Prevalence of Metabolic Syndrome and Associated Factors in a Cohort of Individuals With Treatment-Resistant Depression: Results From the FACE-DR Study

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ABSTRACT

Background: The aim of this study was to estimate the prevalence of metabolic syndrome (MetS) and its components in a cohort of French patients with treatment-resistant depression (TRD) and to determine correlations with sociodemographic, clinical, and treatment-related factors.

Methods: From 2012 to 2018, 205 patients who met *DSM-IV* criteria for major depressive episode with moderate-to-severe symptoms (Montgomery-Asberg Depression Rating Scale score ≥ 20), and at least Stage II resistance according to Thase and Rush criteria were enrolled in the FondaMental Advanced Centers of Expertise in Resistant Depression (FACE-DR) cohort. Data on sociodemographic and clinical characteristics, lifestyle information, and treatment and comorbidities were collected, and a blood sample was drawn. MetS was defined according to the criteria of the International Diabetes Federation.

Results: Overall, 38% of individuals with TRD met criteria for MetS. The frequency of MetS was significantly higher in men than in women only for patients aged 40 years or older (46.3% vs 35.2%, $P = .0427$). Moreover, whereas the management for diabetes was good, less than one-third of the patients with high blood pressure or dyslipidemia were treated for these conditions. Multivariate analysis showed that individuals with abnormal plasma c-reactive protein levels had a 3-fold increased risk (95% CI, 1.5–5.2) of having MetS, independent of other potential confounders.

Conclusion: The prevalence of MetS is higher in patients with TRD than in those with other psychiatric disorders and characterized by a considerable undertreatment of some components of MetS in this population. Diagnosis and treatment of the components of MetS should be systematically performed to prevent the occurrence of cardiovascular diseases in patients with TRD. These findings highlight the need for integrated care, with more interaction and coordination between psychiatrists and primary care providers.

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Clinical Points

- Although metabolic abnormalities may contribute to the chronicity of major depressive disorder, few specific investigations have been conducted in treatment-resistant depression (TRD).
- Metabolic syndrome is highly frequent (38%) in patients with TRD—higher than in other psychiatric disease—and should be systematically screened in this population.
- Integrated care between psychiatrists and primary care providers and early intervention are crucial to reduce cardiovascular diseases, which are known to be important in patients with TRD.

Major depressive disorder (MDD) is a common psychiatric disorder characterized by a high risk of morbidity and mortality and a high level of comorbidities with various psychiatric and nonpsychiatric disorders.[1,2] Despite recent progress in pharmacotherapy, approximately 30% of patients suffering from MDD failed to experience significant clinical benefits from currently available treatments, and up to one-half of patients respond only partially, leading to a chronically deteriorating course of the illness.[3,4] Treatment-resistant depression (TRD) is currently defined by the failure of at least 2 attempts of antidepressant treatments administered sequentially at adequate dose and duration.[5] Several risk factors have been related to pharmacologic resistance, including psychosocial factors, severity and duration of the current depressive episode, or psychiatric comorbidities.[6–8] In addition, medical conditions such as cardiovascular diseases, obesity, or diabetes have also been associated with poor clinical response to antidepressant treatment.[9] This issue is important because large epidemiologic cohort studies have consistently supported that MDD represents a major risk factor for cardiovascular disease (CVD)[10] independent of traditional risk factors,[11] while individuals with MDD have almost twice the risk of developing CVD.[11] Metabolic syndrome (MetS), defined by a collection of clinical and biological abnormalities predisposing to CVD, is widely recognized as a leading cause of CVD-related mortality in the general population.[12,13] MetS is highly prevalent in MDD, with estimated rates of 30.5%, similar to rates reported in schizophrenia and bipolar disorder.[14] The most consistent evidence exists for the relationship between MDD and obesity-related components of MetS (abdominal obesity, low high-density lipoprotein [HDL] cholesterol, hypertriglyceridemia), whereas associations with hyperglycemia and arterial hypertension are less frequently reported.[15] The elevated co-occurrence of depressive symptoms and MetS pleads for a pathophysiologic overlap, even if underlying mechanisms have not been fully elucidated. Plausible pathways include biological, behavioral, psychological, and genetic determinants.[16,17] Reduced access to health care, poor lifestyle conditions, psychotropic medication side effects, and the presence of modifiable behavioral risk factors such as smoking and physical inactivity may explain the higher prevalence of metabolic abnormalities among depressed patients. Moreover, shared pathophysiologic features, such as dysfunction of autonomic nervous system activity, hypothalamic-pituitary-adrenal axis dysregulation, immuno-inflammatory abnormalities, vascular endothelial dysfunction, and dysbiosis of gut microbes, as well as common genetic links may contribute to the association between MetS and MDD.

