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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2024-087640
Article Type:	Original research
Date Submitted by the Author:	15-Apr-2024
Complete List of Authors:	Ma, Jun; Wuhan Mental Health Centre, Department of Psychiatry Zhang, Hong; Wuhan Mental Health Center Wang, Jing; Yunnan Institute For Drug Abuse Zhu, Wenting; Wuhan Mental Health Centre Liu, Xuebing; Wuhan Mental Health Center
Keywords:	Cross-Sectional Studies, Overweight, Obesity, Depression & mood disorders < PSYCHIATRY, Anxiety disorders < PSYCHIATRY

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

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15 **Abstract**

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

19 **Design:** Cross-sectional study.

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

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4 22 **Methods:** A total of 737 initially hospitalized MDD patients with concurrent anxiety
5 23 in the acute phase were enrolled. Socio-demographic data, general clinical information,
6 24 biochemical indicators, depressive and anxiety symptoms, psychotic symptoms, and
7 25 illness severity were assessed. Continuous and categorical variables were analyzed
8 26 using independent samples t-tests and chi-square tests, respectively. Binary logistic
9 27 regression and multivariate linear regression analyses were conducted to determine
10 28 factors influencing the outcomes.

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14 29 **Primary outcome measures:** Prevalence and risk factors for overweight and obesity
15 30 [body mass index (BMI) greater than or equal to 25].

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18 31 **Results:** The prevalence of overweight and obesity in the study population was 55.63%.
19 32 Binary logistic regression identified being married ($B = 0.28$, $p = 0.018$, $OR = 1.10$),
20 33 thyroid stimulating hormone (TSH) levels ($B = 0.10$, $p = 0.001$, $OR = 1.10$), and low-
21 34 density lipoprotein cholesterol (LDL-C) levels ($B = 1.61$, $p = 0.045$, $OR = 1.18$) as risk
22 35 factors associated with overweight and obesity development. Furthermore, multiple
23 36 linear regression indicated that TSH levels ($B = 0.16$, $t = 3.17$, $p = 0.002$) were
24 37 correlated with higher BMI.

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29 38 **Conclusion:** The findings suggest that over half of MDD patients with anxiety
30 39 symptoms present with overweight and obesity. Thyroid function emerges as a crucial
31 40 risk factor for overweight and obesity in this population. Targeted interventions
32 41 focusing on thyroid function may hold promise as a therapeutic approach for managing
33 42 overweight and obesity in MDD patients with co-morbid anxiety symptoms.

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37 43 **Keywords:** Major depression disorder, Anxiety, Overweight, Obesity, Thyroid
38 44 stimulating hormone

41 45 **STRENGTHS AND LIMITATIONS**

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44 46 1. The large-sample cross-sectional study design ensured the stability of the results.
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46 47 2. The target parameters included are common biochemical indicators, which are easy
47 48 to detect and clinically promote at low cost.
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49 49 3. The cross-sectional design limits the ability to infer causality.
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51 50 4. The setting of inclusion criteria introduces potential confounding factors.

51 51 **1. Introduction**

52 Major depressive disorder (MDD) is a common psychiatric disorder characterized
53 by marked depressed mood, diminished interest, and decreased energy¹. Although
54 anxiety disorders and already in MDD are two distinct diagnostic entities, anxiety and
55 depression co-morbidity is a relatively common syndrome². In Western countries, the
56 prevalence of comorbid anxiety in patients with MDD ranges from 11% to 80%³⁻⁵, and
57 in China, similarly, upwards of 70% of patients with MDD have comorbid anxiety
58 symptoms^{6,7}. Comorbid anxiety symptoms often lead to lower treatment response rates,
59 lower remission rates, lower quality of life, suicidal behavior, and higher risk of
60 cardiovascular disease in MDD patients^{2,8,9}.

61 Mood disorders and obesity appear to be twins, often acting as risk factors for each
62 other, and were once collectively referred to as the "metabolic-mood syndrome"¹⁰.
63 Previous studies have shown that patients with MDD frequently experience overweight
64 and obesity¹¹⁻¹³. The presence of obesity in individuals with MDD can have detrimental
65 effects, affecting their clinical outcomes by prolonging recovery time and increasing
66 suicidal ideation^{14,15}. Additionally, both overweight and obese individuals are
67 vulnerable to mood disorders^{16,17}. Various pathways have been identified by
68 researchers, linking obesity and mood disorders, such as lifestyle behavioral habits^{18,19},
69 hypothalamic-pituitary-adrenal (HPA) axis disorders²⁰, altered glucocorticoid receptor
70 function²¹, inflammation²², and genetic variations^{23,24}, among others.

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

83 2. Materials and Methods

84 2.1 Subjects

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

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3 87 treatment at the Wuhan Mental Health Center, recognized as the largest public tertiary
4 88 psychiatric specialty hospital in central China, between July 2017 and August 2022
5 89 (The flow chart is shown in Figure 1).
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9 90 The study included patients who fulfilled the following criteria: (1) met the
10 91 diagnostic criteria for Major Depressive Disorder (MDD) as per the International
11 92 Classification of Diseases, 10th edition (ICD-10); (2) were aged between 18 and 60
12 93 years; (3) were of Chinese Han nationality and either male or female; (4) had no history
13 94 of previous hospitalizations; (5) scored a 17-item Hamilton Depression Scale (HAMD-
14 95 17) of ≥ 24 ; and (6) scored a 14-item Hamilton Anxiety scale (HAMA-14) of ≥ 18 .
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18 96 Patients who fulfilled any of the following criteria were excluded from the study:
19 97 those diagnosed with other severe mental illnesses, pregnant or breastfeeding
20 98 individuals, patients with a history of substance abuse, those with a documented
21 99 diagnosis of a serious physical illness or personality disorder, those with comorbid
22 100 diabetes mellitus, and those who were unable to cooperate in completing a
23 101 psychological evaluation for any reason.
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28 102 The research adhered strictly to the principles outlined in the Declaration of
29 103 Helsinki. The study protocol underwent rigorous review and approval by the Ethics
30 104 Committee of Wuhan Mental Health Center. Furthermore, all participants provided
31 105 their informed consent through a paper-based form.
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35 106 **2.2 Research design**

