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Clinical characteristics of overweight and obesity in patients with acute-phase major depressive disorder co-morbid anxiety symptoms

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Abstract

Objective: This study aimed to investigate the prevalence of overweight and obesity in patients with Major Depressive Disorder (MDD) co-morbid anxiety during the acute phase, and to explore the factors associated with overweight and obesity in this cohort.

Design: Cross-sectional study.

Setting: The MDD co-morbid anxiety symptoms study was conducted from July 2017 and August 2022.

Methods: A total of 737 initially hospitalized MDD patients with concurrent anxiety in the acute phase were enrolled. Socio-demographic data, general clinical information, biochemical indicators, depressive and anxiety symptoms, psychotic symptoms, and illness severity were assessed. Continuous and categorical variables were analyzed using independent samples t-tests and chi-square tests, respectively. Binary logistic regression and multivariate linear regression analyses were conducted to determine factors influencing the outcomes.

Primary outcome measures: Prevalence and risk factors for overweight and obesity [body mass index (BMI) greater than or equal to 25].

Results: The prevalence of overweight and obesity in the study population was 55.63%. Binary logistic regression identified being married (B = 0.28, p = 0.018, OR = 1.10), thyroid stimulating hormone (TSH) levels (B = 0.10, p = 0.001, OR = 1.10), and low-density lipoprotein cholesterol (LDL-C) levels (B = 1.61, p = 0.045, OR = 1.18) as risk factors associated with overweight and obesity development. Furthermore, multiple linear regression indicated that TSH levels (B = 0.16, t = 3.17, p = 0.002) were correlated with higher BMI.

Conclusion: The findings suggest that over half of MDD patients with anxiety symptoms present with overweight and obesity. Thyroid function emerges as a crucial risk factor for overweight and obesity in this population. Targeted interventions focusing on thyroid function may hold promise as a therapeutic approach for managing overweight and obesity in MDD patients with co-morbid anxiety symptoms.

Keywords: Major depression disorder, Anxiety, Overweight, Obesity, Thyroid stimulating hormone

STRENGTHS AND LIMITATIONS

1. The large-sample cross-sectional study design ensured the stability of the results.

2. The target parameters included are common biochemical indicators, which are easy to detect and clinically promote at low cost.

3. The cross-sectional design limits the ability to infer causality.

4. The setting of inclusion criteria introduces potential confounding factors.

1. Introduction

Major depressive disorder (MDD) is a common psychiatric disorder characterized by marked depressed mood, diminished interest, and decreased energy[1]. Although anxiety disorders and already in MDD are two distinct diagnostic entities, anxiety and depression co-morbidity is a relatively common syndrome[2]. In Western countries, the prevalence of comorbid anxiety in patients with MDD ranges from 11% to 80%[3-5], and in China, similarly, upwards of 70% of patients with MDD have comorbid anxiety symptoms[6,7]. Comorbid anxiety symptoms often lead to lower treatment response rates, lower remission rates, lower quality of life, suicidal behavior, and higher risk of cardiovascular disease in MDD patients[2,8,9].

Mood disorders and obesity appear to be twins, often acting as risk factors for each other, and were once collectively referred to as the "metabolic-mood syndrome"[10]. Previous studies have shown that patients with MDD frequently experience overweight and obesity[11-13]. The presence of obesity in individuals with MDD can have detrimental effects, affecting their clinical outcomes by prolonging recovery time and increasing suicidal ideation[14,15]. Additionally, both overweight and obese individuals are vulnerable to mood disorders[16,17]. Various pathways have been identified by researchers, linking obesity and mood disorders, such as lifestyle behavioral habits[18,19], hypothalamic-pituitary-adrenal (HPA) axis disorders[20], altered glucocorticoid receptor function[21], inflammation[22], and genetic variations[23,24], among others.

Given the complex relationship between overweight and obesity and mood disorders and the negative empowerment on the efficacy and prognosis of patients with MDD, actively clarifying the clinical characteristics of overweight and obesity in MDD populations and exploring the potential biomarkers that can be used for clinical interventions is a very critical task. Up to now, although there are many studies related to overweight in MDD patients, there are not enough studies on overweight in MDD patients with comorbid anxiety, and the results of the few studies are inconsistent due to issues such as sample size, population characteristics, cultural and geographic differences. In this study, we investigated the prevalence of overweight in patients with co-morbid MDD in a sample of Chinese Han Chinese patients with MDD hospitalized for the first time in the acute phase and explored the influencing factors affecting the development and severity of overweight.

2. Materials and Methods

2.1 Subjects

This study incorporated a total of 737 patients diagnosed with MDD who also exhibited symptoms of anxiety. These patients underwent their inaugural inpatient

treatment at the Wuhan Mental Health Center, recognized as the largest public tertiary psychiatric specialty hospital in central China, between July 2017 and August 2022 (The flow chart is shown in Figure 1).

The study included patients who fulfilled the following criteria: (1) met the diagnostic criteria for Major Depressive Disorder (MDD) as per the International Classification of Diseases, 10th edition (ICD-10); (2) were aged between 18 and 60 years; (3) were of Chinese Han nationality and either male or female; (4) had no history of previous hospitalizations; (5) scored a 17-item Hamilton Depression Scale (HAMD-17) of $\geqslant$24; and (6) scored a 14-item Hamilton Anxiety scale (HAMA-14) of $\geqslant$18.

Patients who fulfilled any of the following criteria were excluded from the study: those diagnosed with other severe mental illnesses, pregnant or breastfeeding individuals, patients with a history of substance abuse, those with a documented diagnosis of a serious physical illness or personality disorder, those with comorbid diabetes mellitus, and those who were unable to cooperate in completing a psychological evaluation for any reason.

The research adhered strictly to the principles outlined in the Declaration of Helsinki. The study protocol underwent rigorous review and approval by the Ethics Committee of Wuhan Mental Health Center. Furthermore, all participants provided their informed consent through a paper-based form.

2.2 Research design

This study was conducted as a cross-sectional research design. Initially, we determined the prevalence of overweight and obesity within the target population. Subsequently, we compared demographic and general clinical data between two clinical subgroups: those with normal body mass index (BMI) (labeled as normal BMI group) and those with high BMI (labeled as high BMI group). Finally, we analyzed the factors associated with overweight and obesity and their severity.

A self-designed EXCLE form was used to collect demographic and clinical data of the enrolled patients, including age, age at onset, disease duration, gender, marital status, education, history of suicidal behavior, history of outpatient treatment, body mass index (BMI), waist circumference (WC), blood pressure. On admission day, depressive symptoms, anxiety symptoms, psychotic symptoms, illness severity were evaluated using HAMD-17, HAMA-14, Positive Symptom Subscales (P1-P7) of Positive and Negative Symptom Scale (PANSS), Clinical Global Impression Inventory-Severity of Illness (CGI-SI). Then, routine biochemical parameters measured by fasting blood of the patient, including thyroid function, fasting blood glucose (FBG) levels, lipid levels were extracted from electronic medical record system.

The criteria for overweight and obesity (high BMI group) were established based on the weight status classification criteria of the Chinese Obesity Working Group [25], Accordingly, all study subjects were classified into two categories: those with a normal body mass index (BMI < 24 kg/m^2), and those who fell into the overweight and obesity category (BMI $\geqslant$ 24 kg/m^2).

Two psychiatrists conducted the evaluation of pertinent psychological scales, each with a title of attending or higher, who were affiliated with the medical institution from which the sample originated.

2.3 Data analysis

Categorical variables are presented as counts, while data for normally distributed continuous measures are expressed as mean and standard deviation. Continuous variable comparisons across various groups were conducted using independent samples T-tests. Rates were compared using Chi-squared tests. To discern differences in demographic and clinical variables between the overweight subgroup and the normal BMI subgroup, we applied chi-square tests to categorical data and independent samples t-tests to continuous variables. Subsequently, we utilized the variables that varied in univariate analyses as independent variables and constructed binary logistic regression models with overweight as the outcome variable to investigate factors influencing overweight within the target population. Ultimately, a multiple linear regression model was developed to identify factors impacting patients with degree of overweight, utilizing BMI as the dependent variable and factors affecting overweight from binary logistic regression as independent variables. All p values were two-tailed, with significance set at < 0.05. Statistical analyses were executed using SPSS 27 (SPSS, Inc., Chicago, IL).

