

High Prevalence and Clinical Correlates of Sarcopenia and Metabolic Syndrome in Outpatients with Major Depressive Disorder: A Cross-Sectional Study

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Objective: This study aimed to investigate the percentages, clinical characteristics, and risk factors of sarcopenia and metabolic syndrome (MetS) among outpatients with major depressive disorder (MDD).

Methods: This study enrolled 225 MDD outpatients based on DSM-V and age- and sex-matched health controls (HCs). Sarcopenia was diagnosed based on the 2019 Asian Working Group for Sarcopenia diagnostic criteria. Three psychometric scales and the Montreal Cognitive Assessment were used to evaluate the severities of depression, anxiety, and somatic symptoms and cognitive function, respectively. Binary logistic regression models were used to investigate the risk factors of the two disorders.

Results: MDD subjects had significantly higher percentages of sarcopenia (41.3% vs 15.6%), MetS (40.9% vs 28.9%), and sarcopenia and/or MetS (68.9% vs 40.4%) than HCs. For elderly MDD subjects, 89.3% suffered from sarcopenia and/or MetS. MDD subjects had higher unqualified percentages in handgrip strength and three physical performance tests than HCs. MDD subjects with sarcopenia had worse depression than those without. MDD subjects with MetS had poorer cognitive function than those without. MDD subjects with only sarcopenia had worse mood symptoms than those with only MetS. After controlling for age and other variables, full remission of depression decreased the risk of sarcopenia. Being overweight decreased and increased the risk of sarcopenia and MetS, respectively.

Conclusions: Most MDD outpatients, especially elderly outpatients, suffered from sarcopenia and/or MetS. The two disorders should be screened in MDD patients. Treatment of depression might decrease the risk of sarcopenia.

Keywords: depression, sarcopenia, metabolic syndrome, cardiovascular disease

Introduction

Sarcopenia is characterized by the age-related loss of skeletal muscle mass (SMM) and decreased muscle strength and function.^{1,2} Sarcopenia may increase the risk of disability, falls, fractures, dysphagia, cognitive impairment, hospitalization, and all-cause mortality in elderly populations and severely impair quality of life.^{3,4} Several studies have reported that sarcopenia was associated with depression, and depression was a risk factor for sarcopenia.^{5–9} However, most of these studies focused on the elderly population in communities, but not on patients with major depressive disorder (MDD). Studies related to sarcopenia among patients with MDD or depression were rare.^{10–12} None of these studies related to sarcopenia among MDD patients used standard criteria to diagnose sarcopenia and focused on the prevalence of sarcopenia.

MDD was related to obesity, insulin resistance, and inflammation, which were linked to metabolic syndrome (MetS).¹³ Therefore, MetS was common among patients with MDD.^{14,15} MDD was associated with a 4-fold increased risk for premature death, largely due to cardiovascular diseases (CVDs).¹⁶ MetS might mediate the close relationship between depression and CVDs.¹⁶ Moreover, MetS was associated with increased all-cause and disease-related mortality among patients with MDD.¹⁷ During the treatment of depression, some antidepressants, antipsychotics, and mood stabilizers were associated with weight gain and/or MetS.^{18–20}

Low physical activity was associated with MDD, sarcopenia, and MetS.^{21–23} Sarcopenia might induce gain in fat through several pathways, including decreased physical activity, decreased non-exercise activity, and others.²⁴ Therefore, some patients with sarcopenia might develop sarcopenic obesity, which was linked to MetS and associated with increased CVDs and all-cause mortality.²⁵ On the other hand, increased obesity and reduced metabolic health also contribute to sarcopenia.²⁴ Therefore, obesity, which was an important risk factor of MetS, and sarcopenia might develop into a vicious cycle. Among the symptoms of MDD, decreased motivation and fatigue might induce decreased physical activities,²⁶ which might lead to weight gain and reduced muscle mass and power. Appetite changes, including hyperphagia and poor appetite, might affect body mass index (BMI), which was associated with MetS and sarcopenia. Therefore, patients with MDD might simultaneously suffer from sarcopenia and MetS, such as sarcopenic obesity.

As described above, depression, sarcopenia, and MetS interacted with each other. Therefore, sarcopenia and MetS were related to metabolic health and should be investigated simultaneously. However, to the best of our knowledge, no study has simultaneously investigated sarcopenia and MetS among patients with MDD. This might result from sarcopenia and MetS appearing to be two distinct conditions at first glance because sarcopenia was associated with poor nutrition and lower BMI,^{22,23} conversely, MetS was associated with obesity and higher BMI.²⁷ This issue was important because depression, sarcopenia, and MetS were associated with an increased risk of CVDs.^{16,28} Investigation of sarcopenia and MetS among patients with MDD could help physicians to find, treat, and prevent the two disorders.

This study was conducted in Taiwan, which is located in the Asian area. Several factors related to sarcopenia and MetS may contribute to the differences observed between Asian and Western countries, including diagnostic criteria, BMI cutoff points, lifestyle, and diet.^{27,29–31} For example, the BMI cutoff point for overweight in Asian populations (23 vs 25) is lower than the standard WHO definition.³² Moreover, this study was conducted during the COVID-19 pandemic period. Some special factors related to the COVID-19 pandemic period might inflate the prevalence of sarcopenia and MetS, including reduced physical activity due to lockdown, mood symptoms due to decreased social activities, and other lifestyle changes. This study might help further understand sarcopenia and MetS among MDD patients in the Asia-Pacific region during the COVID-19 pandemic period.

Therefore, the study aimed to investigate the percentages, clinical characteristics, and risk factors of sarcopenia and MetS among patients with MDD. We hypothesized that two disorders were common among patients with MDD.