From a clinical point of view, some evidence suggests that the prevalence of MetS abnormalities may partly depend on depression subtype or symptom profile, with more MetS occurring in atypical depression compared to melancholic depression.[18] Metabolic abnormalities may also contribute to the chronicity of MDD.[17,19] Data about the impact of MetS on the effectiveness of antidepressant pharmacotherapy in individuals with MDD are mixed. However, 2 prospective studies[20,21] suggest that the presence of metabolic abnormalities in patients with depressive disorders negatively affects the clinical course and treatment outcome, although MetS was not specifically evaluated. Although the comorbidity between MDD and MetS has clearly been identified, few specific investigations have been conducted in TRD. One cross-sectional study[22] comparing MetS in MDD individuals with and without TRD found no association between MetS and treatment resistance, with a prevalence of MetS of 39.6% in 53 individuals with TRD and of 31.3% in non-TRD depressed patients. However, this study was conducted in a small sample and did not include the assessment of demographic and clinical characteristics that could have affected treatment response. Given the long-term health consequences of both MetS and TRD, it is important to better characterize the association between MetS and TRD. Understanding this relationship should guide treatment efforts aimed at reducing the prevalence of MetS as well as directing future research to better understand mechanisms mediating the link between MetS and TRD. Thus, the objectives of this study were to evaluate (1) the prevalence of MetS and its components in a large multicenter cohort of 205 French individuals with rigorously defined TRD; (2) its correlation with sociodemographic, clinical, and treatment-related factors; and (3) the gap between optimal care and effective care of TRD patients.

MATERIALS AND METHODS

Study Population

The study sample consisted of patients evaluated in the French network of FondaMental Advanced Centers of Expertise in Resistant Depression (FACE-DR). This network is supported by the French Ministry of Health and has been developed under the aegis of the FondaMental Foundation (www.fondation-fondamental.org) to provide support to general practitioners, psychologists, and psychiatrists in the diagnosis and management of individuals with TRD.

Inclusion Criteria

All patients referred to the network of 13 French expert centers for TRD from 2012to 2018 who met *DSM-IV* criteria

Table 1. Prevalence of Metabolic Components[a]

Variable	All (N = 205)	Inpatients With MetS (n = 78)	Men (n = 34)	Women (n = 44)	*P* Value
Hypertension[b]	102 (53.7)	60 (81.1)	29 (90.6)	31 (73.8)	.0673
Low HDL cholesterol[c] or treatment	99 (50.8)	54 (71.0)	20 (60.6)	34 (79.1)	.0785
Hypertriglyceridemia[d] or treatment	71 (35.3)	52 (72.9)	25 (78.1)	27 (61.4)	.1206
High fasting glucose[e] or treatment	47 (25.4)	33 (45.2)	16 (48.5)	17 (42.5)	.6091
Abdominal obesity[f]	129 (72.9)	68 (94.5)	29 (93.6)	39 (95.1)	1.0000
Body mass index (kg/m^2)[g]					.0424
< 25	89 (49.2)	16 (23.5)	5 (16.7)	11 (28.9)	
25–30	53 (29.3)	23 (33.8)	15 (50.0)	8 (21.1)	
> 30	39 (21.6)	29 (42.7)	10 (33.3)	19 (50.0)	

[a]Values are shown as n (%).
[b]Defined as systolic blood pressure ≥ 130 mm Hg, diastolic blood pressure ≥ 85 mm Hg, or requiring use of antihypertensive medication. Data missing for 15 individuals.
[c]Defined as plasma HDL cholesterol < 1.03 mmol/L in men and < 1.29 mmol/L in women. Data missing for 10 individuals.
[d]Defined as plasma concentration ≥ 1.7 mmol/L. Data missing for 4 individuals.
[e]Defined as plasma concentration ≥ 5.6 mmol/L. Data missing for 21 individuals.
[f]Data missing for 28 individuals.
[g]Data missing for 24 individuals.
Abbreviations: HDL = high-density lipoprotein, MetS = metabolic syndrome.

for MDD with moderate-to-severe symptoms (MADRS ≥ 20) and at least Stage II resistance according to Thase and Rush criteria[23] were enrolled in the FACE-DR cohort.