3. Results

3.1 The differences between high BMI group and normal BMI group.

Of all our MDD patients with comorbid anxiety included in the study, 55.63% (410/737) met the diagnostic criteria for overweight. The mean BMI in the two subgroups was (25.39 ± 1.15) kg/m^2 in the high BMI group and (22.71 ± 1.08) kg/m^2 in the normal BMI group. We found that the following parameters were significantly higher in the high BMI group than in the normal BMI group, onset age (t = -2.14, p = 0.033), proportion married (χ^2 = 4.24, p = 0.039), thyrotropin levels(t = -4.00, p < .001), low density lipoprotein cholesterol (LDL-C) levels(t = -2.51, p = 0.012), and systolic blood pressure (SBP) levels(t = -2.73, p = 0.006) (**Table 1**).

3.2 Determinants of overweight and obesity in target patients: a binary logic-based model.

We then developed a binary logistic regression model (Backward: Wald) using the variables that differed in the univariate analysis as independent variables and overweight as dependent variables. As the results in **Table 2** shown, being married (B = 0.28, p = 0.018, OR = 1.10), TSH levels (B = 0.10, p = 0.001, OR = 1.10) and LDL-C (B = 1.61, p = 0.045, OR = 1.18) were risk factor for overweight and obesity.

3.3 Factors affecting severity of overweight and obesity in high BMI subgroup: a multiple linear regression model.

Finally, for the high BMI subgroup of patients, we constructed a multiple linear regression model (input) with BMI as the dependent variable and the factors associated with the previous step affecting overweight and obesity as independent variables and the results are shown in **Table 3**. We found that TSH (B = 0.16, t = 3.17, p = 0.002) was a risk factor for higher BMI.

4. Discussion

In our study, we observed specific clinical characteristics related to overweight and obesity in individuals with MDD co-morbid anxiety symptoms. The prevalence of overweight and obesity in this population was notably high, reaching 55.63%. Additionally, we found that individuals in the overweight and obese subgroups experienced a later onset of MDD and exhibited more pronounced metabolic disturbances. Furthermore, our analysis revealed that being married and elevated levels of TSH and LDL-C were associated with an increased risk of developing overweight and obesity. Notably, TSH levels were also identified as a risk factor for both the development and severity of overweight and obesity.

The prevalence of overweight and obesity among patients with MDD co-morbid anxiety in our study was 55.63%. Previous reports on the prevalence of overweight and obesity in individuals with MDD have shown some variation. For instance, in a study of first episode MDD patients in northern China, the prevalence was reported at 59.72%[26], while a multicenter study in Germany reported a prevalence of 52.16% amongst first episode MDD patients[13]. When the sample extended to multiple European countries, the prevalence of overweight in MDD patients was approximately 48%[14]. These studies, albeit slightly different from our current study, focused on individuals within the general MDD population rather than specifically considering patients with

MDD comorbid anxiety symptoms. A recent study that shared a similar study population with our research found a higher prevalence of overweight (68.3%) in patients with MDD co-morbid anxiety[27]. This rate was higher than in our study, and this heterogeneity may have been caused by the stricter restriction of anxiety symptoms in that study and the fact that some of the patients we included had a history of outpatient treatment. While the exact prevalence may differ across studies, a consistent finding is that a significant portion of individuals in the MDD population are overweight and obesity, focusing on and underscoring the importance of addressing weight concerns in this patient group.

Subsequently, our study examined the risk factors that contribute to the development of overweight and obesity in patients with MDD comorbid anxiety symptoms. Our findings indicate that marital status and TSH levels were identified as risk factors for overweight and obesity in this population. Marital status has been consistently associated with a higher risk of overweight and obesity not only in the general population but also in individuals with MDD[15,28]. Even after adjusting for variables such as employment status, stress levels, and perceived health status, this relationship persists[29]. The gain observed in married individuals may be linked to reduced physical activity[30], and it is also plausible that spouses may provide greater nutritional support during the acute phases of MDD episode.

Elevated TSH levels emerged as a risk factor for the development of overweight, obesity, and elevated BMI in our study population, aligning with numerous existing reports[27,31,32]. Another study exploring MDD patients with comorbid anxiety found that anxiety symptoms were associated with an increased risk of overweight, with thyroid function playing a crucial role as a contributing factor[27]. Evidence indicates that MDD patients with anxiety disorders often exhibit heightened levels of antithyroid antibodies due to stress-induced immune responses[33-35], leading to subclinical hypothyroidism and subsequently elevated serum TSH levels[36,37]. Elevated TSH levels inhibit triglyceride lipase in adipose tissue via the TSH receptor in adipocytes, promoting adipocyte enlargement and consequent weight gain[38]. Conversely, hypertrophied adipose tissue secretes leptin, which activates thyrotropin-releasing hormone (TRH) neurons to stimulate increased TSH levels[39]. Collectively, the reviewed studies underscore the importance of maintaining thyroid function within normal limits to help manage overweight and obesity in individuals with MDD and anxiety symptoms.

This study possesses several strengths. Firstly, our study included a sizable sample size, enhancing the stability and generalizability of the results. Secondly, the target parameters we investigated are common clinical indicators, which facilitates the generalizability and practical application of the findings at a lower cost. The current study also presents several limitations that should be acknowledged. Firstly, our research design was cross-sectional, precluding the establishment of causal

relationships between identified risk factors and BMI in our study population. Secondly, the study predominantly focused on individuals with MDD in the acute phase of disease onset, potentially limiting the generalizability of our findings to other subpopulations of MDD patients. Lastly, a considerable proportion of the participants had a history of outpatient treatment, introducing a confounding factor that may have influenced the study outcomes. To address these limitations, our future research endeavors will aim to undertake more rigorous prospective studies with a broader scope.

In conclusion, over half of patients with MDD co-morbid anxiety symptoms develop overweight and obesity. Furthermore, thyroid function is a risk factor for the development and severity of overweight and obesity. Therefore, targeted interventions on thyroid function could be potential therapeutic targets for overweight and obesity in patients with MDD co-morbid anxiety symptoms.

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Authors' contributions

HZ: Writing – original draft. JW: Formal analysis, Writing – review & Editing. WZ: Investigation, Supervision, Writing – review & editing. XL: Conceptualization, Supervision. JM: Conceptualization, Methodology, Software, Investigation, Formal analysis.

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Competing interests

None.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or

reporting, or dissemination plans of this research.

Patient consent for publication

Consent obtained directly from patient(s).

Ethics approval and consent to participate

The ethics committees of the Wuhan mental health center reviewed and approved this study. All subject guardians knew about this study and signed informed consent. All procedures carried out in studies conformed to the Helsinki Declaration and its subsequent amendments or similar ethical standards.

Availability of data and materials

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

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Figure legend

Figure 1: Flowchart for study sample inclusion

Table caption

Table 1: The demographic and general clinical data in different clinical subgroups.