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39 107 This study was conducted as a cross-sectional research design. Initially, we
40 108 determined the prevalence of overweight and obesity within the target population.
41 109 Subsequently, we compared demographic and general clinical data between two
42 110 clinical subgroups: those with normal body mass index (BMI) (labeled as normal BMI
43 111 group) and those with high BMI (labeled as high BMI group). Finally, we analyzed the
44 112 factors associated with overweight and obesity and their severity.
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48 113 A self-designed EXCLE form was used to collect demographic and clinical data
49 114 of the enrolled patients, including age, age at onset, disease duration, gender, marital
50 115 status, education, history of suicidal behavior, history of outpatient treatment, body
51 116 mass index (BMI), waist circumference (WC), blood pressure. On admission day,
52 117 depressive symptoms, anxiety symptoms, psychotic symptoms, illness severity were
53 118 evaluated using HAMD-17, HAMA-14, Positive Symptom Subscales (P1-P7) of
54 119 Positive and Negative Symptom Scale (PANSS), Clinical Global Impression Inventory-
55 120 Severity of Illness (CGI-SI). Then, routine biochemical parameters measured by fasting
56 121 blood of the patient, including thyroid function, fasting blood glucose (FBG) levels,
57 122 lipid levels were extracted from electronic medical record system.
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4 123 The criteria for overweight and obesity (high BMI group) were established based
5 124 on the weight status classification criteria of the Chinese Obesity Working Group ²⁵,
6 125 Accordingly, all study subjects were classified into two categories: those with a normal
7 126 body mass index ($\text{BMI} < 24 \text{ kg/m}^2$), and those who fell into the overweight and obesity
8 127 category ($\text{BMI} \geq 24 \text{ kg/m}^2$).

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11 128 Two psychiatrists conducted the evaluation of pertinent psychological scales, each
12 129 with a title of attending or higher, who were affiliated with the medical institution from
13 130 which the sample originated.

17 131 **2.3 Data analysis**

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21 132 Categorical variables are presented as counts, while data for normally distributed
22 133 continuous measures are expressed as mean and standard deviation. Continuous
23 134 variable comparisons across various groups were conducted using independent samples
24 135 T-tests. Rates were compared using Chi-squared tests. To discern differences in
25 136 demographic and clinical variables between the overweight subgroup and the normal
26 137 BMI subgroup, we applied chi-square tests to categorical data and independent samples
27 138 t-tests to continuous variables. Subsequently, we utilized the variables that varied in
28 139 univariate analyses as independent variables and constructed binary logistic regression
29 140 models with overweight as the outcome variable to investigate factors influencing
30 141 overweight within the target population. Ultimately, a multiple linear regression model
31 142 was developed to identify factors impacting patients with degree of overweight,
32 143 utilizing BMI as the dependent variable and factors affecting overweight from binary
33 144 logistic regression as independent variables. All *p* values were two-tailed, with
34 145 significance set at < 0.05 . Statistical analyses were executed using SPSS 27 (SPSS, Inc.,
35 146 Chicago, IL).

43 147 **3. Results**

46 148 **3.1 The differences between high BMI group and normal BMI group.**

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49 149 Of all our MDD patients with comorbid anxiety included in the study, 55.63%
50 150 (410/737) met the diagnostic criteria for overweight. The mean BMI in the two
51 151 subgroups was (25.39 ± 1.15) kg/m^2 in the high BMI group and (22.71 ± 1.08) kg/m^2
52 152 in the normal BMI group. We found that the following parameters were significantly
53 153 higher in the high BMI group than in the normal BMI group, onset age ($t = -2.14$, $p =$
54 154 0.033), proportion married ($\chi^2 = 4.24$, $p = 0.039$), thyrotropin levels ($t = -4.00$, $p < .001$),
55 155 low density lipoprotein cholesterol (LDL-C) levels ($t = -2.51$, $p = 0.012$), and systolic
56 156 blood pressure (SBP) levels ($t = -2.73$, $p = 0.006$) (**Table 1**).

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4 157 **3.2 Determinants of overweight and obesity in target patients: a binary logic-based**
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6 158 **model.**
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9 159 We then developed a binary logistic regression model (Backward: Wald) using the
10 160 variables that differed in the univariate analysis as independent variables and
11 161 overweight as dependent variables. As the results in **Table 2** shown, being married (B
12 162 = 0.28, $p = 0.018$, OR = 1.10), TSH levels (B = 0.10, $p = 0.001$, OR = 1.10) and LDL-
13 163 C (B = 1.61, $p = 0.045$, OR = 1.18) were risk factor for overweight and obesity.

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17 164 **3.3 Factors affecting severity of overweight and obesity in high BMI subgroup: a**
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19 165 **multiple linear regression model.**
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22 166 Finally, for the high BMI subgroup of patients, we constructed a multiple linear
23 167 regression model (input) with BMI as the dependent variable and the factors associated
24 168 with the previous step affecting overweight and obesity as independent variables and
25 169 the results are shown in **Table 3**. We found that TSH (B = 0.16, $t = 3.17$, $p = 0.002$)
26 170 was a risk factor for higher BMI.

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31 171 **4. Discussion**
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34 172 In our study, we observed specific clinical characteristics related to overweight and
35 173 obesity in individuals with MDD co-morbid anxiety symptoms. The prevalence of
36 174 overweight and obesity in this population was notably high, reaching 55.63%.
37 175 Additionally, we found that individuals in the overweight and obese subgroups
38 176 experienced a later onset of MDD and exhibited more pronounced metabolic
39 177 disturbances. Furthermore, our analysis revealed that being married and elevated levels
40 178 of TSH and LDL-C were associated with an increased risk of developing overweight
41 179 and obesity. Notably, TSH levels were also identified as a risk factor for both the
42 180 development and severity of overweight and obesity.

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48 181 The prevalence of overweight and obesity among patients with MDD co-morbid
49 182 anxiety in our study was 55.63%. Previous reports on the prevalence of overweight and
50 183 obesity in individuals with MDD have shown some variation. For instance, in a study
51 184 of first episode MDD patients in northern China, the prevalence was reported at
52 185 59.72%²⁶, while a multicenter study in Germany reported a prevalence of 52.16%
53 186 amongst first episode MDD patients¹³. When the sample extended to multiple European
54 187 countries, the prevalence of overweight in MDD patients was approximately 48%¹⁴.
55 188 These studies, albeit slightly different from our current study, focused on individuals
56 189 within the general MDD population rather than specifically considering patients with
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190 MDD comorbid anxiety symptoms. A recent study that shared a similar study
191 population with our research found a higher prevalence of overweight (68.3%) in
192 patients with MDD co-morbid anxiety²⁷. This rate was higher than in our study, and
193 this heterogeneity may have been caused by the stricter restriction of anxiety symptoms
194 in that study and the fact that some of the patients we included had a history of
195 outpatient treatment. While the exact prevalence may differ across studies, a consistent
196 finding is that a significant portion of individuals in the MDD population are
197 overweight and obesity, focusing on and underscoring the importance of addressing
198 weight concerns in this patient group.