Exclusion Criteria

Individuals with a *DSM-IV* diagnosis of bipolar disorder, schizophrenia, obsessive-compulsive disorder, eating disorders (with body mass index [BMI] < 15), somatoform disorders, and mood disorders related to substance abuse or misuse were systematically excluded from the cohort. We also excluded from this specific analysis individuals with serum high-sensitivity c-reactive protein (hs-CRP) levels above 10 mg/L.

There were 13 expert centers in France, and they all used the same set of comprehensive and standardized evaluations, previously described by Yrondi et al.[24]

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The assessment protocol was approved by the institutional review board (French CNIL: DR-2015-673), in accordance with the French laws for non-interventional studies, and requires only an informed consent.

Data Collected

Patients benefited at inclusion from an exhaustive clinical assessment performed by a specialized team comprising senior psychiatrist, nurse, psychologist, and neuropsychologist who systematically recorded information related to the patient's education, marital status, past and present history of MDD (using the Mini-International Neuropsychiatric Interview),[25] psychiatric and somatic comorbidities, and family history. Current psychotropic treatments were systematically reported, and a blood sample was collected. The level of resistance was evaluated with the currently used classification of Thase and Rush Stage II or higher. Current mood state and residual depressive symptoms were assessed with the Montgomery-Asberg Depression Rating Scale[26] and the 16-item Quick Inventory of Depressive Symptomatology Self-Report.[27] Compliance was rated using the Medication Adherence Rating Scale.[28] Physical activity was recorded using a self-rated questionnaire. We considered an individual as doing "no physical activities" if he or she responded "0" to all the following questions: "During the 7 last days, how many days did you do an intense physical activity?" "During the 7 last days, how many days did you do any moderate physical activity?" "During the 7 last days, how many days did you walk at least 10 consecutive minutes?"

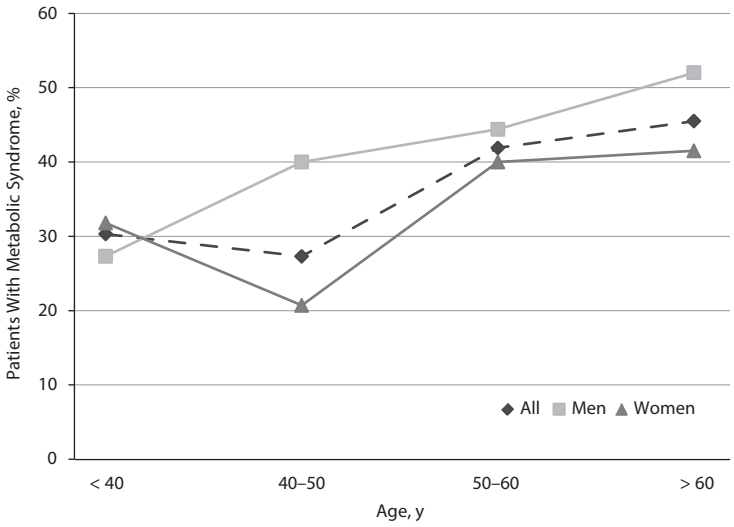
Biological Measurements

A blood draw for routine blood examination was performed, and serum concentrations of triglycerides and low-density lipoprotein, HDL, and total cholesterol as well as glucose (if patients confirmed fasting for at least 10 hours) were ascertained. High sensitivity CRP was measured with an assay using a commercial nephelometer kit according to the manufacturer's instructions (Dade Behring; Deerfield, Illinois) blinded to TRD status. Abnormal CRP level was defined as > 3 mg/L.[29]