Methods

Subjects

The study was performed in the psychiatric outpatient clinic of Chang Gung Memorial Hospital at Linkou, a medical center in northern Taiwan. Subjects with MDD and health controls (HCs) were enrolled from August 2021 to January 2024. Consecutive outpatients with a diagnosis of MDD documented in their medical charts were considered eligible for inclusion. A board-certified psychiatrist interviewed the eligible subjects and confirmed each criterion of MDD based on the DSM-V criteria.²⁶ Moreover, medical charts were reviewed. To avoid symptoms of sarcopenia being confounded by other psychiatric and medical diseases, three exclusion criteria were established: 1) catatonic features, psychotic symptoms, or severe psychomotor retardation; 2) a history of substance use disorders, except for cigarette and alcohol, without full remission in the past four weeks; 3) neurological and medical disorders, which may affect movements and activities, such as stroke, brain injuries and tumors, Parkinson's disease, epilepsy, heart failure, renal failure, rheumatic arthritis, cancers, and others.²² Patients with the first exclusion criteria were excluded because they might be unable to obey orders to accept the examination of the tests for sarcopenia. This study enrolled MDD subjects under pharmacotherapy in outpatient clinics, but not drug-naïve patients, to reflect real-world outpatient clinical practices.

The HCs were enrolled from hospital employees and residents in the communities. Their age and gender matched those of the MDD subjects. At enrollment, the investigators interviewed the HCs. The HCs with a lifetime history of MDD, other mood disorders, and psychotic disorders were excluded. Other exclusion criteria for the HCs were the same as those for MDD subjects. The HCs underwent the same evaluations for mood symptoms, sarcopenia, and MetS as the subjects with MDD, using the same tools.

This study was approved by the Institutional Review Board of the Chang Gung Memorial Hospital (code 202002150A3, approved on 17 March 2021). Written informed consent based on the guidelines regulated in the Declaration of Helsinki was obtained from all participants.

Evaluation of Sarcopenia

Dual-energy X-ray Absorption was performed. Grip Strength was measured using a handgrip dynamometer. Six-meter gait speed and a five-time chair stand test were evaluated. A Short Physical Performance Battery was administered.

Based on the 2019 Asian Working Group for Sarcopenia (AWGS) diagnostic criteria,²⁹ low appendicular skeletal muscle index (ASMI) was defined as dual-energy X-ray absorptiometry $<7.0 \text{ kg/m}^2$ in men and $<5.4 \text{ kg/m}^2$ in women. Low muscle strength was defined as handgrip strength $<28 \text{ kg}$ for men and $<18 \text{ kg}$ for women. Criteria for low physical performance included a six-meter gait speed of $<1.0 \text{ m/s}$, a Short Physical Performance Battery score of ≤ 9 , or a 5-time chair stand test of ≥ 12 seconds. Sarcopenia was defined as low ASMI plus low muscle strength and/or low physical performance.

Evaluation of Indices of MetS

For subjects with MDD and HCs, 12-hour fasting blood samples were collected and analyzed. Indices of MetS were measured, including fasting plasma glucose, high-density lipoprotein cholesterol (HDL), and triglycerides. Using standard instruments, an investigator measured waist circumference, body height and weight, and systolic and diastolic blood pressure (BP). BMI was calculated. $\text{BMI} \geq 23$, which includes overweight and obesity, was considered as overweight for easy understanding.³² Moreover, the elderly age was defined as age ≥ 60 years.³³

Based on the new International Diabetics Federation definition,²⁷ there are five criteria for MetS, including 1) central obesity (waist circumference $\geq 90 \text{ cm}$ in men and $\geq 80 \text{ cm}$ in women for South Asians) or a $\text{BMI} > 30 \text{ kg/m}^2$; 2) elevated ($\geq 150 \text{ mg/dL}$) triglycerides or specific treatment for this lipid abnormality; 3) reduced ($< 40 \text{ mg/dL}$ in males and $< 50 \text{ mg/dL}$ in females) HDL or specific treatment for this lipid abnormality; 4) elevated (systolic BP ≥ 130 or diastolic BP $\geq 85 \text{ mm Hg}$) BP or treatment of previously diagnosed hypertension; 5) elevated ($\geq 100 \text{ mg/dL}$) fasting plasma glucose or previously diagnosed type II diabetes. Three abnormal findings out of the five criteria would qualify subjects for the MetS. Moreover, the total cholesterol/HDL cholesterol ratio (TC/HDL-C ratio) was measured.³⁴

Evaluation of Depression, Anxiety, Somatic Symptoms, and Cognitive Function

The severities of depression and anxiety were measured using the 17-item Hamilton Depression Rating Scale (HAMD) and the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS-A), respectively.^{35,36} The severity of somatic symptoms in the past week was evaluated using the somatic subscale (SS) of the Depression and Somatic Symptoms Scale (DSSS).³⁶ The SS is composed of five pain and five non-pain symptoms. The ranges of scores for the HAMD, HADS-A, and SS were 0–52, 0–21, and 0–30, respectively. A higher score represented a greater severity of symptoms. Full remission of depression was defined as the HAMD score ≤ 7 .³⁵ The Montreal Cognitive Assessment (MoCA), designed to screen for mild cognitive impairment and early signs of dementia, was used to evaluate cognitive functions.³⁷ The MoCA score range was 0–30; a higher score indicated better cognitive function.

Statistical Methods

Statistical analyses were performed using SPSS for Windows 28.0. The Chi-square test, the independent *t*-tests, and the one-way ANOVA with Bonferroni correction were used in appropriate situations.