199 Subsequently, our study examined the risk factors that contribute to the
200 development of overweight and obesity in patients with MDD comorbid anxiety
201 symptoms. Our findings indicate that marital status and TSH levels were identified as
202 risk factors for overweight and obesity in this population. Marital status has been
203 consistently associated with a higher risk of overweight and obesity not only in the
204 general population but also in individuals with MDD^{15,28}. Even after adjusting for
205 variables such as employment status, stress levels, and perceived health status, this
206 relationship persists²⁹. The gain observed in married individuals may be linked to
207 reduced physical activity³⁰, and it is also plausible that spouses may provide greater
208 nutritional support during the acute phases of MDD episode.

209 Elevated TSH levels emerged as a risk factor for the development of overweight,
210 obesity, and elevated BMI in our study population, aligning with numerous existing
211 reports^{27,31,32}. Another study exploring MDD patients with comorbid anxiety found that
212 anxiety symptoms were associated with an increased risk of overweight, with thyroid
213 function playing a crucial role as a contributing factor²⁷. Evidence indicates that MDD
214 patients with anxiety disorders often exhibit heightened levels of antithyroid antibodies
215 due to stress-induced immune responses³³⁻³⁵, leading to subclinical hypothyroidism and
216 subsequently elevated serum TSH levels^{36,37}. Elevated TSH levels inhibit triglyceride
217 lipase in adipose tissue via the TSH receptor in adipocytes, promoting adipocyte
218 enlargement and consequent weight gain³⁸. Conversely, hypertrophied adipose tissue
219 secretes leptin, which activates thyrotropin-releasing hormone (TRH) neurons to
220 stimulate increased TSH levels³⁹. Collectively, the reviewed studies underscore the
221 importance of maintaining thyroid function within normal limits to help manage
222 overweight and obesity in individuals with MDD and anxiety symptoms.

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

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

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

241 **Acknowledgements**

242 We thank all the medical staff and patients in this study for their participation and
243 are very grateful to those who contributed to the diagnosis and clinical evaluation of
244 the subjects.

245 **Authors' contributions**

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

250 **Funding**

251 No funding.

252 **Competing interests**

253 None.

254 **Patient and public involvement**

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

256 reporting, or dissemination plans of this research.

257 **Patient consent for publication**

258 Consent obtained directly from patient(s).

259 **Ethics approval and consent to participate**

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

264 **Availability of data and materials**

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

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5 377 **Figure legend**
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9 378 **Figure 1: Flowchart for study sample inclusion**
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379 **Table caption**380 **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

381 HAMD: Hamilton Depression Scale Score; HAMA: Hamilton Anxiety Scale Score; CGI-SI: Clinical Global

382 Impression Scale - Severity of Illness; PSS: Positive symptom subscale; TSH: thyroid stimulating hormone; FT₃:383 free triiodothyronine; FT₄: free tetraiodothyronine; BMI: body mass index; WC: waist circumference; FBG: fasting

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3 384 blood glucose; TG: triglycerides; TC: total cholesterol; HDL-C: high density lipoprotein cholesterol; LDL-C: low
4 385 density lipoprotein cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure. * $p < 0.05$

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

	Coefficients	Std. error	Wald	<i>p</i> -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

389 TSH: Thyroid stimulating hormone; LDL-C: low density lipoprotein cholesterol. **p* < 0.05

390

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

	Coefficients		Std. error	<i>t</i>	<i>p</i> -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

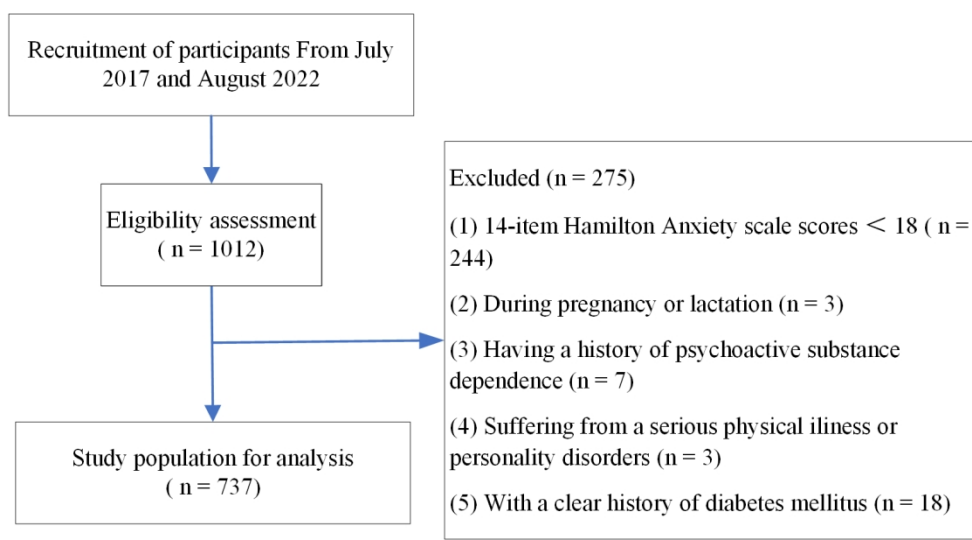
393 TSH: Thyroid stimulating hormone; LDL-C: low density lipoprotein cholesterol. **p* < 0.05

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Participant inclusion flow chart
146x77mm (300 x 300 DPI)

BMJ Open : first published as 10.1136/bmjopen-2024-087640 on 22 February 2025. Downloaded from <http://bmjopen.bmj.com/> on June 8, 2025 at Agence Bibliographique de l'Enseignement Supérieur (ABES). Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2024-087640.R1
Article Type:	Original research
Date Submitted by the Author:	11-Nov-2024
Complete List of Authors:	Zhang, Hong; Wuhan Mental Health Center Wang, Jing; Yunnan Institute For Drug Abuse Zhu, Wenting; Wuhan Mental Health Centre Liu, Xuebing; Wuhan Mental Health Center
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Epidemiology, Diabetes and endocrinology
Keywords:	Cross-Sectional Studies, Overweight, Obesity, Depression & mood disorders < PSYCHIATRY, Anxiety disorders < PSYCHIATRY

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1 Clinical Features of Overweight in Acute-Phase Hospitalized 2 Major Depressive Disorder with Co-morbid Anxiety

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13 Abstract

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

17 **Design:** Cross-sectional study.

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

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

26 factors influencing the outcomes.