Metabolic Syndrome Assessment

Measures of systolic and diastolic blood pressure were performed once the patient was at rest for at least 5 minutes. Weight, height, and waist circumference were also assessed. Metabolic syndrome was defined according to the criteria of the International Diabetes Federation (IDF),[30] which require the presence of 3 or more of the following 5 symptoms: high waist circumference (> 94 cm for men and > 80 cm for women), hypertriglyceridemia (≥ 1.7 mM or on lipid-lowering medication), low HDL cholesterol level (< 1.03 mM in men and < 1.29 mM in women or on lipid-lowering medication), high blood pressure (≥ 130/85 mm Hg or on antihypertensive medication), and high fasting

Figure 1. Prevalence of Metabolic Syndrome[a] According to Age and Sex



[a]International Diabetes Federation definition.

glucose concentration (≥ 5.6 mM or on glucose-lowering medication).

Statistical Analysis

Sociodemographics, clinical characteristics, and psychiatric comorbidities were presented using medians and interquartile ranges (IQRs) for continuous variables and frequency distributions for categorical variables. Associations between demographic, clinical, and therapeutic characteristics of TRD individuals with MetS were analyzed using χ^2 tests for categorical variables and Wilcoxon–Mann-Whitney tests for continuous variables. We estimated crude odds ratios with 95% CIs. Stratified analyses were performed by age and sex. Variables with P values < .15 in univariate analysis were included in the multivariable logistic regression model to estimate the likelihood of having MetS. Statistical analyses were performed with SAS (release 9.3; SAS Statistical Institute; Cary, North Carolina). All statistical tests were 2-tailed, with α level set at .05.

RESULTS

A total of 205 patients were enrolled in the FACE-DR cohort between 2012 and 2018 and were assessed for MetS. The characteristics of those patients are displayed in Table 1; median age was 53.5 years (IQR, 45.6–63.2 years) and 61.9% were women. The median age at TRD onset was 35 years (IQR, 24–46 years), and 11% were considered being at Stage IV or V resistance.

Prevalence of Metabolic Syndrome and Its Components

The prevalence of MetS in the FACE-DR cohort was estimated at 38%. MetS was present in 43.6% of the men and 34.6% of the women. The prevalence of MetS increased with age (Figure 1). After stratification of the sample by age and sex, we found that the frequency of MetS was significantly higher in men than in women for patients aged at least 40 years (46.3% vs 35.2%, $P = .0427$). In younger patients, the prevalence of MetS was similar in both men and women (27.3% vs 31.8%).

Prevalence values for the distinct components of MetS in individuals with TRD are presented in Table 2. We found that 53.7% of the individuals with TRD had high blood pressure, 50.8% had low HDL cholesterol levels, 35.3% had hypertriglyceridemia, 72.9% had abdominal obesity, and 25.4% had high fasting glucose concentrations. We also observed that 50.8% of the patients with TRD were overweight, whereas 29.0% had BMI above 25, and 21.8% were obese with BMI of 30 or greater. In patients with MetS, all of the individual components of the syndrome were highly frequent (> 70%), with the exception of high fasting glucose, which was present in 45.2% of patients. Analyses by sex indicated that men were significantly more likely to be overweight than women (83.3% vs 71.1%, $P = .0424$) and tended to be more likely to have hypertension then women (90.6% vs 73.8%, $P = .0673$).

Risk Factors for Metabolic Syndrome

The factors associated with MetS are shown in Table 3. No association between MetS and clinical characteristics of TRD was observed. As expected, BMI was significantly associated with the frequency of MetS; overweight individuals had 5.9 (95% CI, 3.0–11.7) times higher risk of experiencing MetS compared to individuals who were not overweight. By contrast, no significant association was found between tobacco use and MetS (odds ratio = 0.7; 95% CI, 0.39–1.27). Surprisingly, there was no association with

Table 2. Factors Associated With Treatment-Resistant Depression in a Cohort of 205 Patients With Treatment-Resistant Depression[a]