Binary logistic regression models were used to investigate the independent factors associated with sarcopenia and MetS. The dependent variables were sarcopenia and MetS. The independent variables consisted of 13 variables, including gender, present age, years of formal education, employed or not, married or not, HAMD, SS, HADS-A, and MoCA scores, BMI, smoking or not over the past one month, alcohol use or not over the past one month, and habit of exercise or not. These independent variables were selected because previous studies have reported that older age, underweight, physical inactivity, impaired cognitive function, depressive severity, smoking, and alcohol use were associated with sarcopenia.^{1,22,23,38}

To understand the association of some categorical variables with sarcopenia and MetS. The second model of binary logistic regression was performed. Among the above 13 independent variables, three continuous variables (including present age, BMI, and the HAMD score) were replaced by three categorical variables, including elderly (age ≥ 60 years) or not, overweight (BMI ≥ 23) or not, full remission of depression (HAMD score ≤ 7) or not. The other 10 independent variables were the same. A two-tailed p -value < 0.05 was considered to indicate statistical significance.

Results

Demographic and Clinical Variables of Subjects

This study enrolled 225 subjects with MDD and 225 HCs. Table 1 shows the demographic variables, indices of sarcopenia and MetS, the severity of depression, anxiety, and somatic symptoms, and cognitive function. There were no significant differences in age and the percentage of gender between MDD subjects and HCs. MDD subjects had lower years of education and percentages of married and employed status than HCs. For the total sample, MDD subjects had significantly greater severities of depression, anxiety, and somatic symptoms and poorer cognitive function than HCs.

Among 225 MDD subjects, 209 (92.9%) accepted at least one kind of antidepressant treatment. The most common antidepressants were serotonin-specific reuptake inhibitors ($n = 128$, 56.9%) and serotonin-norepinephrine reuptake inhibitors ($n = 68$, 30.2%). Sixteen subjects (7.1%) were treated with mood stabilizers for augmentation.

Table 1 Demographic and Clinical Variables Among Patients with Major Depressive Disorder and Health Controls

	Total		Women		Men	
	MDD	HC	MDD	HC	MDD	HC
Number	225	225	164	171	61	54
Age (years)	54.0 $\pm$ 13.1	53.6 $\pm$ 12.8	54.1 $\pm$ 12.5	53.9 $\pm$ 11.7	53.7 $\pm$ 14.9	52.8 $\pm$ 15.8
Formal education (years)	12.0 $\pm$ 3.5***	14.1 $\pm$ 3.1	11.6 $\pm$ 3.3***	13.8 $\pm$ 2.9	12.9 $\pm$ 4.0*	14.7 $\pm$ 3.4
Married (yes; %)	63.6**	77.3	64.6*	77.8	60.7	75.9
With employment (%)	47.6***	67.6	42.1***	67.8	62.3	66.7
ASMI (DXA, kg/m ²)	5.8 $\pm$ 1.2	5.9 $\pm$ 1.1	5.4 $\pm$ 0.9	5.4 $\pm$ 0.8	7.0 $\pm$ 1.2	7.2 $\pm$ 1.1
ASMI (Unqualified, %)	56.4	50.2	57.9	52.0	52.5	44.4
Handgrip strength (kg)	26.5 $\pm$ 9.5	27.7 $\pm$ 7.0	22.6 $\pm$ 5.4***	24.7 $\pm$ 4.2	37.1 $\pm$ 9.9	37.1 $\pm$ 5.6
Handgrip strength (Unqualified, %)	17.3**	7.6	18.9**	7.0	13.1	9.3
Gait speed (Unqualified, %)	17.8***	0	17.7***	0	18.0**	0
SPPB ≤ 9 (%)	35.1***	7.1	38.4***	6.4	26.2*	9.3
Chair stand test (Unqualified, %)	58.2***	23.1	58.5***	22.8	57.4***	24.1
Sarcopenia (%)	41.3***	15.6	42.7***	15.2	37.7*	16.7
BMI	24.5 $\pm$ 4.6	23.7 $\pm$ 3.7	24.0 $\pm$ 4.5	23.2 $\pm$ 3.6	25.8 $\pm$ 4.4	25.2 $\pm$ 3.6
Overweight or obesity (BMI ≥ 23) (%)	62.2*	52.4	57.3*	45.6	75.4	74.1
Waist circumference (cm)	83.5 $\pm$ 12.4*	81.2 $\pm$ 11.1	80.3 $\pm$ 11.4	78.5 $\pm$ 9.9	91.8 $\pm$ 11.1	89.7 $\pm$ 10.3
Triglycerides (mg/dl)	140.7 $\pm$ 106.3***	103.7 $\pm$ 72.4	130.0 $\pm$ 95.7***	98.9 $\pm$ 68.6	169.2 $\pm$ 127.1*	119.1 $\pm$ 82.2
HDL Cholesterol (mg/dl)	56.9 $\pm$ 14.5	58.9 $\pm$ 13.5	59.8 $\pm$ 14.4	61.5 $\pm$ 13.3	49.0 $\pm$ 11.7	50.6 $\pm$ 10.5
Systolic BP (mmHg)	129.4 $\pm$ 19.7	127.6 $\pm$ 19.6	127.9 $\pm$ 21.0	126.9 $\pm$ 20.0	133.5 $\pm$ 14.9	129.8 $\pm$ 18.0
Diastolic BP (mmHg)	79.1 $\pm$ 13.3	77.3 $\pm$ 12.2	78.1 $\pm$ 13.6	77.1 $\pm$ 12.3	81.8 $\pm$ 12.4	78.2 $\pm$ 11.9
Fasting Glucose (mg/dl)	99.1 $\pm$ 32.0*	94.2 $\pm$ 16.3	95.7 $\pm$ 16.4	92.6 $\pm$ 13.0	108.3 $\pm$ 54.5	99.2 $\pm$ 23.5
Metabolic Syndrome (%)	40.9*	28.9	37.2*	26.9	50.8	35.2
Total cholesterol/ HDL-C	3.9 $\pm$ 1.2**	3.6 $\pm$ 1.0	3.7 $\pm$ 1.1*	3.4 $\pm$ 0.9	4.4 $\pm$ 1.4	4.0 $\pm$ 1.1
HAMD	12.2 $\pm$ 6.9***	3.8 $\pm$ 3.4	12.7 $\pm$ 6.8***	4.3 $\pm$ 3.6	10.9 $\pm$ 7.0***	2.2 $\pm$ 1.8
SS	8.5 $\pm$ 6.2***	3.2 $\pm$ 3.5	8.9 $\pm$ 6.3***	3.8 $\pm$ 3.8	7.6 $\pm$ 5.7***	1.5 $\pm$ 1.6
HADS-A	8.7 $\pm$ 5.1***	3.7 $\pm$ 3.4	9.3 $\pm$ 5.2***	4.1 $\pm$ 3.6	7.9 $\pm$ 5.1***	2.7 $\pm$ 2.5
MoCA	23.4 $\pm$ 4.3***	25.2 $\pm$ 3.1	23.1 $\pm$ 4.4***	25.4 $\pm$ 3.0	24.3 $\pm$ 3.6	24.6 $\pm$ 3.3