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

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

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

41 **Keywords:** Major depression disorder, Anxiety, Overweight, Thyroid stimulating
42 hormone

43 STRENGTHS AND LIMITATIONS

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

49 1. Introduction

50 Major depressive disorder (MDD) is a common psychiatric disorder characterized
51 by marked depressed mood, diminished interest, and decreased energy¹. Although
52 anxiety disorders and already in MDD are two distinct diagnostic entities, anxiety and
53 depression co-morbidity is a relatively common syndrome². In Western countries, the
54 prevalence of comorbid anxiety in patients with MDD ranges from 11% to 80%³⁻⁵, and
55 in China, similarly, upwards of 70% of patients with MDD have comorbid anxiety
56 symptoms^{6,7}. Comorbid anxiety symptoms often lead to lower treatment response rates,
57 lower remission rates, lower quality of life, suicidal behavior, and higher risk of

58 cardiovascular disease in MDD patients^{2 8 9}.

59 Mood disorders and obesity appear to be twins, often acting as risk factors for each
60 other, and were once collectively referred to as the "metabolic-mood syndrome"¹⁰.
61 Previous studies have shown that patients with MDD frequently experience overweight
62 and obesity¹¹⁻¹³. The presence of obesity in individuals with MDD can have detrimental
63 effects, affecting their clinical outcomes by prolonging recovery time and increasing
64 suicidal ideation^{14 15}. Additionally, both overweight and obese individuals are
65 vulnerable to mood disorders^{16 17}. Studies have demonstrated that weight reduction is
66 crucial for alleviating anxiety and depressive symptoms in patients^{18 19}. Several
67 pathways have been identified that connect obesity and mood disorders, such as
68 lifestyle behavioral habits^{20 21}, hypothalamic-pituitary-adrenal (HPA) axis disorders²²,
69 altered glucocorticoid receptor function²³, inflammation²⁴, and genetic variations^{25 26},
70 among others. Given the complex relationship between overweight and mood disorders
71 and the negative empowerment on the efficacy and prognosis of patients with MDD,
72 actively clarifying the clinical characteristics of obesity in MDD populations and
73 exploring the potential biomarkers that can be used for clinical interventions is a very
74 critical task.

75 Up to now, although there are many studies related to being overweight in MDD
76 patients, there are not enough studies on overweight in MDD patients with comorbid
77 anxiety, and the results of the few studies are inconsistent due to issues such as sample
78 size, population characteristics, cultural and geographic differences^{27 28}. More
79 importantly, co-morbid factors such as obesity are important factors in treatment
80 interruption and disease relapse in the MDD population²⁹. This study examined the
81 incidence of overweight in a sample of hospitalized Chinese Han patients in the acute
82 phase of MDD with co-morbid anxiety. It also explored the factors influencing both the
83 occurrence and severity of overweight, offering valuable insights and warnings for
84 proactive weight management in this target population.

85 2. Subjects and Methods

86 2.1 Subjects

87 We based the sample size prediction on the following formula:

$$88 \quad n = \frac{Z^2 P(1 - P)}{d^2}$$

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

91 prevalence of overweight in the Chinese general population, the value of 0.5 was taken
92 here³⁰), d = Precision or margin of error (equal to 0.05), the statistical power ($1-\beta$) was
93 0.90. Thus, the estimated sample size required was 384 participants.

94 In this study, 737 individuals with MDD who also presented with co-morbid
95 anxiety symptoms were enrolled. These participants were admitted to Wuhan Mental
96 Health Center, the foremost public tertiary psychiatric hospital in central China, due to
97 an acute episode of their mental health condition, spanning from July 2017 to August
98 2022 (The flow chart is shown in **Figure 1**).

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

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

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

115 **2.2 Research design**

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

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

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3 126 anxiety symptoms, psychotic symptoms, illness severity were evaluated using HAMD-
4 127 17, HAMA-14, Positive Symptom Subscales (P1-P7) of Positive and Negative
5 128 Symptom Scale (PANSS), Clinical Global Impression Inventory-Severity of Illness
6 129 (CGI-SI). Then, routine biochemical parameters measured by fasting blood of the
7 130 patient, including thyroid function, fasting blood glucose (FBG) levels, lipid levels
8 131 were extracted from electronic medical record system.

12 132 The criteria for overweight (high BMI group) were established based on the weight
13 133 status classification criteria of the Chinese Obesity Working Group³¹, Accordingly, all
14 134 study subjects were classified into two categories: those with a normal BMI (BMI < 24
15 135 kg/m²), and those who fell into the overweight or obesity category (BMI ≥ 24 kg/m²).

16 136 Two psychiatrists conducted the evaluation of pertinent psychological scales, each
17 137 with a title of attending or higher, who were affiliated with the medical institution from
18 138 which the sample originated.

19 139 **2.3 Data analysis**

20 140 Categorical variables were reported as counts, while continuous variables with
21 141 normal distribution were depicted using means and standard deviations. Continuous
22 142 variables that were not normally distributed were expressed using medians (P₂₅, P₇₅).
23 143 The Shapiro-Wilk test was employed to verify the normality of all continuous variables.
24 144 For both continuous variables, whether normally or non-normally distributed, and
25 145 categorical variables, statistical comparisons were made using independent samples t-
26 146 tests, Mann-Whitney U-tests, and Chi-square tests. To discern differences in
27 147 demographic and clinical variables between the overweight subgroup and the normal
28 148 BMI subgroup, we applied chi-square tests to categorical data and independent samples
29 149 t-tests to continuous variables. Subsequently, we utilized the variables that varied in
30 150 univariate analyses as independent variables and constructed binary logistic regression
31 151 models with overweight as the outcome variable to investigate factors influencing
32 152 overweight within the target population. Ultimately, a multiple linear regression model
33 153 was developed to identify factors impacting patients with degrees of overweight,
34 154 utilizing BMI as the dependent variable and factors affecting overweight from binary
35 155 logistic regression as independent variables. All *p* values were two-tailed, with
36 156 significance set at < 0.05. Statistical analyses were executed using SPSS 27 (SPSS, Inc.,
37 157 Chicago, IL).

38 158 **3. Results**

39 159 **3.1 The differences between high BMI group and normal BMI group.**

160 Of all our MDD patients with comorbid anxiety included in the study, 55.63%
161 (410/737) met the diagnostic criteria for being overweight. The mean BMI in the two
162 subgroups was (25.39 ± 1.15) kg/m² in the high BMI group and (22.71 ± 1.08) kg/m²
163 in the normal BMI group. We found that the following parameters were significantly
164 higher in the high BMI group than in the normal BMI group, onset age ($t = -2.14, p =$
165 0.033), proportion married ($\chi^2 = 4.24, p = 0.039$), thyrotropin levels ($t = -4.00, p < .001$),
166 low density lipoprotein cholesterol (LDL-C) levels ($t = -2.51, p = 0.012$), and systolic
167 blood pressure (SBP) levels ($t = -2.73, p = 0.006$) (Table 1).