Characteristic[b]	All (N = 205)	Metabolic Syndrome		P[c]	OR (95% CI)
		No (n = 127, 62.0%)	Yes (n = 78, 38.0%)		
Demographics					
Sex				.2003	
Male	78 (38.1)	44 (56.4)	34 (43.6)		1.5 (0.82–2.60)
Female	127 (61.9)	83 (65.4)	44 (34.6)		1 (reference)
Age, mean (SD), y	53.5 (12.7)	52.3 (12.7)	55.5 (12.7)	.0805	1.2 (0.98–1.54)
High level of education (GCSE or higher)	94 (48.5)	61 (50.4)	33 (45.2)	.4820	0.8 (0.45–1.45)
Disease Characteristics					
Age at depression onset, mean (SD), y	35.2 (14.7)	33.5 (14.4)	38.4 (14.9)	.0885	1.3 (0.97–1.64)
Duration of illness, mean (SD), y	18.6 (12.6)	19.1 (13.2)	17.7 (11.6)	.7393	1.0 (0.82–1.11)
Stage of illness severity (Thase and Rush criteria)				.1131	
II–III	178 (89.0)	112 (91.8)	66 (84.6)		1 (reference)
IV–V	22 (11.0)	10 (8.2)	12 (15.4)		2.0 (0.83–4.97)
Depressive symptoms (MADRS score), mean (SD)	29.1 (6.8)	29.5 (7.2)	28.5 (6.1)	.2838	1.0 (0.94–1.02)
Age at first psychotropic medication, mean (SD), y	37.1 (14.3)	36.3 (13.9)	38.5 (15.0)	.4697	1.0 (0.98–1.04)
No. of depressive episodes with resistance for at least 2 treatments, mean (SD)	1.3 (0.8)	1.3 (0.9)	1.3 (0.6)	.4508	1.1 (0.67–1.79)
No. of depressive episodes, mean (SD)	3.0 (2.1)	3.1 (2.3)	2.7 (1.5)	.6906	0.9 (0.71–1.11)
Chronicity of current episode > 2 y	67 (60.4)	43 (59.7)	24 (61.5)	.8519	1.1 (0.48–2.40)
Lifetime suicide attempt	74 (37.4)	48 (39.7)	26 (33.8)	.4026	0.8 (0.43–1.41)
No. of hospitalizations, mean (SD)	2.8 (2.3)	2.6 (2.3)	3.0 (2.3)	.3714	1.1 (0.90–1.26)
Global functioning,[d] mean (SD)	43.9 (13.0)	43.7 (12.9)	44.3 (13.2)	.7709	1.0 (0.98–1.03)
Comorbidities					
Current daily tobacco smoking	75 (37.1)	50 (40.3)	25 (32.1)	.2362	0.7 (0.39–1.27)
Anxiety disorders (STAY-A[31] score), mean (SD)	51.4 (9.7)	52.2 (9.6)	50.1 (9.8)	.1431	1.0 (0.95–1.00)
Physical activities				.0921	
No	134 (76.6)	75 (72.1)	59 (83.1)		1.9 (0.89–4.04)
Yes	41 (23.4)	29 (27.9)	12 (16.9)		1 (reference)
Body mass index (kg/m^2)				**<.0001**	
<25	89 (49.2)	**73 (64.6)**	**16 (23.5)**		**1 (reference)**
25–30	53 (29.3)	**30 (26.6)**	**23 (33.8)**		**3.7 (1.75–7.93)**
>30	39 (21.6)	**10 (8.9)**	**29 (42.7)**		**13.9 (5.66–34.02)**
Abnormal CRP levels (> 3 mg/L)				**.0009**	
No	130 (67.4)	**90 (76.3)**	**40 (53.3)**		**1 (reference)**
Yes	63 (32.6)	**28 (23.7)**	**35 (46.7)**		**2.8 (1.51–5.23)**
Treatments at Baseline					
Adherence to medication (MARS score), mean (SD)	3.9 (1.5)	4.0 (1.5)	3.7 (1.7)	.2064	0.9 (0.74–1.09)
Second-generation antipsychotic	48 (32.0)	32 (34.8)	16 (27.6)	.3575	0.7 (0.35–1.46)
First-generation antipsychotic	17 (11.3)	7 (7.6)	10 (17.2)	.0699	2.5 (0.90–7.08)
Antidepressant					
SSRI	21 (14.0)	15 (16.3)	6 (10.3)	.3057	0.6 (0.22–1.63)
SNRI	50 (33.3)	29 (31.5)	21 (36.2)	.5533	1.2 (0.62–2.47)
MAOI	12 (8.0)	6 (6.5)	6 (10.3)	.5381	1.7 (0.51–5.40)
Tricyclic	32 (21.3)	19 (20.6)	13 (22.4)	.7976	1.1 (0.50–2.46)
Other	31 (20.7)	22 (23.9)	9 (15.5)	.2162	0.6 (0.25–1.38)
Mood stabilizer	23 (15.3)	12 (13.0)	11 (19.0)	.3269	1.6 (0.64–3.81)
Anxiolytics/hypnotics	80 (53.3)	48 (52.2)	32 (55.2)	.7200	1.1 (0.58–2.18)
No. of antipsychotic treatments, mean (SD)	2.9 (1.6)	2.8 (1.4)	3.0 (2.0)	.8977	1.1 (0.86–1.28)
rTMS	12 (6.7)	5 (4.6)	7 (10.3)	.1372	2.4 (0.73–7.29)
ECT	49 (26.9)	28 (24.6)	21 (30.9)	.3524	1.4 (0.70–2.68)

