972 ± 1.75	24.622 ± 1.989	$p < 0.0001$
SBP	113.395 ± 10.623	123.414 ± 9.158	$p < 0.0001$
DBP	73.282 ± 6.422	77.671 ± 6.375	$p < 0.0001$
Disease Course (months)	4.164 ± 4.332	7.002 ± 4.851	$p < 0.0001$
Clinical symptoms			
HAMD	28.858 ± 2.693	31.226 ± 2.715	$p < 0.0001$
HAMA	20.209 ± 3.116	21.177 ± 3.636	$p = 0.015$
Positive subscale in PANSS	7.895 ± 3.150	9.468 ± 4.943	$p < 0.0001$
Thyroid parameters			
TG-Ab (IU/L)	52.519 ± 144.363	114.237 ± 280.312	$p < 0.0001$
TPO-Ab (IU/L)	37.808 ± 101.987	94.515 ± 190.203	$p < 0.0001$
FT3 (pmol/L)	4.873 ± 0.699	4.924 ± 0.739	$p = 0.160$
FT4 (pmol/L)	16.778 ± 3.101	16.654 ± 3.092	$p = 0.418$
Fasting Blood Glucose	5.091 ± 0.548	5.595 ± 1.048	$p < 0.001$
TC	4.642 ± 0.897	5.54± (1.25)	$p < 0.001$
HDL-C	1.313 ± 0.234	1.160 ± 0.304	$p < 0.001$
TG	2.056 ± 0.994	2.239 ± 0.975	$p = 0.008$
LDL-C	2.626 ± 0.719	3.215 ± 0.866	$p < 0.001$

TSH-NOR: participants with normal level of thyroid-stimulating hormone; TSH-AB: participants with abnormal level of thyroid-stimulating hormone; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HAMD: Hamilton Depression Rating Scale; HAMA: Hamilton Anxiety Scale; PANSS: positive and negative symptom scale; TG-Ab: thyroglobulin antibody; TPO-Ab: thyroid peroxidase antibody; FT3: free triiodothyronine; FT4: free thyroxine; TC: total cholesterol; HDLC: high-density lipoprotein; TG: triglycerides; LDLC: low-density lipoprotein; M/W: Male/Female; S/M: Single/ Married

Patients' exclusion criteria: patients with psychiatric disorders other than MDD diagnosed by SCID; patients with unstable or serious medical conditions including epilepsy, liver or kidney disease, diabetes mellitus, cardiac disease, aplastic anaemia, systemic lupus erythematosus, or asthma, as well as patients who were receiving immunosuppressive medication, or taking medication to treat a physical illness; patients who were planning to become pregnant, were pregnant, or were breastfeeding; patients who abused or were dependent on drugs other than tobacco drugs (based on participants and family reports); patients who had difficulty understanding the study process or refused to consent to the study process; patients whose interviews were unreliable due to an acute clinical condition and were not recorded for other reasons; patients with a history of significant thyroid disease and/or with thyroid disease other than subclinical hypothyroidism evidenced by laboratory tests during the study.

The study was approved by the Institutional Review Board (IRB) of the First Clinical Medical College of Shanxi Medical University (ID No. 2016-Y27). After a full explanation of the study, each participant signed an informed consent form.

Clinical assessment tools

Depressive symptoms were assessed using the 17-item Hamilton Depression Rating Scale (HAMD-17) [12]. The cut-off values were as follows: ≤ 7 not depressed, ≥ 8 depressed, ≤ 17 mild to moderate depressive symptoms, and ≥24 severe depression. According to the study inclusion criteria, patients with a total HAMD -17 score of ≥24 could be included.

Anxiety status was assessed using the 14-item Hamilton Anxiety Rating Scale (HAMA) [13], with the following cut-off values: ≥ 29 points may indicates severe anxiety; > 21 points indicates that there must be significant anxiety; > 14 points indicates that there must be anxiety; > 7 points indicates that there may be anxiety; and <7 points indicates that there are no anxiety symptoms. According to this study, a total HAMA score of >14 indicates that the patient has clinical symptoms of anxiety.

Psychotic symptoms were assessed using the positive subscale of the Positive and Negative Syndrome Scale (PANSS) [14]. Positive symptoms include delusions, disorganised thinking, hallucinations, euphoria, exaggeration, suspicion/persecution and hostility. Each item is rated on a 7-point scale ranging from 1 to 7 (no symptoms to extreme severity). The total score of positive symptom (TSPS) is the sum scores of the seven items. Thus, TSPS scores range from 7 to 49. Patients with TSPS of ≥15 were defined as having psychotic symptoms according to the study's inclusion criteria.