Index	Total patients (n = 737)	Overweight (n = 410)	Normal BMI (n = 327)	t/χ^2	p - value
Age - years	35.83±12.47	36.63±12.37	34.83±12.54	-1.94	0.052
Onset age - years	34.32±12.41	35.19±12.29	33.22±12.48	-2.14	0.033*
Course of disease - months	10.80±4.36	10.66±4.51	10.98±4.17	0.99	0.321
Gender - (n, %)				0.06	0.940
Male	249, 33.79%	139, 33.90%	110,33.64 %		
Female	488, 66.21%	271, 66.10%	217, 66.36%		
Marital status - (n, %)				4.24	0.039*
Unmarried	228, 30.94%	114, 27.80%	114, 34.86%		
Married	509,69.06%	296, 72.20%	213, 65.14%		
Treatment history - (n, %)				0.83	0.361
Yes	482, 65.40%	274, 66.83%	208, 63.61%		
NO	255, 34.60%	136, 33.17%	119, 36.39%		
Educational background - (n, %)				0.75	0.387
High school and below	508, 68.93%	288, 70.24%	220, 67.28%		
Bachelor and above	229, 31.07%	122, 29.76%	107, 32.72%		
History of suicidal behavior				0.55	0.458
Yes	128, 17.37%	75, 18.29%	53, 16.21%		
No	609, 82.63%	335, 81.71%	274, 83.79%		
HAMD	30.07±2.93	30.06±2.90	30.09±2.97	0.13	0.898
HAMA	21.59±3.00	21.68±3.19	21.48±2.76	-0.89	0.374
CGI-SI	5.92±0.73	5.89±0.73	5.96±0.73	1.23	0.218
PSS	9.20±4.92	9.33±5.12	9.04±4.68	-0.80	0.424
TSH - uIU/mL	4.27±2.85	4.64±2.85	3.80±2.79	-4.00	< .001*
FT_3 - pmol/L	4.92±0.67	4.93±0.65	4.90±0.70	-0.43	0.667
FT_4 - pmol/L	16.81±3.01	16.95±3.18	16.75±3.01	-0.86	0.391
WC - cm	80.07±8.34	80.17±8.45	79.94±8.22	-0.37	0.714
FBG - mmol/L	5.29±0.65	5.32±0.66	5.27±0.64	-1.04	0.299
TG - mmol/L	2.15±1.00	2.14±0.92	2.16±1.09	0.19	0.850
TC - mmol/L	4.88±0.94	4.83±0.89	4.94±1.00	1.63	0.105
HDL-C - mmol/L	1.32±0.23	1.33±0.22	1.32±0.24	-0.20	0.838
LDL-C - mmol/L	2.69±0.84	2.76±0.71	2.60±0.96	-2.51	0.012*
SBP - mmHg	117.03±11.47	118.07±10.71	115.72±12.24	-2.73	0.006*
DBP - mmHg	75.10±7.04	75.45±6.86	74.65±7.24	-1.53	0.126

HAMD: Hamilton Depression Scale Score; HAMA: Hamilton Anxiety Scale Score; CGI-SI: Clinical Global Impression Scale - Severity of Illness; PSS: Positive symptom subscale; TSH: thyroid stimulating hormone; FT_3: free triiodothyronine; FT_4: free tetraiodothyronine; BMI: body mass index; WC: waist circumference; FBG: fasting

blood glucose; TG: triglycerides; TC: total cholesterol; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure. $^{*}p < 0.05$

Table 2: Binary logistic regression analysis of the determinants of overweight in MDD patients with anxiety.

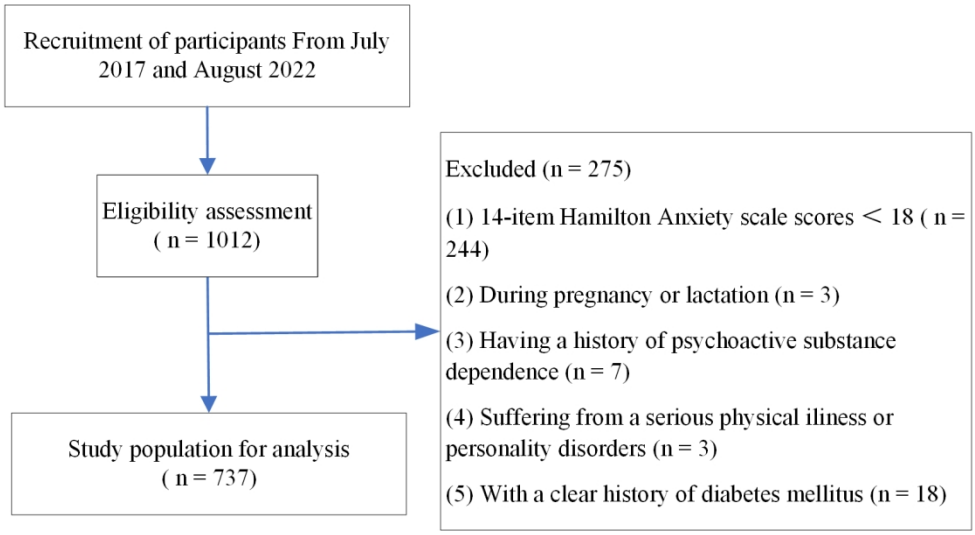
	Coefficients	Std. error	Wald	*p*-value	95% CI for EXP (B)		
	B				Exp(B)	Lower	Upper
Constant	-0.80	0.29	7.73				
Marital status (Unmarried *vs.* Married)	0.28	0.16	2.92	0.018*	1.32	1.06	1.81
TSH	0.10	0.03	11.01	0.001*	1.10	1.04	1.17
LDL-C	0.16	0.10	2.79	0.045*	1.18	1.00	1.43

TSH: Thyroid stimulating hormone; LDL-C: low density lipoprotein cholesterol. $^{*}p < 0.05$

Table 3: Multiple linear regression analysis of factors associated with BMI in MDD patients with anxiety.

	Coefficients	Std. error	*t*	*p*-value	95% CI	
	B				Lower	Upper
TSH - uIU/mL	0.16	0.02	3.17	0.002*	0.02	0.11
LDL-C - mmol/L	0.08	0.08	1.63	0.103	-0.03	0.29

TSH: Thyroid stimulating hormone; LDL-C: low density lipoprotein cholesterol. $^{*}p < 0.05$



Participant inclusion flow chart

146x77mm (300 x 300 DPI)

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Clinical Features of Overweight in Acute-Phase Hospitalized Major Depressive Disorder with Co-morbid Anxiety

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Abstract

Objective: This study aimed to investigate the incidence of overweight and obesity in patients with Major Depressive Disorder (MDD) co-morbid anxiety during the acute phase, and to explore the factors associated with overweight and obesity in this cohort.

Design: Cross-sectional study.

Setting: The MDD co-morbid anxiety symptoms study was conducted from July 2017 and August 2022.

Methods: A total of 737 hospitalized MDD patients with co-morbid anxiety symptoms in the acute phase were enrolled. Socio-demographic data, general clinical information, biochemical indicators, depressive and anxiety symptoms, psychotic symptoms, and illness severity were assessed. Continuous and categorical variables were analyzed using independent samples t-tests and chi-square tests, respectively. Binary logistic regression and multivariate linear regression analyses were conducted to determine

factors influencing the outcomes.

Primary outcome measures: Incidence and clinical correlations of overweight [body mass index (BMI) greater than or equal to 25].

Results: In the study population, 55.63% were identified as overweight. Binary logistic regression analysis revealed that being married (B = 0.28, p = 0.018, OR = 1.10), thyroid-stimulating hormone (TSH) levels (B = 0.10, p = 0.001, OR = 1.10), and low-density lipoprotein cholesterol (LDL-C) levels (B = 1.61, p = 0.045, OR = 1.18) were significant positive predictors of overweight development. Additionally, multiple linear regression indicated that TSH levels (B = 0.16, t = 3.17, p = 0.002) were positively predicted higher BMI values.

Conclusion: The findings suggest that over half of MDD patients with anxiety symptoms present with overweight. Thyroid function emerges as a crucial clinical factor for being overweight in this population. Targeted interventions focusing on thyroid function may hold promise as a therapeutic approach for managing overweight in MDD patients with co-morbid anxiety.

Keywords: Major depression disorder, Anxiety, Overweight, Thyroid stimulating hormone

STRENGTHS AND LIMITATIONS

1. The large-sample cross-sectional study design ensured the stability of the results.
2. The target parameters included are common biochemical indicators, which are easy to detect and clinically promoted at low cost.
3. The cross-sectional design limits the ability to infer causality.
4. The setting of inclusion criteria introduces potential confounding factors.

1. Introduction

Major depressive disorder (MDD) is a common psychiatric disorder characterized by marked depressed mood, diminished interest, and decreased energy[1]. Although anxiety disorders and already in MDD are two distinct diagnostic entities, anxiety and depression co-morbidity is a relatively common syndrome[2]. In Western countries, the prevalence of comorbid anxiety in patients with MDD ranges from 11% to 80%[3-5], and in China, similarly, upwards of 70% of patients with MDD have comorbid anxiety symptoms[6 7]. Comorbid anxiety symptoms often lead to lower treatment response rates, lower remission rates, lower quality of life, suicidal behavior, and higher risk of

cardiovascular disease in MDD patients[2 8 9].