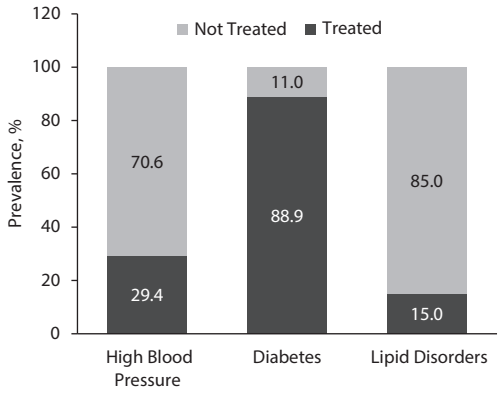
[a]Values are shown as n (%) unless otherwise noted. Boldface indicates statistical significance.
[b]Data were missing for the following variables: high school, n = 11; tobacco smoking, n = 2; age at depression onset, n = 25; duration of illness, n = 25; depressive symptoms, n = 2; age at first psychotropic medication, n = 27; No. of depressive episodes with resistance for at least 2 treatments, n = 97; No. of depressive episodes, n = 99; chronicity of current episode, n = 94; lifetime suicide attempt, n = 7; No. of hospitalizations, n = 93; global functioning, n = 32; anxiety disorders, n = 10; physical activities, n = 30; abnormal CRP levels, n = 12; adherence to medication, n = 15; treatments, n = 55; rTMS, n = 27; ECT, n = 23.
[c]χ^2 Tests for categorical variables and Wilcoxon–Mann-Whitney tests for continuous variables.
[d]Global functioning (and within subdomains) was measured using the Functioning Assessment Short Test (FAST).[32] The FAST score is a score specifically developed to assess the level of functioning among individuals with bipolar disorder and includes items in 6 domains (cognition, autonomy, occupational functioning, financial issues, leisure time, and interpersonal relationships). A high score indicates worse social functioning.
Abbreviations: CRP = c-reactive protein, ECT = electroconvulsive therapy, GCSE = General Certificate of Secondary Education, MADRS = Montgomery-Asberg Depression Rating Scale, MAOI = monoamine oxidase inhibitor, MARS = Medication Adherence Rating Scale, OR = odds ratio, rTMS = repetitive transcranial magnetic stimulation, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, STAY-A = Spielberger Anxiety Scale.

Table 3. Multivariable Model of the Factors Associated With Metabolic Syndrome in Individuals With Treatment-Resistant Depression[a]

Variable	OR	95% CI
Abnormal CRP (> 3 mg/L)	3.00	1.19–7.43
Age	1.03	1.01–1.06
High level of resistance (Thase level ≥ 4)	0.93	0.24–3.62
No physical activities	1.93	0.75–4.94
First-generation antipsychotic	2.21	0.44–11.04
Anxiety (STAY-A score)	1.00	0.95–1.03

[a]Multivariable logistic regression analysis.
Abbreviations: CRP = c-reactive protein, OR = odds ratio, STAY-A = Spielberger Anxiety Scale.