Peripheral blood biochemical parameters

All participating patients were asked to collect fasting blood samples, which were collected between 6 am and 8 am on the day of clinical data collection. TSH, thyroglobulin antibody (TG-Ab), anti-thyroid peroxidase antibody (TPO-Ab), FT3, FT4 and other biochemical parameters were measured at the Testing Centre of the First Clinical Medical College of Shanxi Medical University before 11:00 a.m. on the day of collection. **The normal range of TSH was 0.27–4.20 mIU/L. Patients whose THS levels were not in this range were assigned to the abnormal TSH (TSH-AB) group and, conversely, to the normal TSH (TSH-NOR) group.**

Statistical analysis

SPSS 26 software was used for statistical analysis. The independent samples *t*- test was used for continuous variables, the χ^2 test was used for categorical variables, the differences of all parameters between groups were analysed, and the correlation coefficients were tested by the Pearson test. **The analysis of covariance (ANCOVA) was used to control for confounding variables.** A two-tailed *P* value of less than 0.05 was considered statistically significant.

Results

Demographic characteristics

Of the 1718 participants recruited, 588 (34.23%) were male and 1130 (65.77%) were female. There were 674 participants in the group with normal TSH levels (TSH-NOR), 230 (34.12%) males and 444 (65.88%) females, while 1044 participants in the group with abnormal TSH levels (TSH-AB), 358 (34.29%) males and 686 (65.71%) females. The mean age of onset in the TSH-NOR group was 20.249±2.364 years and mean age of onset in TSH-AB group was 35.44±12.28 years, Table 1 shows that there was a significant difference in gender, onset age, and marital status between TSH-NOR and TSH-AB groups ($p<0.0001$).

Differences in clinical indicators between participants in TSH-NOR and TSH-AB groups

Independent samples *t*-test was performed for comparison as shown in Table 1. There were significant differences in the total scores of HAMD, HAMA and positive symptoms of the participants between the two groups, in which the total scores of HAMD and positive symptoms of the participants in the TSH-AB group were significantly higher than those of the participants in the TSH-NOR group, with a statistically significant difference ($p<0.0001$). The total scores of HAMA of the participants in the TSH-AB group were also significantly higher than those of the participants in the TSH-NOR group, with a statistically significant difference ($p=0.015$). **ANCOVA showed that the total scores of HAMD, HAMA and positive symptoms of the participants were significantly higher in TSH-AB group than those in TSH-NOR group (all$p<0.0001$) after adjusting for confounding factors including sex, marital status, onset age and body mass index (BMI).**

Differences in blood pressure, body mass index and peripheral blood biochemistry indices between participants in TSH-NOR and TSH-AB groups

The independent samples *t*-test was used to compare the BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), TG-Ab, TPO-Ab, FT3, FT4, fasting blood glucose value, TC, TG, HDL-C, and LDL-C between participants in the TSH-NOR and the TSH-AB groups, as shown in Table 1. The BMI, SBP and DBP values in the TSH-AB group were significantly higher than those in the TSH-NOR group (all *p* values <0.0001); both TG-Ab and TPO-Ab values in the TSH-AB group were significantly higher than those in the TSH-NOR group (all *p* values <0.0001); and the differences of FT3 and FT4 values between two groups were not statistically significant (both *p* values >0.05). Fasting blood glucose ($p<0.001$), TC ($p<0.001$), TG ($p=0.008$), and LDL-C ($p<0.001$) values in the TSH-AB group were statistically higher than those in the TSH-NOR group. while HDL-C value was significantly lower in the TSH-NOR group than that in the TSH-AB group ($p<0.001$). **ANCOVA showed that the fasting blood glucose, TC, TG, and LDL-C values remained significantly higher, HDL-C value remained significantly lower in TSH-AB group than those in TSH-NOR group (all$p<0.0001$) after adjusting for confounding factors including sex, marital status, onset age and BMI.**

Correlation between TSH values and lipid indicators in patients with first-episode MDD

In order to better understand the relationship between TSH and lipids in patients with first-episode depression, we performed Pearson correlation analyses between TSH values and the values of the four lipid indicators in all participants. The results showed that participants' TSH values were positively correlated with TC, TG, and LDL-C values ($r=0.055$, $P<0.0001$; $r=0.17$, $P<0.0001$; and $r=0.38$, $P<0.0001$, respectively), and negatively correlated with HDL-C values (r = -0.34, $P<0.0001$), as shown in Fig. 1.