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

Abbreviations: ASMI, appendicular skeletal muscle index; BMI, body mass index; BP, blood pressure; HAMD, Hamilton Depression Rating Scale; HADS-A, Anxiety subscale of the Hospital Anxiety and Depression Scale; HDL-C, High-density lipoprotein cholesterol; MoCA, Montreal Cognitive Assessment; SPPB, Short Physical Performance Battery; SS, Somatic subscale of the Depression and Somatic Symptoms Scale.

Table 2 The Most Commonly Used Medications in This Study

	N (%)	Dosages (mg)
Antidepressants		
Paroxetine	78 (34.6)	22.7 ± 10.9
Escitalopram	38 (16.9)	12.9 ± 7.8
Venlafaxine	34 (15.1)	164.3 ± 58.4
Mood stabilizer		
Valproic acid	10 (4.4)	320.0 ± 103.3
Lamotrigine	3 (1.3)	133.3 ± 57.7
Antipsychotics		
Quetiapine	39 (17.3)	64.8 ± 63.3
Aripiprazole	19 (8.4)	3.4 ± 1.2
Benzodiazepines		
Alprazolam	69 (30.7)	0.6 ± 0.4
Lorazepam	48 (21.3)	1.2 ± 0.5
Hypnotics		
Zolpidem	67 (29.8)	11.2 ± 4.7
Estazolam	42 (18.7)	2.0 ± 0.9

Antipsychotics were used in 71 subjects (31.5%) for augmentation. Benzodiazepines and hypnotics were prescribed in 148 (65.8%) and 111 (49.3%) subjects for anxiety and insomnia, respectively. Table 2 shows the most commonly used medications in the study. The treatment durations for these medications were over three months.

One hundred forty-six subjects (64.9%) reported regular exercise over the past month, with walking ($n = 57$) and yoga ($n = 19$) being the most common exercises. Forty-four (19.6%) subjects reported alcohol use (a mean of 6.6 ± 7.9 days) over the past month. Forty-seven (20.9%) subjects reported smoking over the past month. Most smokers were not heavy smokers, as 68.1% smoked 10 or fewer cigarettes per day. Compared with non-smokers, smokers were younger (49.7 ± 13.0 vs 55.1 ± 13.0 years, $p = 0.01$), more likely to be male (42.6% vs 23.0%, $p = 0.01$), and more likely to be employed (70.2% vs 41.6%, $p = 0.001$).

Indices and Percentages of Sarcopenia and MetS

For indices of sarcopenia, no significant difference was noted in the ASMI between MDD subjects and HCs (Table 1). Handgrip strength in female MDD subjects was lower than that in female HCs. The unqualified percentages for handgrip strength and three physical performance tests in the MDD subjects were higher than those in HCs.

For the indices of MetS, MDD subjects had significantly higher triglycerides, waist circumference, and fasting glucose than HCs. There was no significant difference in HDL cholesterol and systolic and diastolic BP between MDD subjects and HCs. Moreover, MDD subjects had a significantly higher TC/HDL-C ratio than HCs.

MDD subjects had higher percentages of sarcopenia (41.3% vs 15.6%, $p < 0.001$), MetS (40.9% vs 28.9%, $p = 0.01$), sarcopenia, and/or MetS (68.9% and 40.4%, $p < 0.001$), and both the two disorders (13.3% vs 4.0%, $p = 0.001$) than HCs (Figure 1). Elderly MDD subjects also had higher percentages of sarcopenia (53.3% vs 27.6%, $p = 0.002$), MetS (60.0% vs 42.1%, $p = 0.035$), sarcopenia and/or MetS (89.3% and 60.5%, $p < 0.001$), and both two disorders (24.0% vs 9.2%, $p = 0.017$) than elderly HCs (Figure 2). Among elderly MDD subjects, 100% and 85.2% of the subjects with BMI < 23 and BMI ≥ 23 suffered from sarcopenia and/or MetS, respectively (Figure 3). There was no significant difference in the percentage of sarcopenia and/or MetS between elderly MDD subjects (85.2%) and elderly HCs (73.8%) with BMI ≥ 23 . However, elderly MDD with BMI < 23 had a significantly higher percentage of sarcopenia and/or MetS (100.0% vs 44.1%, $p < 0.001$) than elderly HCs with BMI < 23 .