168 3.2 Determinants of overweight and obesity in target patients: a binary logic-based 169 model.

170 We then developed a binary logistic regression model (Backward: Wald) using the
171 variables that differed in the univariate analysis as independent variables and
172 overweight as dependent variables. As the results in Table 2 show, being married ($B =$
173 $0.28, p = 0.018, OR = 1.10$), TSH levels ($B = 0.10, p = 0.001, OR = 1.10$) and LDL-C
174 ($B = 1.61, p = 0.045, OR = 1.18$) were positively predictive of clinical factors for being
175 overweight.

176 3.3 Factors affecting severity of overweight and obesity in high BMI subgroup: a 177 multiple linear regression model.

178 Finally, for the high BMI subgroup of patients, we constructed a multiple linear
179 regression model (input) with BMI as the dependent variable and the factors associated
180 with the previous step affecting overweight and obesity as independent variables and
181 the results are shown in Table 3. We found that thyroid-stimulating hormone ($B = 0.16,$
182 $t = 3.17, p = 0.002$) was a positive predictor of elevated BMI.

183 4. Discussion

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

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4 192 The incidence of overweight in patients with MDD co-morbid anxiety in our study
5 193 was 55.63%. Previous reports on the prevalence of overweight in individuals with
6 194 MDD have shown some variation. For instance, in a study of first episode MDD
7 195 patients in northern China, the prevalence was reported at 59.72%³², while a multicenter
8 196 study in Germany reported a prevalence of 52.16% amongst first episode MDD
9 197 patients¹³. When the sample extended to multiple European countries, the prevalence
10 198 of overweight in MDD patients was approximately 48%¹⁴. These studies, albeit slightly
11 199 different from our current study, focused on individuals within the general MDD
12 200 population rather than specifically considering patients with MDD comorbid anxiety
13 201 symptoms. A recent study that shared a similar study population with our research
14 202 found a higher prevalence of overweight (68.3%) in patients with MDD co-morbid
15 203 anxiety³³. This rate was higher than in our study, and this heterogeneity may have been
16 204 caused by the stricter restriction of anxiety symptoms in that study and the fact that
17 205 some of the patients we included had a history of outpatient treatment. While the exact
18 206 prevalence may differ across studies, a consistent finding is that a significant portion of
19 207 individuals in the MDD population are overweight, focusing on and underscoring the
20 208 importance of addressing weight concerns in this patient group.

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28 209 Subsequently, our study examined the clinical factors that contribute to the
29 210 development of overweight in patients with comorbid anxiety symptoms in MDD. Our
30 211 findings indicate that being married and TSH levels were identified as contributing
31 212 factors to overweight formation in this population. Marital status has been consistently
32 213 associated with a higher risk of overweight not only in the general population but also
33 214 in individuals with MDD^{15 34}. Even after adjusting for variables such as employment
34 215 status, stress levels, and perceived health status, this relationship persists³⁵. The gain
35 216 observed in married individuals may be linked to reduced physical activity³⁶, and it is
36 217 also plausible that spouses may provide greater nutritional support during the acute
37 218 phases of MDD episode. This suggests that spouses of married individuals with MDD
38 219 may provide more balanced nutritional support during the onset of depression to help
39 220 prevent obesity.

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45 221 Elevated TSH levels emerged as a contributing factor for the development of
46 222 overweight, obesity, and elevated BMI in our study population, aligning with numerous
47 223 existing reports^{33 37 38}. Another study exploring MDD patients with comorbid anxiety
48 224 found that anxiety symptoms were associated with an increased risk of being
49 225 overweight, with thyroid function playing a crucial role as a contributing factor³³.
50 226 Evidence indicates that MDD patients with anxiety disorders often exhibit heightened
51 227 levels of antithyroid antibodies due to stress-induced immune responses³⁹⁻⁴¹, leading to
52 228 subclinical hypothyroidism and subsequently elevated serum TSH levels^{42 43}. Elevated
53 229 TSH levels inhibit triglyceride lipase in adipose tissue via the TSH receptor in
54 230 adipocytes, promoting adipocyte enlargement and consequent weight gain⁴⁴.
55 231 Conversely, hypertrophied adipose tissue secretes leptin, which activates thyrotropin-

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3 232 releasing hormone (TRH) neurons to stimulate increased TSH levels⁴⁵. Collectively,
4 233 the reviewed studies underscore the importance of maintaining thyroid function within
5 234 normal limits to help manage overweight and obesity in individuals with MDD and
6 235 anxiety symptoms.
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10 236 This study possesses several strengths. Firstly, our study included a sizable sample
11 237 size, enhancing the stability and generalizability of the results. Secondly, the target
12 238 parameters we investigated are common clinical indicators, which facilitates the
13 239 generalizability and practical application of the findings at a lower cost. The current
14 240 study also presents several limitations that should be acknowledged. Firstly, our
15 241 research design was cross-sectional, precluding the establishment of causal
16 242 relationships between identified clinical factors and BMI in our study population.
17 243 Secondly, the study predominantly focused on individuals with MDD in the acute phase
18 244 of disease onset, potentially limiting the generalizability of our findings to other
19 245 subpopulations of MDD patients. Lastly, a considerable proportion of the participants
20 246 had a history of outpatient treatment, introducing a confounding factor that may have
21 247 influenced the study outcomes. To address these limitations, our future research
22 248 endeavors will aim to undertake more rigorous prospective studies with a broader scope.
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29 249 In conclusion, over half of patients with MDD co-morbid anxiety symptoms
30 250 develop overweight. Furthermore, thyroid function is a crucial clinical factor for the
31 251 development and severity of overweight and obesity. Therefore, targeted interventions
32 252 on thyroid function could be potential therapeutic targets for overweight and obesity in
33 253 patients with MDD co-morbid anxiety symptoms.
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38 254 **Acknowledgements**

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40
41 255 We thank all the medical staff and patients in this study for their participation and
42 256 are very grateful to those who contributed to the diagnosis and clinical evaluation of
43 257 the subjects. The authors would like to express their sincere gratitude to Jun Ma, a
44 258 current PhD student at Wuhan University, for advising on the design of the study and
45 259 making linguistic changes to the manuscript.
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49 260 **Authors' contributions**