Mood disorders and obesity appear to be twins, often acting as risk factors for each other, and were once collectively referred to as the "metabolic-mood syndrome"[10]. Previous studies have shown that patients with MDD frequently experience overweight and obesity[11-13]. The presence of obesity in individuals with MDD can have detrimental effects, affecting their clinical outcomes by prolonging recovery time and increasing suicidal ideation[14 15]. Additionally, both overweight and obese individuals are vulnerable to mood disorders[16 17]. Studies have demonstrated that weight reduction is crucial for alleviating anxiety and depressive symptoms in patients[18 19]. Several pathways have been identified that connect obesity and mood disorders, such as lifestyle behavioral habits[20 21], hypothalamic-pituitary-adrenal (HPA) axis disorders[22], altered glucocorticoid receptor function[23], inflammation[24], and genetic variations[25 26], among others. Given the complex relationship between overweight and mood disorders and the negative empowerment on the efficacy and prognosis of patients with MDD, actively clarifying the clinical characteristics of obesity in MDD populations and exploring the potential biomarkers that can be used for clinical interventions is a very critical task.

Up to now, although there are many studies related to being overweight in MDD patients, there are not enough studies on overweight in MDD patients with comorbid anxiety, and the results of the few studies are inconsistent due to issues such as sample size, population characteristics, cultural and geographic differences[27 28] . More importantly, co-morbid factors such as obesity are important factors in treatment interruption and disease relapse in the MDD population[29]. This study examined the incidence of overweight in a sample of hospitalized Chinese Han patients in the acute phase of MDD with co-morbid anxiety. It also explored the factors influencing both the occurrence and severity of overweight, offering valuable insights and warnings for proactive weight management in this target population.

2. Subjects and Methods

2.1 Subjects

We based the sample size prediction on the following formula:

$$n = \frac{Z^2 P(1-P)}{d^2}$$

where: n = Sample size, Z = Z-statistic for the chosen level of confidence (1.96 for a 95% confidence level), P = Expected prevalence or proportion (With reference to the

prevalence of overweight in the Chinese general population, the value of 0.5 was taken here[30]), d = Precision or margin of error (equal to 0.05), the statistical power (1-β) was 0.90. Thus, the estimated sample size required was 384 participants.

In this study, 737 individuals with MDD who also presented with co-morbid anxiety symptoms were enrolled. These participants were admitted to Wuhan Mental Health Center, the foremost public tertiary psychiatric hospital in central China, due to an acute episode of their mental health condition, spanning from July 2017 to August 2022 (The flow chart is shown in **Figure 1**).

The study included patients who fulfilled the following criteria: (1) met the diagnostic criteria for MDD as per the International Classification of Diseases, 10th edition (ICD-10); (2) were aged between 18 and 60 years; (3) were of Chinese Han nationality; (4) either male or female; (5) scored a 17-item Hamilton Depression Scale (HAMD-17) of ⩾24; and (6) scored a 14-item Hamilton Anxiety scale (HAMA-14) of ⩾18.

Patients who fulfilled any of the following criteria were excluded from the study: those diagnosed with other severe mental illnesses, pregnant or breastfeeding individuals, patients with a history of substance abuse, those with a documented diagnosis of a serious physical illness or personality disorder, those with comorbid diabetes mellitus, and those who were unable to cooperate in completing a psychological evaluation for any reason.

The research adhered strictly to the principles outlined in the Declaration of Helsinki. The study protocol underwent rigorous review and approval by the Ethics Committee of Wuhan Mental Health Center. Furthermore, all participants provided their informed consent through a paper-based form.

2.2 Research design

This study was conducted as a cross-sectional research design. Initially, we determined the incidence of being overweight within the target population. Subsequently, we compared demographic and general clinical data between two clinical subgroups: those with normal body mass index (BMI) (labeled as normal BMI group) and those with high BMI (labeled as high BMI group). Finally, we analyzed the factors associated with overweight and its severity.

A self-designed EXCLE form was used to collect demographic and clinical data of the enrolled patients, including age, age at onset, disease duration, gender, marital status, education, history of suicidal behavior, history of outpatient treatment, BMI, waist circumference (WC), blood pressure. On admission day, depressive symptoms,

anxiety symptoms, psychotic symptoms, illness severity were evaluated using HAMD-17, HAMA-14, Positive Symptom Subscales (P1-P7) of Positive and Negative Symptom Scale (PANSS), Clinical Global Impression Inventory-Severity of Illness (CGI-SI). Then, routine biochemical parameters measured by fasting blood of the patient, including thyroid function, fasting blood glucose (FBG) levels, lipid levels were extracted from electronic medical record system.

The criteria for overweight (high BMI group) were established based on the weight status classification criteria of the Chinese Obesity Working Group[31], Accordingly, all study subjects were classified into two categories: those with a normal BMI (BMI < 24 kg/m^2), and those who fell into the overweight or obesity category (BMI $\geqslant$ 24 kg/m^2).

Two psychiatrists conducted the evaluation of pertinent psychological scales, each with a title of attending or higher, who were affiliated with the medical institution from which the sample originated.

2.3 Data analysis

Categorical variables were reported as counts, while continuous variables with normal distribution were depicted using means and standard deviations. Continuous variables that were not normally distributed were expressed using medians (P_{25}, P_{75}). The Shapiro-Wilk test was employed to verify the normality of all continuous variables. For both continuous variables, whether normally or non-normally distributed, and categorical variables, statistical comparisons were made using independent samples t-tests, Mann-Whitney U-tests, and Chi-square tests. To discern differences in demographic and clinical variables between the overweight subgroup and the normal BMI subgroup, we applied chi-square tests to categorical data and independent samples t-tests to continuous variables. Subsequently, we utilized the variables that varied in univariate analyses as independent variables and constructed binary logistic regression models with overweight as the outcome variable to investigate factors influencing overweight within the target population. Ultimately, a multiple linear regression model was developed to identify factors impacting patients with degrees of overweight, utilizing BMI as the dependent variable and factors affecting overweight from binary logistic regression as independent variables. All p values were two-tailed, with significance set at < 0.05. Statistical analyses were executed using SPSS 27 (SPSS, Inc., Chicago, IL).

3. Results

3.1 The differences between high BMI group and normal BMI group.

Of all our MDD patients with comorbid anxiety included in the study, 55.63% (410/737) met the diagnostic criteria for being overweight. The mean BMI in the two subgroups was (25.39 ± 1.15) kg/m^2 in the high BMI group and (22.71 ± 1.08) kg/m^2 in the normal BMI group. We found that the following parameters were significantly higher in the high BMI group than in the normal BMI group, onset age (t = -2.14, p = 0.033), proportion married (χ^2 = 4.24, p = 0.039), thyrotropin levels (t = -4.00, p < .001), low density lipoprotein cholesterol (LDL-C) levels (t = -2.51, p = 0.012), and systolic blood pressure (SBP) levels(t = -2.73, p = 0.006) (**Table 1**).

3.2 Determinants of overweight and obesity in target patients: a binary logic-based model.

We then developed a binary logistic regression model (Backward: Wald) using the variables that differed in the univariate analysis as independent variables and overweight as dependent variables. As the results in **Table 2** show, being married (B = 0.28, p = 0.018, OR = 1.10), TSH levels (B = 0.10, p = 0.001, OR = 1.10) and LDL-C (B = 1.61, p = 0.045, OR = 1.18) were positively predictive of clinical factors for being overweight.

3.3 Factors affecting severity of overweight and obesity in high BMI subgroup: a multiple linear regression model.

Finally, for the high BMI subgroup of patients, we constructed a multiple linear regression model (input) with BMI as the dependent variable and the factors associated with the previous step affecting overweight and obesity as independent variables and the results are shown in **Table 3**. We found that thyroid-stimulating hormone (B = 0.16, t = 3.17, p= 0.002) was a positive predictor of elevated BMI.

4. Discussion

In our study, we observed specific clinical characteristics related to being overweight in individuals with MDD co-morbid anxiety symptoms. The incidence of overweight in this population was notably high, reaching 55.63%. Additionally, we found that individuals in the overweight subgroups experienced a later onset of MDD and exhibited more pronounced metabolic disturbances. Furthermore, our analysis revealed that being married and elevated levels of TSH and LDL-C were associated with an increased risk of developing overweight and obesity. Notably, TSH levels were also identified as a clinical factor that promotes overweight and greater severity.