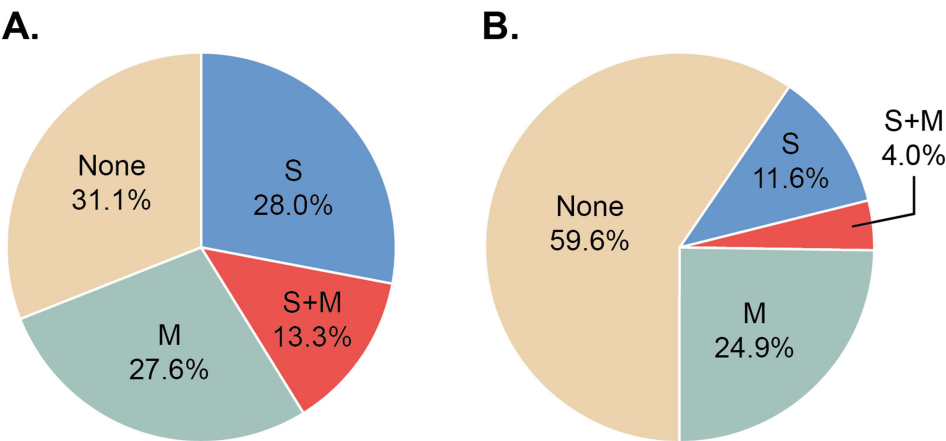


Figure 1 The percentages of sarcopenia and metabolic syndrome among outpatients with major depressive disorder (A) and healthy controls (B).
Abbreviations: S, sarcopenia; M, metabolic syndrome; S+M, sarcopenia and metabolic syndrome.

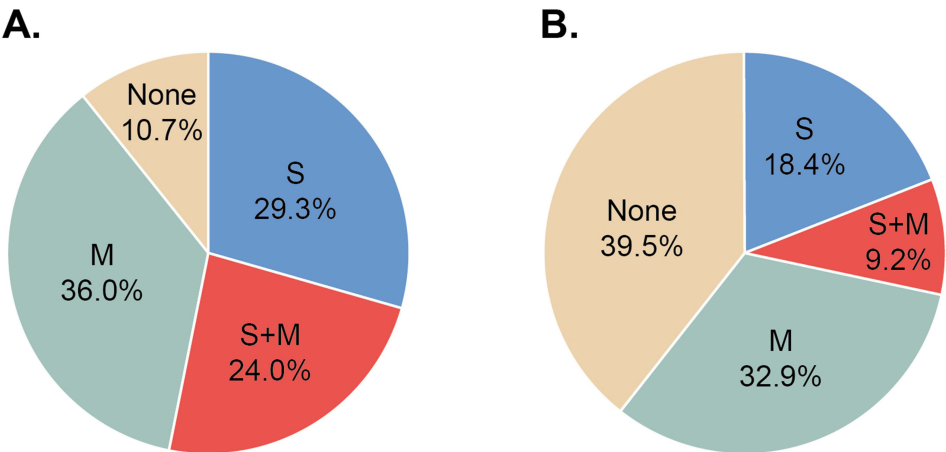


Figure 2 The percentages of sarcopenia and metabolic syndrome among elderly outpatients with major depressive disorder (A) and elderly healthy controls (B).
Abbreviations: S, sarcopenia; M, metabolic syndrome; S+M, sarcopenia and metabolic syndrome.

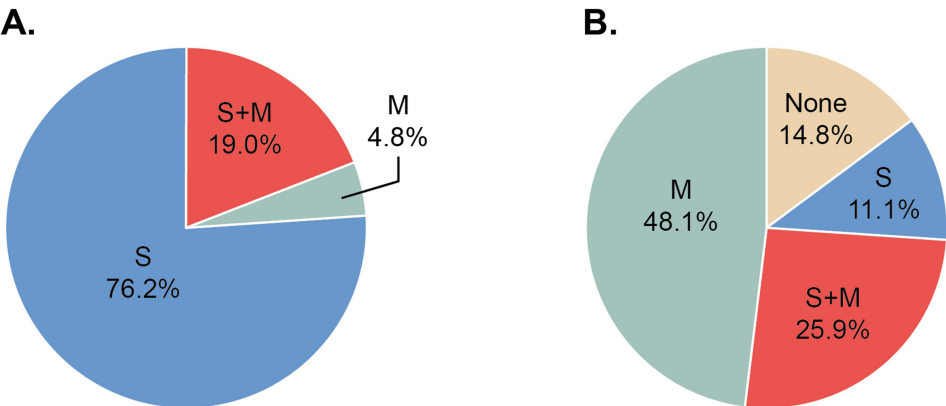


Figure 3 The percentages of sarcopenia and metabolic syndrome among elderly major depressive disorder outpatients with BMI < 23 (A) and BMI ≥ 23 (B).
Abbreviations: S, sarcopenia; M, metabolic syndrome; S+M, sarcopenia and metabolic syndrome.

Differences in Clinical Variables Between MDD Subjects with and without Sarcopenia and MetS

Table 3 shows MDD subjects with sarcopenia had significantly older age, lower years of education and BMI, and greater severities of depression, anxiety, and somatic symptoms than those without. MDD subjects with MetS had significantly older age, lower years of education, higher BMI and TC/HDL-C ratio, lower anxiety severity, and poorer cognitive function than those without.

Table 4 shows MDD subjects with the two disorders had significantly greater severities of depression and somatic symptoms than those with only MetS. Moreover, MDD subjects with only sarcopenia had significantly greater severities of depression, anxiety, and somatic symptoms than those with only MetS. MDD subjects with the two disorders and with only MetS had significantly poorer cognitive function than those without the two disorders. MDD subjects with the two disorders and with only MetS had a higher TC/HDL-C ratio than those with only sarcopenia and without the two disorders.

Table 3 Differences in Demographic and Clinical Variables Between MDD Patients with and without Sarcopenia and Metabolic Syndrome

	Sarcopenia		Metabolic Syndrome	
	Yes	No	Yes	No
Number	93	132	92	133
Age (years)	56.6±12.5*	52.1±13.3	60.0±11.0***	49.8±12.8
Formal education (years)	11.3±3.3*	12.4±3.6	11.0±3.8**	12.6±3.1
BMI	22.3±2.8***	26.0±4.9	27.3±4.5***	22.5±3.4
Total cholesterol /HDL-C	3.7±1.1	4.0±1.2	4.6±3.3***	3.4±0.8
HAMD	14.5±6.8***	10.6±6.5	11.3±7.1	12.8±6.7
SS	9.9±6.6**	7.5±5.7	7.7±6.3	9.1±6.0
HADS-A	9.8±5.3**	7.9±4.8	7.2±5.4***	9.7±4.7
MoCA	23.2±3.9	23.6±4.5	22.2±4.7***	24.3±3.7

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

Abbreviations: BMI, body mass index; HAMD, Hamilton Depression Rating Scale; MDD, major depressive disorder; HADS-A, Anxiety subscale of the Hospital Anxiety and Depression Scale; HDL-C, High-density lipoprotein cholesterol; MoCA, Montreal Cognitive Assessment; SS, Somatic subscale of the Depression and Somatic Symptoms Scale.