Figure 2. Prevalence of Treatment for Lipid Disorders, High Blood Pressure, and Diabetes in Patients With These Conditions



any class of medication, including tricyclic antidepressants and second-generation antipsychotics. The only factor associated with a greater risk of having MetS in individuals with TRD was an abnormal plasma CRP levels at baseline, as attested by individuals with plasma CRP levels outside the normal range showing almost 3 times higher risk (95% CI, 1.19–7.43) of experiencing MetS compared to individuals without CRP levels outside the normal range.

Treatment of Metabolic Syndrome Components

The percentages of patients with lipid disorders, hypertension, and high fasting glucose receiving treatment for these conditions are presented in Figure 2. Whereas the management for diabetes is good (89% of patients with high fasting glucose concentration were receiving a treatment), we found that only 29% of the patients with high blood pressure and 15% of those with dyslipidemia were treated for these conditions.

Older age (≥ 50 years) and lower adherence to psychotropic medication were significantly associated with the likelihood of receiving treatment for these medical conditions. No influence of sex, education level, or depressive symptoms was found (data not shown).

DISCUSSION

To our knowledge, the present study is the first to investigate the prevalence of MetS and its components in a large cohort of French patients with well-defined TRD. Our major findings were that (1) MetS is highly frequent in French individuals with TRD, with a prevalence of 38%; (2) the likelihood of MetS is independently related to BMI and higher plasma CRP levels; and (3) there is a considerable gap between optimal and effective treatment for patients with MetS components.

The prevalence of MetS in our French TRD cohort was higher than the rates generally reported in the general population and in non-TRD depressed patients.[14,33] Indeed, epidemiologic studies[33,34] of MetS prevalence based on the National Cholesterol Education Program Adult Treatment Panel III criteria in the French general population (mean age = 48 years) have shown a rate of 7.0%–8.8%, which is 4 times lower than that of our large sample. Moreover, a meta-analysis[14] of 18 randomized controlled trials, representing 5,531 European and North American subjects with a mean age of 45.5 years, has found a prevalence for MetS of 30.5% in nonresistant depressed patients. So far, only 1 study[22] has provided prevalence estimates in TRD consistent with our findings, with an overall rate of 39.6% in 53 Croatian patients aged 57.2 years on average. Although the mean age of our sample (53 years) was relatively high, the prevalence of MetS in individuals aged less than 60 years (mean age = 46 years) was still higher (34.5%) than the rates reported in the general population and in non-TRD depressed patients. Moreover, although we did not include a control group matched for sex and age, we were able to compare the prevalence of MetS in TRD with that reported in other serious mental conditions among French cohorts since we recently published findings[35,36] in schizophrenia and bipolar disorder showing prevalence of MetS reaching 24.2% and 20%, respectively. While previous meta-analyses[37,38] revealed that MetS prevalence was commonly elevated in schizophrenia, bipolar disorder, and MDD without significant differences across the 3 diagnostic subgroups, our results have shown that MetS prevalence was higher in individuals with TRD, including in patients under the age of 40 years, thereby leading us to consider that intensive monitoring and treatment efforts should target this at-risk group.

The prevalence of MetS in our study was higher in men than in women, in line with some previous findings[39] in nonresistant depressed patients. However, sex differences in terms of MetS prevalence remain a controversial issue, as suggested in earlier population studies[40] and a more recent meta-analysis[14] showing no significant differences among men and women. Our results also indicate a linear increase in MetS prevalence with age. The large prevalence of MetS in older adults can possibly be explained by a lifetime accumulation of risk factors such as excess caloric intake, dyslipidemia, a sedentary lifestyle, hormonal changes, or changes in the secretory functions of pancreatic β cells.

After stratification by sex, the risk of developing MetS for patients aged 40 years or older was significantly higher in men than in women, whereas the risk seemed to be similar for the 2 sexes before this age. Moreover, MetS components

differ between men (higher frequency of hypertension and overweight) and women. This sex-specific association in the distribution of high blood pressure is in line with data in the French general population and earlier works in nonresistant depressed patients.[33,34,39] These differences have been attributed to variations in fat distribution patterns and endocrine profiles. Greater visceral fat accumulation and lower plasma adiponectin concentrations in men than in women are candidates for mediating sex differences in insulin sensitivity and higher vulnerability to cardiovascular disease. Among young and middle-aged adults, women have lower blood pressure and triglycerides and less visceral fat accumulation than men. However, the protection conferred on women is not lifelong, dissipating rapidly after the age of 50. This dissipation supports the protective effects of female sex hormones and the unfavorable effects of testosterone on substrate metabolism in view of the MetS.