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53 261 HZ: Writing – original draft. JW: Formal analysis, Writing – review & Editing.
54 262 WZ: Investigation, Supervision, Writing – review & editing. XL: Conceptualization,
55 263 Methodology, Software, Investigation, Formal analysis.
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59 264 **Funding**

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3
4 265 No funding.
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7 266 **Competing interests**
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10 267 None.
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14 268 **Patient and public involvement**
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17 269 Patients and/or the public were not involved in the design, or conduct, or
18 270 reporting, or dissemination plans of this research.
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21 271 **Patient consent for publication**
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24 272 Consent obtained directly from patient(s).
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26 273 **Ethics approval and consent to participate**
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29 274 The ethics committees of the Wuhan mental health center reviewed and approved
30 275 this study. All subject guardians knew about this study and signed informed consent.
31
32 276 All procedures carried out in studies conformed to the Helsinki Declaration and its
33 277 subsequent amendments or similar ethical standards.
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36 278 **Availability of data and materials**
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39 279 The datasets used and/or analyzed during the current study are available from the
40 280 corresponding author on reasonable request.
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44 281 **References**
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5 418 **Figure legend**
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9 419 **Figure 1: Flowchart for study sample inclusion**
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420 Tables

421 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/ 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	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

422 HAMD: Hamilton Depression Scale Score; HAMA: Hamilton Anxiety Scale Score; CGI-SI: Clinical Global

423 Impression Scale - Severity of Illness; PSS: Positive symptom subscale; TSH: thyroid stimulating hormone; FT₃:424 free triiodothyronine; FT₄: free tetraiodothyronine; BMI: body mass index; WC: waist circumference; FBG: fasting

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3 425 blood glucose; TG: triglycerides; TC: total cholesterol; HDL-C: high density lipoprotein cholesterol; LDL-C: low
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5 426 density lipoprotein cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure. * $p < 0.05$
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428 **Table 2: Binary logistic regression analysis of the determinants of overweight in MDD patients**
 429 **with anxiety.**

	Coefficients	Std. error	Wald	<i>p</i> -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

430 TSH: Thyroid stimulating hormone; LDL-C: low density lipoprotein cholesterol. **p* < 0.05

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

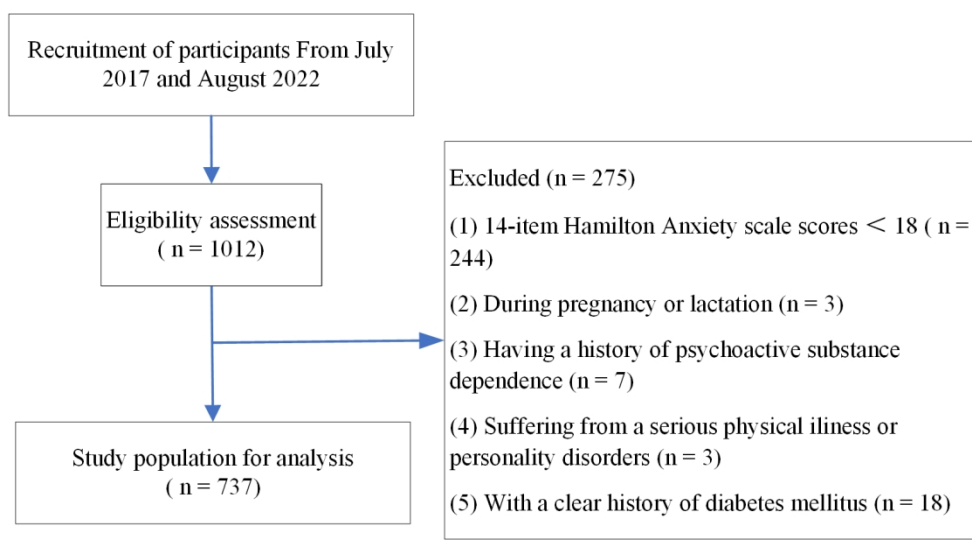
	Coefficients		Std. error	<i>t</i>	<i>p</i> -value	95% CI	
	B					Lower	Upper
TSH - uIU/mL	0.16		0.02	3.17	0.002*	0.02	0.11
LDL-C - mmol/L	0.08		0.08	1.63	0.103	-0.03	0.29

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

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Participant inclusion flow chart
146x77mm (300 x 300 DPI)

BMJ Open : first published as 10.1136/bmjopen-2024-087640 on 22 February 2025. Downloaded from <http://bmjopen.bmj.com/> on June 8, 2025 at Agence Bibliographique de l'Enseignement Supérieur (ABES). Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2024-087640.R2
Article Type:	Original research
Date Submitted by the Author:	05-Feb-2025
Complete List of Authors:	Zhang, Hong; Wuhan Mental Health Center Ma, Jun; Wuhan Mental Health Centre, Department of Psychiatry Wang, Jing; Yunnan Institute For Drug Abuse Zhu, Wenting; Wuhan Mental Health Centre Liu, Xuebing; Wuhan Mental Health Center
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Epidemiology, Diabetes and endocrinology
Keywords:	Cross-Sectional Studies, Overweight, Depression & mood disorders < PSYCHIATRY, Anxiety disorders < PSYCHIATRY

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

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13 **Abstract**

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

17 **Design:** Cross-sectional study.

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

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

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

23 **Results:** Among the study population, 55.63% were classified as overweight. Binary
24 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 energy¹. Although anxiety disorders and already in MDD are two distinct diagnostic entities, anxiety and depression co-morbidity is a relatively common syndrome². 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 obesity¹¹⁻¹³. The presence of obesity in individuals with MDD can have detrimental effects, affecting their clinical outcomes by prolonging recovery time and increasing

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3 58 suicidal ideation^{14 15}. Additionally, both overweight and obese individuals are
4 59 vulnerable to mood disorders^{16 17}. Studies have demonstrated that weight reduction is
5 60 crucial for alleviating anxiety and depressive symptoms in patients^{18 19}. Several
6 61 pathways have been identified that connect obesity and mood disorders, such as
7 62 lifestyle behavioral habits^{20 21}, hypothalamic-pituitary-adrenal (HPA) axis disorders²²,
8 63 altered glucocorticoid receptor function²³, inflammation²⁴, and genetic variations^{25 26},
9 64 among others. Given the complex relationship between overweight and mood disorders
10 65 and the negative empowerment on the efficacy and prognosis of patients with MDD,
11 66 actively clarifying the clinical characteristics of obesity in MDD populations and
12 67 exploring the potential biomarkers that can be used for clinical interventions is a very
13 68 critical task.