Table 4 Differences in Demographic and Clinical Variables Among Four Subgroups of MDD Subjects

	S+M	OS	OM	N	Statistical Significance
Number	30	63	62	70	
Age (years)	63.1±10.8	53.5±12.1	58.6±11.0	45.5±12.6	a, c, e, f
BMI	24.5±2.3	21.3±2.4	28.6±4.8	23.6±3.9	a, b, d, e, f
Formal education (years)	10.0±3.1	12.0±3.2	11.5±4.2	13.2±2.8	c, f
HAMD	14.8±7.2	14.3±6.6	9.7±6.5	11.4±6.5	b, d
SS	10.3±7.1	9.8±6.4	6.5±5.5	8.5±5.6	b, d
HADS-A	8.0±6.0	10.7±4.7	6.8±5.0	8.9±4.5	d
MoCA	22.3±3.7	23.6±3.9	22.2±5.2	25.0±3.3	c, f
Total cholesterol /HDL-C	4.5±1.4	3.3±0.7	4.6±1.3	3.4±0.8	a, c, d, f

Notes: Significant differences between the two subgroups after the Bonferroni correction were represented by using “a” to “f”. (a: S+M vs OS; b: S+M vs OM; c: S+M vs N; d: OS vs OM; e: OS vs N; f: OM vs N).

Abbreviations: S+M, sarcopenia and metabolic syndrome; OS, only sarcopenia; OM, only metabolic syndrome; N, none; BMI, body mass index; HAMD, Hamilton Depression Rating Scale; HADS-A, Anxiety subscale of the Hospital Anxiety and Depression Scale; HDL-C, High-density lipoprotein cholesterol; MetS, metabolic syndrome; MoCA, Montreal Cognitive Assessment; SS, Somatic subscale of the Depression and Somatic Symptoms Scale.

Difference in the Percentages of Sarcopenia and MetS Between MDD Subjects with and without Three Categorical Variables

Table 5 shows that elderly age increased the risk of sarcopenia and MetS. Full remission of depression significantly decreased the risk of sarcopenia. Being overweight reduced the risk of sarcopenia and increased the risk of MetS.

Independent Factors Associated with Sarcopenia and MetS

For the independent factors of sarcopenia (Table 6), older age and more severe depression increased the risk of sarcopenia in regression model I; however, cigarette smoking and higher BMI decreased the risk of sarcopenia. In regression model II, elderly age increased the risk of sarcopenia; conversely, full remission of depression and overweight decreased the risk of sarcopenia. For the independent factors of MetS, older age and higher BMI increased the risk of MetS in regression model I. Elderly age and overweight increased the risk of MetS in regression model II.

Table 5 Differences in Percentages of Sarcopenia and Metabolic Syndrome Between MDD Patients with and without Three Categorical Variables

		Sarcopenia			MetS		
		(%)	Odds Ratio (95% CI)	P	(%)	Odds Ratio (95% CI)	P
Elderly age	Yes	53.3	2.09 (1.19–3.68)	0.01	60.0	3.29 (1.85–5.85)	<0.001
	No	35.3			31.0		
Full remission of depression	Yes	20.9	0.26 (0.14–0.51)	<0.001	49.3	1.63 (0.92–1.2.90)	0.11
	No	50.0			37.3		
Overweight	Yes	28.6	0.24 (0.14–0.43)	<0.001	59.3	12.30 (5.70–26.53)	<0.001
	No	62.4			10.6		

Notes: Elderly age, full remission of depression, and overweight were defined as age ≥ 60 , the Hamilton Depression Rating score ≤ 7 , and body mass index ≥ 23 , respectively.

Abbreviation: MetS, metabolic syndrome.

Table 6 Independent Variables Associated with MDD Subjects with Sarcopenia and Metabolic Syndrome

	Model	Independent Variable	B	Wald	Odds Ratio (95% CI)	P
Sarcopenia	I	Age	0.07	19.5	1.07 (1.04–1.10)	< 0.001
		Smoking	−0.94	4.40	0.39 (0.16–0.94)	0.04
		BMI	−0.35	35.2	0.71 (0.63–0.79)	< 0.001
		HAMD	0.12	18.7	1.13 (1.07–1.19)	< 0.001
	II	Elderly age	1.32	14.4	3.74 (1.89–7.38)	< 0.001
MetS	I	Full remission of depression	−1.41	14.3	0.25 (0.12–0.51)	< 0.001
		Overweight	−1.62	24.3	0.20 (0.10–0.38)	< 0.001
		Age	0.10	27.4	1.10 (1.07–1.14)	< 0.001
		BMI	0.40	42.5	1.50 (1.33–1.69)	< 0.001
	II	Elderly age	1.14	11.3	3.12 (1.61–6.07)	0.001
		Overweight	2.51	38.8	12.24 (5.57–26.93)	< 0.001

Notes: Elderly age, full remission of depression, and overweight were defined as age ≥ 60 , the Hamilton Depression Rating score ≤ 7 , and body mass index ≥ 23 , respectively.

Abbreviations: BMI, body mass index; HAMD, Hamilton Depression Rating Scale; MetS, metabolic syndrome.