TSH values and rate of suicide attempts

In order to explore the effect of TSH on the suicidal attempts in the first episode MDD patients, the included participants were divided into TSH-NOR and TSH-AB groups, the number of patients with suicide attempts in each group was counted separately and the rate of suicide attempts in each group was calculated. As shown in Table 2, there were 83 patients in the TSH-NOR group who had suicide attempts before their first visit, accounting for 12.31%. In the TSH-AB group, there were 263 patients had suicide attempts before their first visit, accounting for 25.19%. The incidence of suicide attempts in the TSH-AB group was more than twice that in TSH-NOR group.

Discussion

Our results showed that participants in the TSH-AB group had significantly higher scores of HAMD, HAMA and positive symptoms, as well as a higher incidence of suicide attempts than those in the TSH-NOR group,

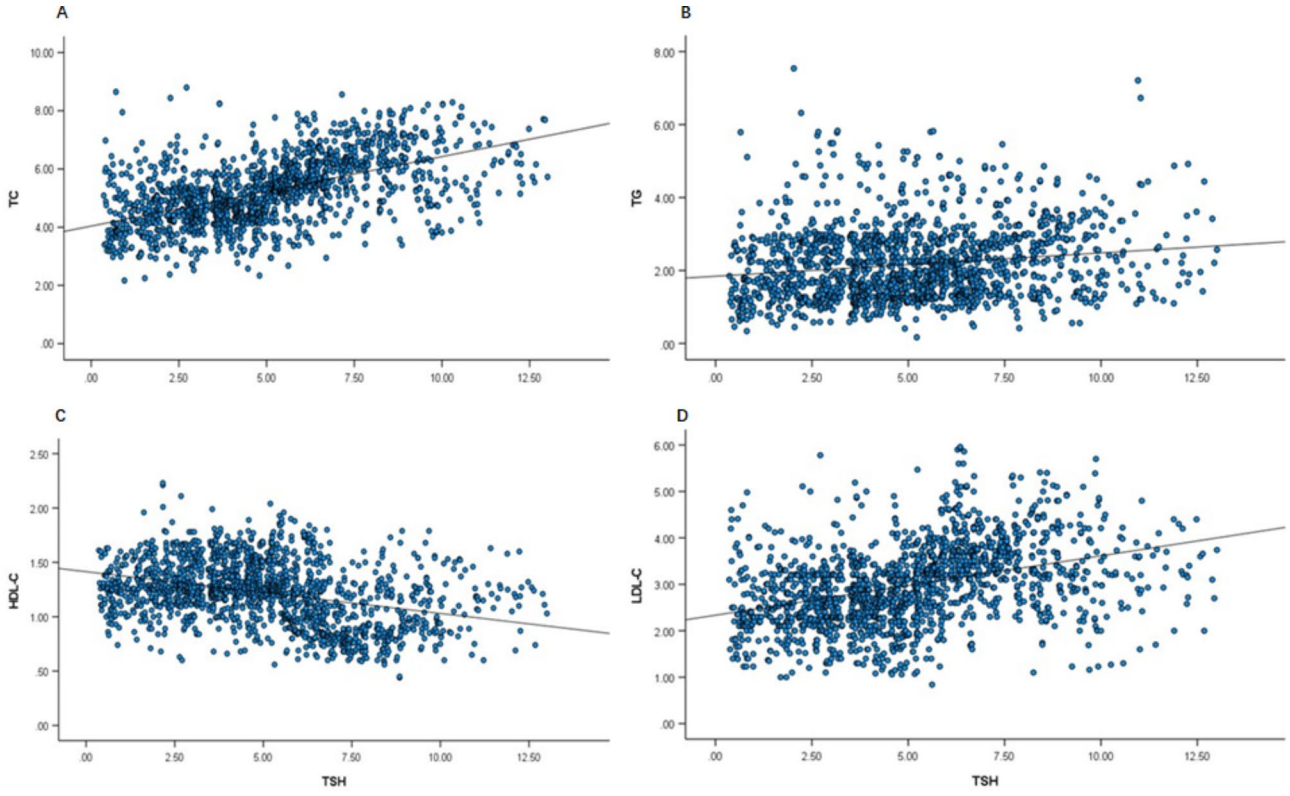

Fig. 1 Relationship between TSH and lipids in patients with first-episode depression. (**A**) Relationship between TSH and TC; (**B**) Relationship between TSH and TG; (**C**) Relationship between TSH and HDL-C; (**D**) Relationship between TSH and LDL-C. TSH: thyroid-stimulating hormone; TC: total cholesterol: HDL-C: high-density lipoprotein cholesterol: TG: triglycerides: LDL-C: low-density lipoprotein cholesterol