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19 69 Up to now, although there are many studies related to being overweight in MDD
20 70 patients, there are not enough studies on overweight in MDD patients with comorbid
21 71 anxiety, and the results of the few studies are inconsistent due to issues such as sample
22 72 size, population characteristics, cultural and geographic differences^{27 28}. More
23 73 importantly, co-morbid factors such as obesity are important factors in treatment
24 74 interruption and disease relapse in the MDD population²⁹. This study examined the
25 75 incidence of overweight in a sample of hospitalized Chinese Han patients in the acute
26 76 phase of MDD with co-morbid anxiety. It also explored the factors influencing both the
27 77 occurrence and severity of overweight, offering valuable insights and warnings for
28 78 proactive weight management in this target population.

35 79 **2. Subjects and Methods**

36 37 38 39 80 **2.1 Subjects**

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43 81 We based the sample size prediction on the following formula:

$$44
45 82 n = \frac{Z^2 P(1 - P)}{d^2}$$

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48 83 where: n = Sample size, Z = Z-statistic for the chosen level of confidence (1.96 for a 95%
49 84 confidence level), P = Expected prevalence or proportion (With reference to the
50 85 prevalence of overweight in the Chinese general population, the value of 0.5 was taken
51 86 here³⁰), d = Precision or margin of error (equal to 0.05), the statistical power (1-β) was
52 87 0.90. Thus, the estimated sample size required was 384 participants.

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56 88 In this study, 737 individuals with MDD who also presented with co-morbid
57 89 anxiety symptoms were enrolled. These participants were admitted to Wuhan Mental
58 90 Health Center, the foremost public tertiary psychiatric hospital in central China, due to

91 an acute episode of their mental health condition, spanning from July 2017 to August
92 2022 (The flow chart is shown in **Figure 1**).

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

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

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

109 **2.2 Research design**

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

116 A self-designed EXCLE form was used to collect demographic and clinical data
117 of the enrolled patients, including age, age at onset, disease duration, gender, marital
118 status, education, history of suicidal behavior, history of outpatient treatment, BMI,
119 waist circumference (WC), blood pressure. On admission day, depressive symptoms,
120 anxiety symptoms, psychotic symptoms, illness severity were evaluated using HAMD-
121 17, HAMA-14, Positive Symptom Subscales (P1-P7) of Positive and Negative
122 Symptom Scale (PANSS), Clinical Global Impression Inventory-Severity of Illness
123 (CGI-SI). Then, routine biochemical parameters measured by fasting blood of the
124 patient, including thyroid function, fasting blood glucose (FBG) levels, lipid levels
125 were extracted from electronic medical record system.

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4 126 The criteria for overweight (high BMI group) were established based on the weight
5 127 status classification criteria of the Chinese Obesity Working Group³¹. Accordingly, all
6 128 study subjects were classified into two categories: those with a normal BMI (BMI < 24
7 129 kg/m²), and those who fell into the overweight or obesity category (BMI ≥ 24 kg/m²).

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10 130 Two psychiatrists conducted the evaluation of pertinent psychological scales, each
11 131 with a title of attending or higher, who were affiliated with the medical institution from
12 132 which the sample originated.

133 2.3 Data analysis

134 Categorical variables were reported as counts, while continuous variables with
135 136 normal distribution were depicted using means and standard deviations. Continuous
137 138 variables that were not normally distributed were expressed using medians (p25, p75).
139 140 The Shapiro-Wilk test was employed to verify the normality of all continuous variables.
141 142 For both continuous variables, whether normally or non-normally distributed, and
143 144 categorical variables, statistical comparisons were made using independent samples t-
145 146 tests, Mann-Whitney U-tests, and Chi-square tests. To discern differences in
147 148 demographic and clinical variables between the overweight subgroup and the normal
149 150 BMI subgroup, we applied chi-square tests to categorical data and independent samples
151 152 t-tests to continuous variables. Subsequently, we utilized the variables that varied in
153 154 univariate analyses as independent variables and constructed binary logistic regression
155 156 models with overweight as the outcome variable to investigate factors influencing
157 158 overweight within the target population. Ultimately, a multiple linear regression model
159 160 was developed to identify factors impacting patients with degrees of overweight,
161 162 utilizing BMI as the dependent variable and factors affecting overweight from binary
163 164 logistic regression as independent variables. All *p* values were two-tailed, with
165 166 significance set at < 0.05. Statistical analyses were executed using SPSS 27 (SPSS, Inc.,
167 168 Chicago, IL).

169 3. Results

170 3.1 The differences between high BMI group and normal BMI group.

171 172 Of all our MDD patients with comorbid anxiety included in the study, 55.63%
173 174 (410/737) met the diagnostic criteria for being overweight. The mean BMI in the two
175 176 subgroups was (25.39 ± 1.15) kg/m² in the high BMI group and (22.71 ± 1.08) kg/m²
177 178 in the normal BMI group. We found that the following parameters were significantly
179 180 higher in the high BMI group than in the normal BMI group, onset age (*t* = -2.14, *p* =
181 182 0.033), proportion married ($\chi^2 = 4.24, p = 0.039$), thyrotropin levels (*t* = -4.00, *p* < .001),

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

162 **3.2 Determinants of overweight in target patients: a binary logic-based model.**

163 We then developed a binary logistic regression model (Backward: Wald) using the
164 variables that differed in the univariate analysis as independent variables and
165 overweight as dependent variables. As the results in **Table 2** show, being married ($B =$
166 $0.28, p = 0.018, OR = 1.10$), TSH levels ($B = 0.10, p = 0.001, OR = 1.10$) and LDL-C
167 ($B = 1.61, p = 0.045, OR = 1.18$) were positively predictive of clinical factors for being
168 overweight.

169 **3.3 Factors affecting severity of overweight in high BMI subgroup: a multiple** 170 **linear regression model.**

171 Finally, for the high BMI subgroup of patients, we constructed a multiple linear
172 regression model (input) with BMI as the dependent variable and the factors associated
173 with the previous step affecting overweight as independent variables and the results are
174 shown in **Table 3**. We found that thyroid-stimulating hormone ($B = 0.16, t = 3.17, p =$
175 0.002) was a positive predictor of elevated BMI.