Contrary to our expectations, we found no relationship between clinical characteristics of the illness and MetS. Especially, we could detect no association between illness duration or chronicity and MetS or its components, while some evidence suggests that a combination of multiple metabolic dysregulations contributes to the sustained chronicity of MDD and reports a strong association between history of MDD and current metabolic syndrome.[20,41] Among biological factors, we provide first evidence that higher peripheral CRP levels, which indicate subclinical inflammation, and MetS are associated in TRD. CRP represents a stable plasma biomarker for a systemic inflammation. Alterations in the immune response system, including higher serum levels of CRP and proinflammatory cytokines, have been previously reported in individuals with either MDD or TRD compared with healthy individuals.[42] Given that low-grade chronic inflammation is linked to obesity, MetS, and an increased cardiovascular risk in MDD, the co-occurrence of metabolic disturbances and inflammation in TRD is not surprising.[43]

Relationships between MetS and antidepressants or antipsychotic drugs have been repeatedly reported in published studies.[44–46] However, we found no association between the prescription of psychotropic medications and MetS in our TRD cohort. The use of most classes of antidepressants, such as tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs), has largely been associated with higher waist circumference, triglycerides, and MetS abnormalities, with higher effect sizes for TCAs than for SSRIs and SNRIs.[47] However, effects vary greatly among individual agents. Moreover, the literature is still inconclusive on a possible association between antidepressants and some components of MetS, including glucose dysregulation, diabetes, and dyslipidemia.[46] Similarly, antipsychotics may produce independent effects on metabolic regulation, increasing risk for MetS, obesity, and diabetes in schizophrenia and bipolar disorder,[37] and there is clear evidence that individual antipsychotics differ in their cardiometabolic risk profile.[48] However, our data were insufficient to compare the risk for MetS according to the different antipsychotics and to take into account the duration of treatment and the cumulative exposure to psychotropic drugs, thus precluding firm conclusions. Our results highlighted the extent of undertreatment for cardiometabolic risk factors in patients with TRD. In particular, we found that only 29% of those with hypertension and 15% of those with dyslipidemia received active medical therapy, whereas management of TRD patients for diabetes is relatively good (89%). Given the high rates of CVD-related mortality and morbidity in this population, adequate monitoring of MetS and its potential deterioration during treatment is necessary to provide timely treatments. Suboptimal medical care reinforces the need to systematically assess, diagnose, and treat MetS during management of TRD and justify the relevance of integrated care associating psychiatrists and primary care providers.

The precise mechanisms connecting MetS and MDD have not yet been elucidated, although background socioeconomic and lifestyle conditions along with the presence of modifiable behavioral risk factors (unhealthy diet, smoking, physical inactivity) are assumed to facilitate the development and persistence of MetS.[16] As supported in our study, impaired immune-inflammatory mechanisms have a critical role in underlying the link between MetS and TRD. Also, emerging evidence suggests that they share other pathophysiologic features, including autonomic nervous system malfunction, hypothalamic-pituitary-adrenal axis dysregulation, coagulation abnormalities and vascular endothelial dysfunction, and dysbiosis of gut microbiota, as well as common genetic links and epigenetic interactions.[16]

The main limitation of our study was its cross-sectional character so that causal inferences cannot be drawn. Indeed, as depression symptoms were measured only at a given time-point, this study cannot directly evaluate the long-term impact of MetS on the incidence of TRD or whether MetS precedes MDD and pharmacologic resistance or vice versa. Moreover, we did not include a control group to compare MetS prevalence.

In conclusion, our work points to a high prevalence of MetS in patients with TRD. Further studies are needed to better understand the causal and temporal relationship between MetS, MDD, and treatment resistance. Of importance, TRD patients received inferior quality of care for MetS components, despite the availability of monitoring treatment guidelines. The screening of MetS coupled with the implementation of appropriate strategies for efficiently managing patients and preventing the future development of CVD and related diseases is necessary to reduce the significant morbidity and mortality associated with TRD.

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