Table 2 Rate of suicide attempts between TSH-NOR and TSH-AB groups

	TSH-NOR	TSH-AB
Number of suicide attempts	83	263
Total number of participants	674	1044
Rate of suicide attempts	12.31%	25.19%

TSH-NOR: patients whose TSH value in the normal range; TSH-AB: patients whose TSH value was out of the normal range

accompanied by TG-Ab, TPO-Ab, fasting blood glucose, TC, TG, and LDL-C levels were also higher than those of TSH-NOR patients, whereas HDL-C levels were lower than that of TSH-NOR patients, **by adjusting with sex, marital status, BMI, and onset age**. TSH values were positively correlated with TC, TG, and LDL-C values, and negatively correlated with HDL-C. Our findings are consistent with those of previous studies, in which the higher the TSH value, the more pronounced the disorder of lipid metabolism, when blood TSH value was elevated by 1.0 mmol/L, TC levels were correspondingly elevated by 0.09–0.16 mmol/L [15, 16]. TG, TC, and LDL-C levels were found to be significantly elevated in patients with subclinical hypothyroidism (elevated TSH levels and normal FT3 and FT4) compared to the normal population [17]. Patients with MDD had elevated levels of TC and LDL-C compared to non-MDD patients, but lower levels of HDL-C [18]. For the relationship of TSH value with values of TG-Ab and TPO-Ab, a previous study showed that TPO-Ab and/or TG-Ab increased significantly with increasing TSH levels and was associated with the prevalence of hypothyroidism [19, 20], which is to some extent consistent with the results of this study. These studies have confirmed that TSH concentration is highly associated with abnormal lipid metabolism. In addition, it has been shown that TSH level is one of the risk factors for type 2 diabetes in subjects with normal thyroid function [21]. Our results showed that patients in the TSH-AB group had significantly higher fasting glucose levels than those in the TSH-NOR group, **without being affected by sex, marital status, BMI, and onset age**, although the fasting glucose levels of our participants did not reach the diagnostic level of diabetes, it seems to support the idea that TSH levels are a risk factor for developing type 2 diabetes. There is evidence that MDD is highly associated with the risk of developing type 2 diabetes. However, although the risk of MDD is increased in people with type 2 diabetes, the correlation is not significant [22, 23]. **A previous study using Mendelian randomization demonstrated that depression is causal for type 2 diabetes, with BMI mediating up to 37% of this effect; no evidence was found for causality in the reverse**

direction [24]. **Regarding potential pathophysiological functions underlying the comorbidity between depression and type 2 diabetes, insulin secretion and inflammation as shared mechanisms demonstrated by using multitrait GWAS followed by expression quantitative trait locus analyses** [24]. This needs to be further validated in future large-sample, prospective cohort studies.

Overweight and obesity are commonly measured using BMI. BMI is also influenced by TSH levels. **Multiple studies have shown that BMI is positively correlated with TSH** [25–27]. Results of a study examining the relationship between TSH and BMI in the normal levels showed that men with higher TSH concentrations had higher body weight and BMI after adjusting for relevant confounders [28]. A recent study indicated that TSH levels positively correlated with BMI in patients with papillary thyroid carcinoma [29]. **As for the underlying causal association between TSH and BMI, the inverse variance-weighted (IVW) and MR-Egger methods indicated that TSH can be significantly elevated by a gene-driven increase in BMI, rather than vice versa** [30].

Previous study suggested that there may be a link between adipocyte and hepatocyte-derived metabolic regulators with metabolic syndrome and thyroid function [31]. Studies have found that a low-grade inflammatory state during obesity is considered to be a major trigger for depressive episodes in obese patients [32–34]. On the one hand, persistent low-grade inflammation leads to the emergence of underlying neuroinflammation for the development of a depressive state, resulting in structural and excitatory changes in the brain [33]; on the other hand, due to dysregulation of the HPA axis, brain glucocorticoid receptors induced by cortisol in stressed populations are activated to promote the intake of palatable foods and modulate the dysregulation of the HPA axis in order to alleviate negative emotions [35]. The latter's promotion of eating high-fat, high-sugar, and high-calorie foods invariably adds to weight gain.