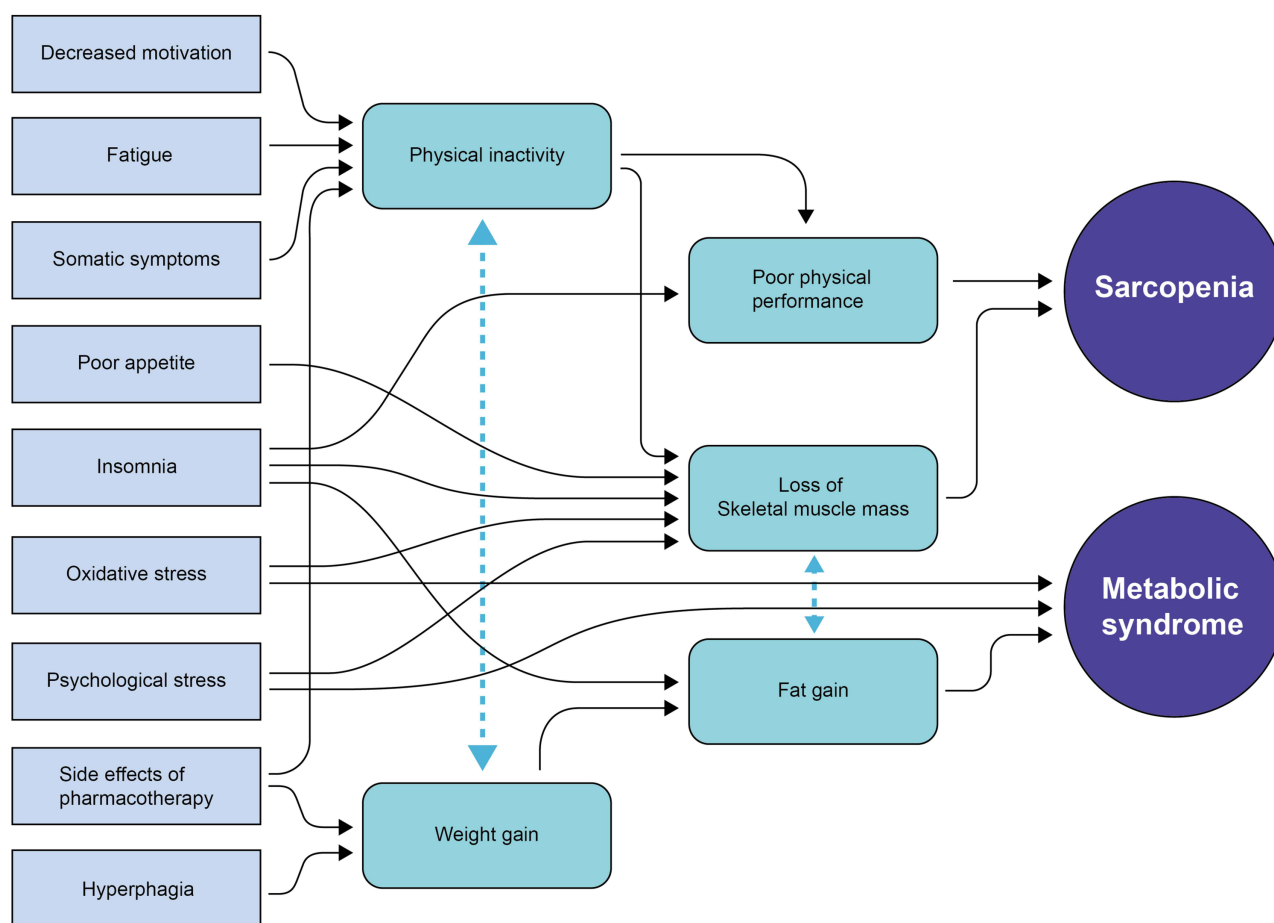


Figure 4 The associations of depressive symptoms and side effects of pharmacotherapy with sarcopenia and metabolic syndrome.

Discussion

The study aimed to investigate the percentages, clinical characteristics, and risk factors of sarcopenia and MetS among MDD outpatients. This study found that sarcopenia and MetS were common among MDD outpatients. MDD subjects had higher percentages of sarcopenia (41.3% vs 15.6%) and MetS (40.9% vs 28.9%) than HCs. Most (68.9%) MDD subjects, especially elderly MDD subjects (89.3%), faced a dilemma that they might suffer from at least one of two disorders, regardless of whether they were overweight or not.

In the regression model I, lower and higher BMI were associated with increased risks of sarcopenia and MetS, respectively. In regression model II, overweight was associated with an increased risk of MetS and a decreased risk of sarcopenia. Our results demonstrated a clinically significant paradox: BMI had dual roles, with overweight being a protective factor for sarcopenia but a risk factor for MetS. Previous studies also reported that being underweight was a risk factor for sarcopenia.^{22,23} Our results demonstrated that most (68.9%) MDD patients, especially elderly patients (89.3%), might suffer from at least one of the two disorders. Therefore, encouraging elderly MDD patients to lose weight to prevent MetS might increase the risk of sarcopenia. Our result demonstrated that elderly MDD subjects with BMI < 23 had a high percentage (81.0%) of sarcopenia (Figure 3). Appropriate exercise could improve the two disorders simultaneously because exercise can improve physical fitness and glycemic and lipid profiles,²¹ and a combination of resistance exercise with aerobic and balance training could improve the quality of life in sarcopenia.³⁹

The results that high prevalences of sarcopenia and MetS among patients with MDD might result from several factors (Figure 4). 1) Symptoms of MDD, including fatigue, lack of motivation, and somatic symptoms, might cause physical inactivity. Poor appetite and hyperphagia might cause loss of SMM and weight gain, respectively. Insomnia might simultaneously cause decreased SMM, increased fat mass, and impaired physical performance;^{40,41} 2) Side effects of

pharmacotherapy, such as weight gain and sedation, might cause physical inactivity and MetS;¹⁸ 3) Chronic stress might lead to loss of SMM and metabolic dysfunction.^{42,43} 4) Oxidative stress was associated with MDD, sarcopenia, and MetS.^{44–46} In this study, MDD subjects had higher waist circumference and a higher percentage of being overweight than HCs (Table 1). One previous study reported that MDD was associated with increased visceral and subcutaneous adipose tissue.⁴⁷ High-fat mass and obesity were simultaneously associated with sarcopenia and MetS.^{1,27} In fact, some of the above factors might interact and simultaneously increase the risk of sarcopenia and MetS. This might partially explain the high comorbidity of sarcopenia and/or MetS among patients with MDD in this study.