The incidence of overweight in patients with MDD co-morbid anxiety in our study was 55.63%. Previous reports on the prevalence of overweight in individuals with MDD have shown some variation. For instance, in a study of first episode MDD patients in northern China, the prevalence was reported at 59.72%[32], while a multicenter study in Germany reported a prevalence of 52.16% amongst first episode MDD patients[13]. When the sample extended to multiple European countries, the prevalence of overweight in MDD patients was approximately 48%[14]. These studies, albeit slightly different from our current study, focused on individuals within the general MDD population rather than specifically considering patients with MDD comorbid anxiety symptoms. A recent study that shared a similar study population with our research found a higher prevalence of overweight (68.3%) in patients with MDD co-morbid anxiety[33]. This rate was higher than in our study, and this heterogeneity may have been caused by the stricter restriction of anxiety symptoms in that study and the fact that some of the patients we included had a history of outpatient treatment. While the exact prevalence may differ across studies, a consistent finding is that a significant portion of individuals in the MDD population are overweight, focusing on and underscoring the importance of addressing weight concerns in this patient group.

Subsequently, our study examined the clinical factors that contribute to the development of overweight in patients with comorbid anxiety symptoms in MDD. Our findings indicate that being married and TSH levels were identified as contributing factors to overweight formation in this population. Marital status has been consistently associated with a higher risk of overweight not only in the general population but also in individuals with MDD[15 34]. Even after adjusting for variables such as employment status, stress levels, and perceived health status, this relationship persists[35]. The gain observed in married individuals may be linked to reduced physical activity[36], and it is also plausible that spouses may provide greater nutritional support during the acute phases of MDD episode. This suggests that spouses of married individuals with MDD may provide more balanced nutritional support during the onset of depression to help prevent obesity.

Elevated TSH levels emerged as a contributing factor for the development of overweight, obesity, and elevated BMI in our study population, aligning with numerous existing reports[33 37 38]. Another study exploring MDD patients with comorbid anxiety found that anxiety symptoms were associated with an increased risk of being overweight, with thyroid function playing a crucial role as a contributing factor[33]. Evidence indicates that MDD patients with anxiety disorders often exhibit heightened levels of antithyroid antibodies due to stress-induced immune responses[39-41], leading to subclinical hypothyroidism and subsequently elevated serum TSH levels[42 43]. Elevated TSH levels inhibit triglyceride lipase in adipose tissue via the TSH receptor in adipocytes, promoting adipocyte enlargement and consequent weight gain[44]. Conversely, hypertrophied adipose tissue secretes leptin, which activates thyrotropin-

releasing hormone (TRH) neurons to stimulate increased TSH levels[45]. Collectively, the reviewed studies underscore the importance of maintaining thyroid function within normal limits to help manage overweight and obesity in individuals with MDD and anxiety symptoms.

This study possesses several strengths. Firstly, our study included a sizable sample size, enhancing the stability and generalizability of the results. Secondly, the target parameters we investigated are common clinical indicators, which facilitates the generalizability and practical application of the findings at a lower cost. The current study also presents several limitations that should be acknowledged. Firstly, our research design was cross-sectional, precluding the establishment of causal relationships between identified clinical factors and BMI in our study population. Secondly, the study predominantly focused on individuals with MDD in the acute phase of disease onset, potentially limiting the generalizability of our findings to other subpopulations of MDD patients. Lastly, a considerable proportion of the participants had a history of outpatient treatment, introducing a confounding factor that may have influenced the study outcomes. To address these limitations, our future research endeavors will aim to undertake more rigorous prospective studies with a broader scope.

In conclusion, over half of patients with MDD co-morbid anxiety symptoms develop overweight. Furthermore, thyroid function is a crucial clinical factor for the development and severity of overweight and obesity. Therefore, targeted interventions on thyroid function could be potential therapeutic targets for overweight and obesity in patients with MDD co-morbid anxiety symptoms.

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Authors' contributions

HZ: Writing – original draft. JW: Formal analysis, Writing – review & Editing. WZ: Investigation, Supervision, Writing – review & editing. XL: Conceptualization, Methodology, Software, Investigation, Formal analysis.

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Competing interests

None.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication

Consent obtained directly from patient(s).

Ethics approval and consent to participate

The ethics committees of the Wuhan mental health center reviewed and approved this study. All subject guardians knew about this study and signed informed consent. All procedures carried out in studies conformed to the Helsinki Declaration and its subsequent amendments or similar ethical standards.

Availability of data and materials

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

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Figure legend

Figure 1: Flowchart for study sample inclusion

Tables

Table 1: The demographic and general clinical data in different clinical subgroups.

Index	Total patients (n = 737)	Overweight (n = 410)	Normal BMI (n = 327)	$t/Z/\chi^2$	p - value
Age - years	35.83±12.47	36.63±12.37	34.83±12.54	-1.94	0.052
Onset age - years	34.32±12.41	31(21-43)	35(23-45)	-2.21	0.027*
Course of disease - months	10.80±4.36	10.5(9-13)	10(7-12)	-1.87	0.061
Gender - (n, %)				0.06	0.940
Male	249, 33.79%	139, 33.90%	110,33.64 %		
Female	488, 66.21%	271, 66.10%	217, 66.36%		
Marital status - (n, %)				4.24	0.039*
Unmarried	228, 30.94%	114, 27.80%	114, 34.86%		
Married	509,69.06%	296, 72.20%	213, 65.14%		
Treatment history - (n, %)				0.83	0.361
Yes	482, 65.40%	274, 66.83%	208, 63.61%		
NO	255, 34.60%	136, 33.17%	119, 36.39%		
Educational background - (n, %)				0.75	0.387
High school and below	508, 68.93%	288, 70.24%	220, 67.28%		
Bachelor and above	229, 31.07%	122, 29.76%	107, 32.72%		
History of suicidal behavior				0.55	0.458
Yes	128, 17.37%	75, 18.29%	53, 16.21%		
No	609, 82.63%	335, 81.71%	274, 83.79%		
HAMD	30.07±2.93	30.06±2.90	30.09±2.97	0.13	0.898
HAMA	21.59±3.00	21.68±3.19	21.48±2.76	-0.89	0.374
CGI-SI	5.92±0.73	6(5-6)	6(5-6)	-1.12	0.217
PSS	9.20±4.92	7(7-7)	7(7-7)	-0.42	0.676
TSH - uIU/mL	4.27±2.85	4.64±2.85	3.80±2.79	-4.00	< .001*
FT_3 - pmol/L	4.92±0.67	4.93±0.65	4.90±0.70	-0.43	0.667
FT_4 - pmol/L	16.81±3.01	16.95±3.18	16.75±3.01	-0.86	0.391
WC - cm	80.07±8.34	80(74.5-86.5)	81(73-86.5)	-0.38	0.706
FBG - mmol/L	5.29±0.65	5.32±0.66	5.27±0.64	-1.04	0.299
TG - mmol/L	2.15±1.00	2.14±0.92	2.16±1.09	0.19	0.850
TC - mmol/L	4.88±0.94	4.83±0.89	4.94±1.00	1.63	0.105
HDL-C - mmol/L	1.32±0.23	1.33±0.22	1.32±0.24	-0.20	0.838
LDL-C - mmol/L	2.69±0.84	2.76±0.71	2.60±0.96	-2.51	0.012*
SBP - mmHg	117.03±11.47	115(108-124)	118(110-125)	-2.77	0.006*
DBP - mmHg	75.10±7.04	74(70-78)	75(70-80)	-1.59	0.706

HAMD: Hamilton Depression Scale Score; HAMA: Hamilton Anxiety Scale Score; CGI-SI: Clinical Global Impression Scale - Severity of Illness; PSS: Positive symptom subscale; TSH: thyroid stimulating hormone; FT_3: free triiodothyronine; FT_4: free tetraiodothyronine; BMI: body mass index; WC: waist circumference; FBG: fasting

blood glucose; TG: triglycerides; TC: total cholesterol; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure. $^{*}p < 0.05$

Table 2: Binary logistic regression analysis of the determinants of overweight in MDD patients with anxiety.