Previous studies have shown that increased suicide attempts risk appears to be associated with abnormalities in the serotonergic system, the HPA axis, lipid metabolism, the immune system, and neuronal plasticity [36], and have found higher TSH levels in MDD patients with suicide attempts than that in MDD patients without suicide attempts [37, 38], which is consistent with our results. Meanwhile, a meta-analysis [39] showed that patients with a history of suicide attempts had significantly lower levels of FT3 and FT4 and higher levels of TSH, suggesting that TSH levels in patients with MDD are associated with suicide attempts, which is also consistent with our results.

Limitations and prospects

There are some limitations should be concern. This study is a cross-sectional study, which can only draw correlation but not causality conclusion, and the results should be further validated by longitudinal clinical studies in the future. Second, this study has not yet clarified the relationship between TSH, lipid metabolism and the onset of MDD. Therefore, a large-sample cohort studies are needed in the future to elucidate the relationship between THS, lipid metabolism and the onset of MDD. **Third, we did not include healthy control group, all participants suffered from MDD and were from the outpatient department of one general hospital in China. Therefore, these findings are limited and cannot be generalized to other conditions. In the future, a larger sample size, multi-centre, well-designed prospective nested case-control study is needed for further verification. Fourth, regarding assessment to suicide attempts, a standardized suicidal behavior screening scale should be used, but not through interviews and medical histories. Future studies should adapt suicide questionnaires and collect some other information related to suicide attempts, such as the severity, plans, or ideas. Fifth, we recruited first-episode and drug-naive patients with depression, who may also be a bipolar or primary psychotic disorder, which is difficult to discern at the time. So, subjects with bipolar or primary psychotic disorder could not be excluded from the included participants.** Meanwhile, we hope that our study will provide supportive data for future studies related to MDD, TSH and lipid metabolism.

Abbreviations

BMI	Body Mass Index
CNS	Central Nervous System
DBP	Diastolic Blood Pressure
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
FT3	Free triiodothyronine
FT4	Free thyroxine
HAMA	14-item Hamilton Anxiety Rating Scale
HAMD-17	17-item Hamilton Depression Rating Scale
HDL-C	High-density Lipoprotein Cholesterol
HPA	Hypothalamic-pituitary-adrenal
IRB	Institutional Review Board
LDL-C	Low-density Lipoprotein Cholesterol
MDD	Major depression disorder
PANSS	Positive and Negative Syndrome Scale
SAs	Suicide Attempts
SBP	Systolic Blood Pressure
SCID	Structured Clinical Interview for DSM-IV
TC	Total Cholesterol
TG-Ab	Thyroglobulin Antibodies
TG	Triglycerides
TPO-Ab	Thyroid Peroxidase Antibodies
TSH-AB	TSH Abnormal Group
TSH-NOR	TSH Normal Group
TSPS	Total Scores of Positive Symptoms

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Author contributions
All authors contributed to the concept of this study; Zhe Li, Dong-Hua Tian, and Xiang-Yang Zhang designed the study; Chun-Qing Cui, Zhe Li, Zi-Rong Hou did the statistical analysis and wrote the draft manuscript; Chun-Qing Cui, Zhe Li, Zi-Rong Hou, Yu-Mei Zhang, Xue-Zhu Feng, Xuan Tan, and Yu-Yu Zhao managed and combed data or interpreted data, review & edited the manuscript; Zhe Li, Su-Xia Li, Dong-Hua Tian and Xiang-Yang Zhang did the critical revision of the manuscript for important intellectual content. All the authors reviewed and approved the final manuscript.

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Data availability
All data associated with this study are present in the paper. All the datasets are available from the corresponding authors with the approval of reasonable causes.

Declarations

Ethics approval and consent to participate
The study was approved by the Institutional Review Board (IRB) of the First Clinical Medical College of Shanxi Medical University (ID No. 2016-Y27). After a full explanation of the study, each participant signed an informed consent form.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Role of the sponsors
The sponsors contributed only financially to the study and played no role in planning or designing the study.

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