176 **4. Discussion**

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

185 The incidence of overweight in patients with MDD co-morbid anxiety in our study
186 was 55.63%. Previous reports on the prevalence of overweight in individuals with
187 MDD have shown some variation. For instance, in a study of first episode MDD
188 patients in northern China, the prevalence was reported at 59.72%³², while a multicenter
189 study in Germany reported a prevalence of 52.16% amongst first episode MDD
190 patients¹³. When the sample extended to multiple European countries, the prevalence
191 of overweight in MDD patients was approximately 48%¹⁴. These studies, albeit slightly
192 different from our current study, focused on individuals within the general MDD

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3 193 population rather than specifically considering patients with MDD comorbid anxiety
4 194 symptoms. A recent study that shared a similar study population with our research
5 195 found a higher prevalence of overweight (68.3%) in patients with MDD co-morbid
6 196 anxiety³³. This rate was higher than in our study, and this heterogeneity may have been
7 197 caused by the stricter restriction of anxiety symptoms in that study and the fact that
8 198 some of the patients we included had a history of outpatient treatment. While the exact
9 199 prevalence may differ across studies, a consistent finding is that a significant portion of
10 200 individuals in the MDD population are overweight, focusing on and underscoring the
11 201 importance of addressing weight concerns in this patient group.

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17 202 Subsequently, our study examined the clinical factors that contribute to the
18 203 development of overweight in patients with comorbid anxiety symptoms in MDD. Our
19 204 findings indicate that being married and TSH levels were identified as contributing
20 205 factors to overweight formation in this population. Marital status has been consistently
21 206 associated with a higher risk of overweight not only in the general population but also
22 207 in individuals with MDD^{15 34}. Even after adjusting for variables such as employment
23 208 status, stress levels, and perceived health status, this relationship persists³⁵. The gain
24 209 observed in married individuals may be linked to reduced physical activity³⁶, and it is
25 210 also plausible that spouses may provide greater nutritional support during the acute
26 211 phases of MDD episode. This suggests that spouses of married individuals with MDD
27 212 may provide more balanced nutritional support during the onset of depression to help
28 213 prevent obesity.

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34 214 Elevated TSH levels emerged as a contributing factor for the development of
35 215 overweight, obesity, and elevated BMI in our study population, aligning with numerous
36 216 existing reports^{33 37 38}. Another study exploring MDD patients with comorbid anxiety
37 217 found that anxiety symptoms were associated with an increased risk of being
38 218 overweight, with thyroid function playing a crucial role as a contributing factor³³.
39 219 Evidence indicates that MDD patients with anxiety disorders often exhibit heightened
40 220 levels of antithyroid antibodies due to stress-induced immune responses³⁹⁻⁴¹, leading to
41 221 subclinical hypothyroidism and subsequently elevated serum TSH levels^{42 43}. Elevated
42 222 TSH levels inhibit triglyceride lipase in adipose tissue via the TSH receptor in
43 223 adipocytes, promoting adipocyte enlargement and consequent weight gain⁴⁴.
44 224 Conversely, hypertrophied adipose tissue secretes leptin, which activates thyrotropin-
45 225 releasing hormone (TRH) neurons to stimulate increased TSH levels⁴⁵. Collectively,
46 226 the reviewed studies underscore the importance of maintaining thyroid function within
47 227 normal limits to help manage overweight in individuals with MDD and anxiety
48 228 symptoms.

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56 229 This study possesses several strengths. Firstly, our study included a sizable sample
57 230 size, enhancing the stability and generalizability of the results. Secondly, the target
58 231 parameters we investigated are common clinical indicators, which facilitates the

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

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

247 **Acknowledgement**

248 We thank all the medical staff and patients in this study for their participation and
249 are very grateful to those who contributed to the diagnosis and clinical evaluation of
250 the subjects.

251 **Contributions**

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

256 **Funding**

257 No funding.

258 **Competing interests**

259 None.

260 **Patient and public involvement**

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

263 **Patient consent for publication**

264 Consent obtained directly from patient(s).

265 **Ethics approval and consent to participate**

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

270 **Availability of data and materials**

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

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5 410 **Figure legend**
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9 411 **Figure 1: Flowchart for study sample inclusion**
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412 Tables

413 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/ 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	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

414 HAMD: Hamilton Depression Scale Score; HAMA: Hamilton Anxiety Scale Score; CGI-SI: Clinical Global

415 Impression Scale - Severity of Illness; PSS: Positive symptom subscale; TSH: thyroid stimulating hormone; FT₃:416 free triiodothyronine; FT₄: free tetraiodothyronine; BMI: body mass index; WC: waist circumference; FBG: fasting

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3 417 blood glucose; TG: triglycerides; TC: total cholesterol; HDL-C: high density lipoprotein cholesterol; LDL-C: low
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5 418 density lipoprotein cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure. * $p < 0.05$
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420 **Table 2: Binary logistic regression analysis of the determinants of overweight in MDD patients**
 421 **with anxiety.**

	Coefficients	Std. error	Wald	<i>p</i> -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

422 TSH: Thyroid stimulating hormone; LDL-C: low density lipoprotein cholesterol. **p* < 0.05

423

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

	Coefficients		Std. error	<i>t</i>	<i>p</i> -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

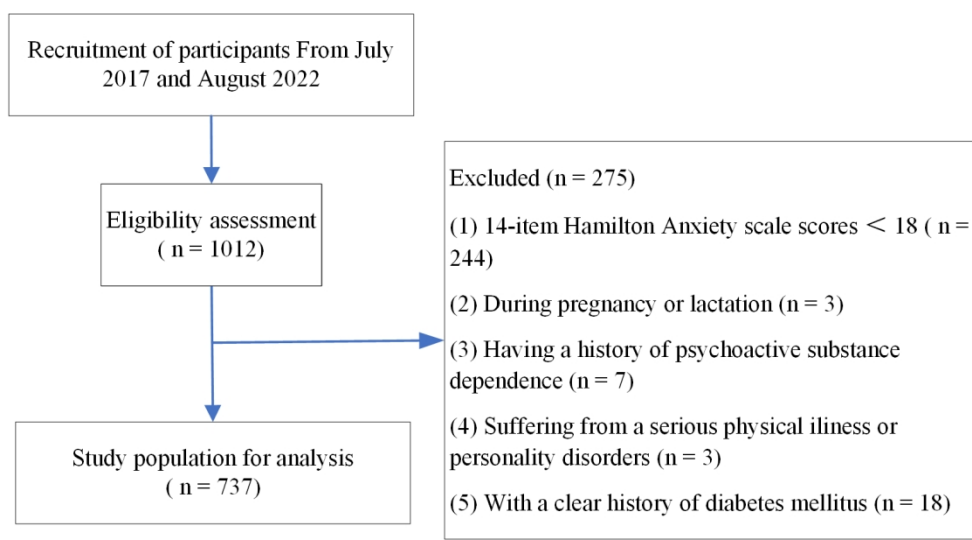
426 TSH: Thyroid stimulating hormone; LDL-C: low density lipoprotein cholesterol. * $p < 0.05$

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Participant inclusion flow chart
146x77mm (300 x 300 DPI)

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