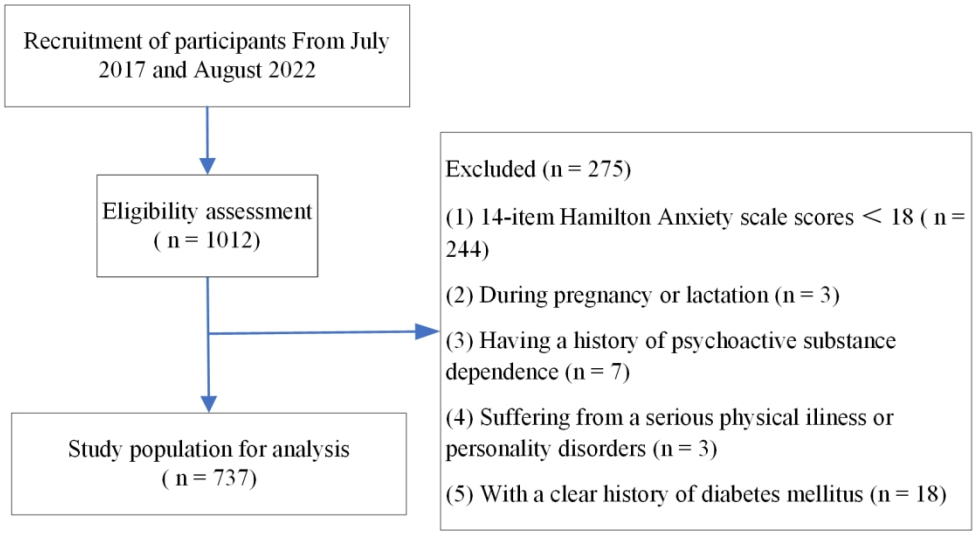
	Coefficients	Std. error	Wald	*p*-value	95% CI for EXP (B)		
	B				Exp(B)	Lower	Upper
Constant	-0.80	0.29	7.73				
Marital status (Unmarried *vs.* Married)	0.28	0.16	2.92	0.018*	1.32	1.06	1.81
TSH	0.10	0.03	11.01	0.001*	1.10	1.04	1.17
LDL-C	0.16	0.10	2.79	0.045*	1.18	1.00	1.43

TSH: Thyroid stimulating hormone; LDL-C: low density lipoprotein cholesterol. $^{*}p < 0.05$

Table 3: Multiple linear regression analysis of factors associated with BMI in MDD patients with anxiety.

	Coefficients	Std. error	*t*	*p*-value	95% CI	
	B				Lower	Upper
TSH - uIU/mL	0.16	0.02	3.17	0.002*	0.02	0.11
LDL-C - mmol/L	0.08	0.08	1.63	0.103	-0.03	0.29

TSH: Thyroid stimulating hormone; LDL-C: low density lipoprotein cholesterol. $^{*}p < 0.05$



Participant inclusion flow chart

146x77mm (300 x 300 DPI)

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Clinical Features of Overweight in Acute-Phase Hospitalized Major Depressive Disorder with Co-morbid Anxiety: a cross-sectional study

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Abstract

Objective: This study aimed to investigate the incidence of overweight in patients with major depressive disorder (MDD) co-morbid anxiety during the acute phase and to explore associated factors.

Design: Cross-sectional study.

Setting: Wuhan Mental Health Center, China, from July 2017 to August 2022.

Participants: 737 hospitalized patients diagnosed with MDD in the acute phase with co-morbid anxiety symptoms.

Primary outcome measures: Incidence and clinical correlations of overweight [body mass index (BMI) greater than or equal to 24].

Results: Among the study population, 55.63% were classified as overweight. Binary logistic regression analysis revealed that being married (B = 0.28, p = 0.018, OR = 1.10),

thyroid-stimulating hormone (TSH) levels (B = 0.10, p = 0.001, OR = 1.10), and low-density lipoprotein cholesterol (LDL-C) levels (B = 1.61, p = 0.045, OR = 1.18) were significant positive predictors of overweight. Additionally, multiple linear regression indicated that TSH levels (B = 0.16, t = 3.17, p = 0.002) were positively associated with higher BMI values.

Conclusion: Over half of hospitalized MDD patients with co-morbid anxiety are overweight. Thyroid function emerges as a crucial clinical factor for overweight in this population. Targeted interventions focusing on thyroid function may be a promising approach for managing overweight in these patients.

Keywords: Major depression disorder, Anxiety, Overweight, Thyroid stimulating hormone

STRENGTHS AND LIMITATIONS

1. This study includes a relatively large sample, ensuring the stability of the results.
2. The biochemical indicators analyzed are commonly used in clinical practice, making the findings easily applicable.
3. The cross-sectional design limits the ability to infer causality.
4. Unmeasured confounding factors may have influenced the observed associations.

1. Introduction

Major depressive disorder (MDD) is a common psychiatric disorder characterized by marked depressed mood, diminished interest, and decreased energy[1]. Although anxiety disorders and already in MDD are two distinct diagnostic entities, anxiety and depression co-morbidity is a relatively common syndrome[2]. In Western countries, the prevalence of comorbid anxiety in patients with MDD ranges from 11% to 80%[3-5], and in China, similarly, upwards of 70% of patients with MDD have comorbid anxiety symptoms[6 7]. Comorbid anxiety symptoms are frequently associated with lower treatment response rates, lower remission rates, diminished quality of life, an increased likelihood of suicidal behavior, and a higher risk of cardiovascular disease in MDD patients[2 8 9].

Mood disorders and obesity appear to be twins, often acting as risk factors for each other, and were once collectively referred to as the "metabolic-mood syndrome"[10]. Previous studies have shown that patients with MDD frequently experience overweight and obesity[11-13]. The presence of obesity in individuals with MDD can have detrimental effects, affecting their clinical outcomes by prolonging recovery time and increasing

suicidal ideation[14 15]. Additionally, both overweight and obese individuals are vulnerable to mood disorders[16 17]. Studies have demonstrated that weight reduction is crucial for alleviating anxiety and depressive symptoms in patients[18 19]. Several pathways have been identified that connect obesity and mood disorders, such as lifestyle behavioral habits[20 21], hypothalamic-pituitary-adrenal (HPA) axis disorders[22], altered glucocorticoid receptor function[23], inflammation[24], and genetic variations[25 26], among others. Given the complex relationship between overweight and mood disorders and the negative empowerment on the efficacy and prognosis of patients with MDD, actively clarifying the clinical characteristics of obesity in MDD populations and exploring the potential biomarkers that can be used for clinical interventions is a very critical task.

Up to now, although there are many studies related to being overweight in MDD patients, there are not enough studies on overweight in MDD patients with comorbid anxiety, and the results of the few studies are inconsistent due to issues such as sample size, population characteristics, cultural and geographic differences[27 28] . More importantly, co-morbid factors such as obesity are important factors in treatment interruption and disease relapse in the MDD population[29]. This study examined the incidence of overweight in a sample of hospitalized Chinese Han patients in the acute phase of MDD with co-morbid anxiety. It also explored the factors influencing both the occurrence and severity of overweight, offering valuable insights and warnings for proactive weight management in this target population.

2. Subjects and Methods

2.1 Subjects

We based the sample size prediction on the following formula:

$$n = \frac{Z^2 P(1-P)}{d^2}$$

where: n = Sample size, Z = Z-statistic for the chosen level of confidence (1.96 for a 95% confidence level), P = Expected prevalence or proportion (With reference to the prevalence of overweight in the Chinese general population, the value of 0.5 was taken here[30]), d = Precision or margin of error (equal to 0.05), the statistical power (1-β) was 0.90. Thus, the estimated sample size required was 384 participants.

In this study, 737 individuals with MDD who also presented with co-morbid anxiety symptoms were enrolled. These participants were admitted to Wuhan Mental Health Center, the foremost public tertiary psychiatric hospital in central China, due to

an acute episode of their mental health condition, spanning from July 2017 to August 2022 (The flow chart is shown in **Figure 1**).

The study included patients who fulfilled the following criteria: (1) met the diagnostic criteria for MDD as per the International Classification of Diseases, 10th edition (ICD-10); (2) were aged between 18 and 60 years; (3) were of Chinese Han nationality; (4) either male or female; (5) scored a 17-item Hamilton Depression Scale (HAMD-17) of ⩾24; and (6) scored a 14-item Hamilton Anxiety scale (HAMA-14) of ⩾18.