The regression model I shows that greater depressive severity was associated with an increased risk of sarcopenia. Conversely, full remission of depression was associated with a decreased risk of sarcopenia. Our study found that unqualified percentages for handgrip strength and three physical performance tests in the MDD subjects were higher than those in HCs. However, there was no significant difference in the ASMI between MDD subjects and HCs. This demonstrated that a higher percentage of sarcopenia among patients with MDD might result mainly from decreased muscle strength and poorer physical performance tests. One previous study reported that depression was associated with reduced handgrip strength among elderly people in communities.⁴⁸ Although two studies reported that depression was associated with decreased SMM in men but not in women,^{11,49} some studies reported that depressive mood was not associated with decreased SMM, but was associated with decreased muscle strength and worse physical performances.^{50,51}

Several points were worth noting. 1) Elderly MDD subjects (89.3%), especially those with BMI < 23 (100%), had a high percentage of sarcopenia and/or MetS. This demonstrated that the two disorders should be screened in elderly MDD subjects. Based on the aspect of comorbid with sarcopenia and/or MetS, elderly MDD subjects with BMI < 23 had significantly poorer health conditions (100.0% vs 44.1%, $p < 0.001$) than elderly HCs with BMI < 23. 2) MDD patients with MetS had poorer cognitive function than those without. One review article reported that metabolic disturbances were associated with cognitive dysfunction in MDD patients.⁵² 3) MDD subjects with only sarcopenia had worse depression, anxiety, and somatic symptoms than those with only MetS (Table 4). This demonstrated that mood symptoms in MDD subjects with sarcopenia were more severe than those with MetS. 4) Smoking was associated with a decreased risk of sarcopenia in regression model I (Table 6). However, previous studies reported that smoking was a risk factor for sarcopenia.^{22,53} One study reported that cumulative dose and smoking duration were positively associated with sarcopenia; moreover, the risk of sarcopenia increased with increasing duration of smoking after more than 40 years.⁵⁴ Most of the smokers in this study were not heavy smokers, with a mean age of 49.7 years. The negative impacts of smoking on sarcopenia among the smokers in this study might be limited. The result that smokers were associated with less sarcopenia in this study might result from the fact that the smokers were younger and more likely to be employed than the non-smokers. Whether smoking was a significant factor related to sarcopenia among MDD patients might need more evidence. 5) In Table 2, the three antidepressants, quetiapine, and valproic acid were associated with weight gain to different degrees after long-term treatment.^{18,20,55} Aripiprazole had a low risk of causing weight gain.⁵⁵ Lamotrigine was not associated with weight gain.⁵⁶ One study reported that Z-drugs and benzodiazepines do not appear to impact weight.⁵⁷

Several limitations should be noted. 1) This study was observational. Pharmacotherapy was not controlled. Polypharmacy was associated with sarcopenia.¹ 2) One review article reported that sarcopenia prevalence in elderly Asia people based on different diagnostic modalities ranged from 7.5% (95% CI: 6.0%–9.4%) to 20.8% (18.9%–23.0%).² The percentage of sarcopenia was high (27.6%) in elderly HCs. This might be because this study enrolled MDD subjects and HCs during the COVID-19 pandemic. Decreased physical activities due to lockdown or avoiding going outside might cause worse physical performances, decreased SMM, and increased obesity. 3) This study adopted a cross-sectional design, and the subjects were recruited based on all eligible cases during a fixed period. As mentioned in the introduction, no previous study has simultaneously investigated the two disorders among patients with MDD. The effect size of the two disorders was difficult to estimate. Therefore, the study did not conduct a priori power analysis. 4) This study focused on patients with MDD. Therefore, variables related to depression were overemphasized, and other confounding factors were under-addressed.

Conclusion

MDD subjects had higher percentages of sarcopenia (41.3% vs 15.6%), MetS (40.9% vs 28.9%), and sarcopenia and/or MetS (68.9% vs 40.4%) than HCs. Most (68.9%) MDD subjects, especially elderly subjects (89.3%), faced a dilemma that they might suffer from at least one of the two disorders, no matter whether they were overweight or not. Therefore, the two disorders should be screened in MDD patients. A higher percentage of sarcopenia among MDD patients than HCs might mainly come from decreased muscle strength and worse physical performance. MDD subjects with sarcopenia had worse depression than those without. MDD subjects with MetS had poorer cognitive function and a higher TC/HDL-C ratio than those without. Being overweight was independently associated with a decreased risk of sarcopenia and an increased risk of MetS, respectively. Full remission of depression was associated with a decreased risk of sarcopenia. Therefore, treatment of depression might reduce the risk of sarcopenia. The cross-sectional design was unable to clarify the causal relationships regarding the bidirectional relationships between depression, sarcopenia, and MetS. In future studies, potential confounding by psychopharmacotherapy needs further prospective investigations.

Data Sharing Statement

The data supporting the findings of this study are available on request from the corresponding author.

Ethics Approval

This study was approved by the Institutional Review Board of the Chang Gung Memorial Hospital (code 202002150A3, approved on 17 March 2021). Written informed consent was obtained from all participants.

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Disclosure

All authors declare that they have no conflicts of interest in this work.

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