Patients who fulfilled any of the following criteria were excluded from the study: those diagnosed with other severe mental illnesses, pregnant or breastfeeding individuals, patients with a history of substance abuse, those with a documented diagnosis of a serious physical illness or personality disorder, those with comorbid diabetes mellitus, and those who were unable to cooperate in completing a psychological evaluation for any reason.

The research adhered strictly to the principles outlined in the Declaration of Helsinki. The study protocol underwent rigorous review and approval by the Ethics Committee of Wuhan Mental Health Center. Furthermore, all participants provided their informed consent through a paper-based form.

2.2 Research design

This study was conducted as a cross-sectional research design. Initially, we determined the incidence of being overweight within the target population. Subsequently, we compared demographic and general clinical data between two clinical subgroups: those with normal body mass index (BMI) (labeled as normal BMI group) and those with high BMI (labeled as high BMI group). Finally, we analyzed the factors associated with overweight and its severity.

A self-designed EXCLE form was used to collect demographic and clinical data of the enrolled patients, including age, age at onset, disease duration, gender, marital status, education, history of suicidal behavior, history of outpatient treatment, BMI, waist circumference (WC), blood pressure. On admission day, depressive symptoms, anxiety symptoms, psychotic symptoms, illness severity were evaluated using HAMD-17, HAMA-14, Positive Symptom Subscales (P1-P7) of Positive and Negative Symptom Scale (PANSS), Clinical Global Impression Inventory-Severity of Illness (CGI-SI). Then, routine biochemical parameters measured by fasting blood of the patient, including thyroid function, fasting blood glucose (FBG) levels, lipid levels were extracted from electronic medical record system.

The criteria for overweight (high BMI group) were established based on the weight status classification criteria of the Chinese Obesity Working Group[31], Accordingly, all study subjects were classified into two categories: those with a normal BMI (BMI < 24 kg/m^2), and those who fell into the overweight or obesity category (BMI⩾24 kg/m^2).

Two psychiatrists conducted the evaluation of pertinent psychological scales, each with a title of attending or higher, who were affiliated with the medical institution from which the sample originated.

2.3 Data analysis

Categorical variables were reported as counts, while continuous variables with normal distribution were depicted using means and standard deviations. Continuous variables that were not normally distributed were expressed using medians (p25, p75). The Shapiro-Wilk test was employed to verify the normality of all continuous variables. For both continuous variables, whether normally or non-normally distributed, and categorical variables, statistical comparisons were made using independent samples t-tests, Mann-Whitney U-tests, and Chi-square tests. To discern differences in demographic and clinical variables between the overweight subgroup and the normal BMI subgroup, we applied chi-square tests to categorical data and independent samples t-tests to continuous variables. Subsequently, we utilized the variables that varied in univariate analyses as independent variables and constructed binary logistic regression models with overweight as the outcome variable to investigate factors influencing overweight within the target population. Ultimately, a multiple linear regression model was developed to identify factors impacting patients with degrees of overweight, utilizing BMI as the dependent variable and factors affecting overweight from binary logistic regression as independent variables. All p values were two-tailed, with significance set at < 0.05. Statistical analyses were executed using SPSS 27 (SPSS, Inc., Chicago, IL).

3. Results

3.1 The differences between high BMI group and normal BMI group.

Of all our MDD patients with comorbid anxiety included in the study, 55.63% (410/737) met the diagnostic criteria for being overweight. The mean BMI in the two subgroups was (25.39 ± 1.15) kg/m^2 in the high BMI group and (22.71 ± 1.08) kg/m^2 in the normal BMI group. We found that the following parameters were significantly higher in the high BMI group than in the normal BMI group, onset age (t = -2.14, p = 0.033), proportion married (χ^2 = 4.24, p = 0.039), thyrotropin levels (t = -4.00, p < .001),

low density lipoprotein cholesterol (LDL-C) levels (t = -2.51, p = 0.012), and systolic blood pressure (SBP) levels(t = -2.73, p = 0.006) (**Table 1**).

3.2 Determinants of overweight in target patients: a binary logic-based model.

We then developed a binary logistic regression model (Backward: Wald) using the variables that differed in the univariate analysis as independent variables and overweight as dependent variables. As the results in **Table 2** show, being married (B = 0.28, p = 0.018, OR = 1.10), TSH levels (B = 0.10, p = 0.001, OR = 1.10) and LDL-C (B = 1.61, p = 0.045, OR = 1.18) were positively predictive of clinical factors for being overweight.

3.3 Factors affecting severity of overweight in high BMI subgroup: a multiple linear regression model.

Finally, for the high BMI subgroup of patients, we constructed a multiple linear regression model (input) with BMI as the dependent variable and the factors associated with the previous step affecting overweight as independent variables and the results are shown in **Table 3**. We found that thyroid-stimulating hormone (B = 0.16, t = 3.17, p= 0.002) was a positive predictor of elevated BMI.

4. Discussion

In our study, we observed specific clinical characteristics related to being overweight in individuals with MDD co-morbid anxiety symptoms. The incidence of overweight in this population was notably high, reaching 55.63%. Additionally, we found that individuals in the overweight subgroups experienced a later onset of MDD and exhibited more pronounced metabolic disturbances. Furthermore, our analysis revealed that being married and elevated levels of TSH and LDL-C were associated with an increased risk of developing overweight. Notably, TSH levels were also identified as a clinical factor that promotes overweight and greater severity.

The incidence of overweight in patients with MDD co-morbid anxiety in our study was 55.63%. Previous reports on the prevalence of overweight in individuals with MDD have shown some variation. For instance, in a study of first episode MDD patients in northern China, the prevalence was reported at 59.72%[32], while a multicenter study in Germany reported a prevalence of 52.16% amongst first episode MDD patients[13]. When the sample extended to multiple European countries, the prevalence of overweight in MDD patients was approximately 48%[14]. These studies, albeit slightly different from our current study, focused on individuals within the general MDD

population rather than specifically considering patients with MDD comorbid anxiety symptoms. A recent study that shared a similar study population with our research found a higher prevalence of overweight (68.3%) in patients with MDD co-morbid anxiety[33]. This rate was higher than in our study, and this heterogeneity may have been caused by the stricter restriction of anxiety symptoms in that study and the fact that some of the patients we included had a history of outpatient treatment. While the exact prevalence may differ across studies, a consistent finding is that a significant portion of individuals in the MDD population are overweight, focusing on and underscoring the importance of addressing weight concerns in this patient group.

Subsequently, our study examined the clinical factors that contribute to the development of overweight in patients with comorbid anxiety symptoms in MDD. Our findings indicate that being married and TSH levels were identified as contributing factors to overweight formation in this population. Marital status has been consistently associated with a higher risk of overweight not only in the general population but also in individuals with MDD[15 34]. Even after adjusting for variables such as employment status, stress levels, and perceived health status, this relationship persists[35]. The gain observed in married individuals may be linked to reduced physical activity[36], and it is also plausible that spouses may provide greater nutritional support during the acute phases of MDD episode. This suggests that spouses of married individuals with MDD may provide more balanced nutritional support during the onset of depression to help prevent obesity.

Elevated TSH levels emerged as a contributing factor for the development of overweight, obesity, and elevated BMI in our study population, aligning with numerous existing reports[33 37 38]. Another study exploring MDD patients with comorbid anxiety found that anxiety symptoms were associated with an increased risk of being overweight, with thyroid function playing a crucial role as a contributing factor[33]. Evidence indicates that MDD patients with anxiety disorders often exhibit heightened levels of antithyroid antibodies due to stress-induced immune responses[39-41], leading to subclinical hypothyroidism and subsequently elevated serum TSH levels[42 43]. Elevated TSH levels inhibit triglyceride lipase in adipose tissue via the TSH receptor in adipocytes, promoting adipocyte enlargement and consequent weight gain[44]. Conversely, hypertrophied adipose tissue secretes leptin, which activates thyrotropin-releasing hormone (TRH) neurons to stimulate increased TSH levels[45]. Collectively, the reviewed studies underscore the importance of maintaining thyroid function within normal limits to help manage overweight in individuals with MDD and anxiety symptoms.

This study possesses several strengths. Firstly, our study included a sizable sample size, enhancing the stability and generalizability of the results. Secondly, the target parameters we investigated are common clinical indicators, which facilitates the

generalizability and practical application of the findings at a lower cost. The current study also presents several limitations that should be acknowledged. Firstly, our research design was cross-sectional, precluding the establishment of causal relationships between identified clinical factors and BMI in our study population. Secondly, the study predominantly focused on individuals with MDD in the acute phase of disease onset, potentially limiting the generalizability of our findings to other subpopulations of MDD patients. Lastly, a considerable proportion of the participants had a history of outpatient treatment, introducing a confounding factor that may have influenced the study outcomes. To address these limitations, our future research endeavors will aim to undertake more rigorous prospective studies with a broader scope.

In conclusion, over half of patients with MDD co-morbid anxiety symptoms develop overweight. Furthermore, thyroid function is a crucial clinical factor for the development and severity of overweight. Therefore, targeted interventions on thyroid function could be potential therapeutic targets for overweight in patients with MDD co-morbid anxiety symptoms.

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Contributions

HZ: Writing – original draft. JW: Formal analysis, Writing – review & Editing. WZ: Investigation, Supervision, Writing – review & editing. XL: Conceptualization, Methodology, Software, Investigation, Formal analysis. Hong Zhang/HZ acted as guarantor.

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Competing interests

None.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication

Consent obtained directly from patient(s).

Ethics approval and consent to participate

The ethics committees of the Wuhan mental health center reviewed and approved this study. All subject guardians knew about this study and signed informed consent. All procedures carried out in studies conformed to the Helsinki Declaration and its subsequent amendments or similar ethical standards.

Availability of data and materials

Data are available upon reasonable request. The data sets analyzed during the current study are available from the corresponding author upon reasonable request.

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Figure legend

Figure 1: Flowchart for study sample inclusion

Tables

Table 1: The demographic and general clinical data in different clinical subgroups.

Index	Total patients (n = 737)	Overweight (n = 410)	Normal BMI (n = 327)	$t/Z/\chi^2$	p - value
Age - years	35.83±12.47	36.63±12.37	34.83±12.54	-1.94	0.052
Onset age - years	34.32±12.41	31(21-43)	35(23-45)	-2.21	0.027*
Course of disease - months	10.80±4.36	10.5(9-13)	10(7-12)	-1.87	0.061
Gender - (n, %)				0.06	0.940
Male	249, 33.79%	139, 33.90%	110,33.64 %		
Female	488, 66.21%	271, 66.10%	217, 66.36%		
Marital status - (n, %)				4.24	0.039*
Unmarried	228, 30.94%	114, 27.80%	114, 34.86%		
Married	509,69.06%	296, 72.20%	213, 65.14%		
Treatment history - (n, %)				0.83	0.361
Yes	482, 65.40%	274, 66.83%	208, 63.61%		
NO	255, 34.60%	136, 33.17%	119, 36.39%		
Educational background - (n, %)				0.75	0.387
High school and below	508, 68.93%	288, 70.24%	220, 67.28%		
Bachelor and above	229, 31.07%	122, 29.76%	107, 32.72%		
History of suicidal behavior				0.55	0.458
Yes	128, 17.37%	75, 18.29%	53, 16.21%		
No	609, 82.63%	335, 81.71%	274, 83.79%		
HAMD	30.07±2.93	30.06±2.90	30.09±2.97	0.13	0.898
HAMA	21.59±3.00	21.68±3.19	21.48±2.76	-0.89	0.374
CGI-SI	5.92±0.73	6(5-6)	6(5-6)	-1.12	0.217
PSS	9.20±4.92	7(7-7)	7(7-7)	-0.42	0.676
TSH - uIU/mL	4.27±2.85	4.64±2.85	3.80±2.79	-4.00	< .001*
FT_3 - pmol/L	4.92±0.67	4.93±0.65	4.90±0.70	-0.43	0.667
FT_4 - pmol/L	16.81±3.01	16.95±3.18	16.75±3.01	-0.86	0.391
WC - cm	80.07±8.34	80(74.5-86.5)	81(73-86.5)	-0.38	0.706
FBG - mmol/L	5.29±0.65	5.32±0.66	5.27±0.64	-1.04	0.299
TG - mmol/L	2.15±1.00	2.14±0.92	2.16±1.09	0.19	0.850
TC - mmol/L	4.88±0.94	4.83±0.89	4.94±1.00	1.63	0.105
HDL-C - mmol/L	1.32±0.23	1.33±0.22	1.32±0.24	-0.20	0.838
LDL-C - mmol/L	2.69±0.84	2.76±0.71	2.60±0.96	-2.51	0.012*
SBP - mmHg	117.03±11.47	115(108-124)	118(110-125)	-2.77	0.006*
DBP - mmHg	75.10±7.04	74(70-78)	75(70-80)	-1.59	0.706

HAMD: Hamilton Depression Scale Score; HAMA: Hamilton Anxiety Scale Score; CGI-SI: Clinical Global Impression Scale - Severity of Illness; PSS: Positive symptom subscale; TSH: thyroid stimulating hormone; FT_3: free triiodothyronine; FT_4: free tetraiodothyronine; BMI: body mass index; WC: waist circumference; FBG: fasting

blood glucose; TG: triglycerides; TC: total cholesterol; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure. $^{*}p < 0.05$

Table 2: Binary logistic regression analysis of the determinants of overweight in MDD patients with anxiety.

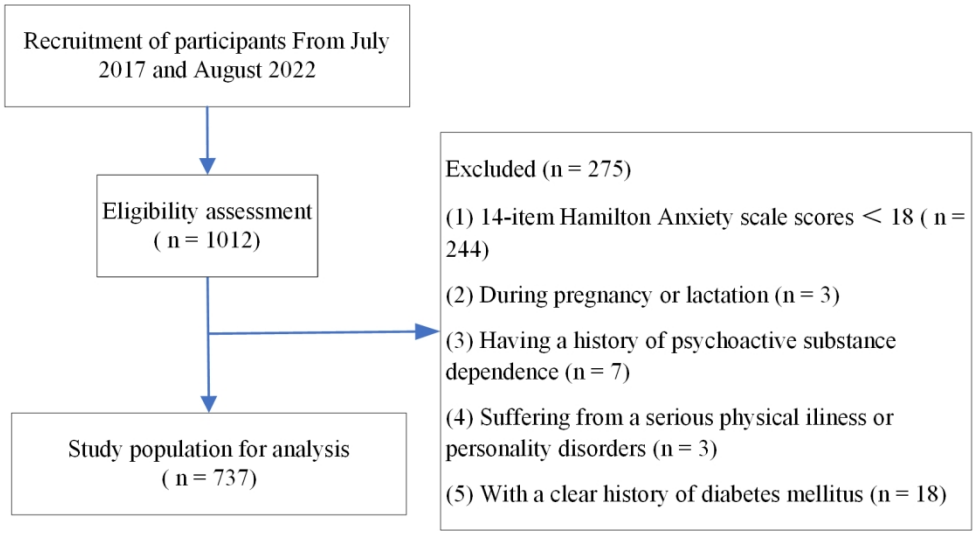
	Coefficients	Std. error	Wald	*p*-value	95% CI for EXP (B)		
	B				Exp(B)	Lower	Upper
Constant	-0.80	0.29	7.73				
Marital status (Unmarried *vs.* Married)	0.28	0.16	2.92	0.018*	1.32	1.06	1.81
TSH	0.10	0.03	11.01	0.001*	1.10	1.04	1.17
LDL-C	0.16	0.10	2.79	0.045*	1.18	1.00	1.43

TSH: Thyroid stimulating hormone; LDL-C: low density lipoprotein cholesterol. $^{*}p < 0.05$

Table 3: Multiple linear regression analysis of factors associated with BMI in MDD patients with anxiety.

	Coefficients	Std. error	*t*	*p*-value	95% CI	
	B				Lower	Upper
TSH - uIU/mL	0.16	0.02	3.17	0.002*	0.02	0.11
LDL-C - mmol/L	0.08	0.08	1.63	0.103	-0.03	0.29

TSH: Thyroid stimulating hormone; LDL-C: low density lipoprotein cholesterol. $^{*}p < 0.05$



Participant inclusion flow chart

146x77mm (300 x 300 DPI)