The Impact of Obesity on Cognitive Functioning in Euthymic Bipolar Patients:

A Cross-Sectional and Longitudinal Study

Ester Mora, MD, PhD[a,b]; Maria J. Portella, PhD[c,*]; Montserrat Martinez-Alonso, PhD[d]; Montse Teres, DClinPsy[a]; Irene Forcada, MD, PhD[a]; Eduard Vieta, MD, PhD[e]; and Maria Mur, MD, PhD[a,*]

ABSTRACT

Objective: To determine the influence of body mass index (BMI) on cognition in euthymic bipolar patients and healthy matched controls in a post hoc study of 2 cross-sectional and longitudinal exploratory studies.

Method: A total sample of 121 individuals was examined, which included 52 euthymic bipolar disorder I or II patients (*DSM-IV-TR* criteria) and 69 healthy controls matched by age and gender, categorized in 2 subgroups in terms of body mass index (BMI-factor): normal weight (BMI: 18.5–24.9 kg/m^2) versus overweight-obesity (overweight, BMI: 25.0–29.9 kg/m^2; and obese, BMI ≥ 30 kg/m^2). Demographic, clinical, cognitive, and psychosocial functioning data were collected from 2003 until 2011. Cognitive domains studied were executive function, attention, processing speed, verbal memory, and visual memory. Fifty-four subjects (28 bipolar and 26 healthy controls) were reevaluated after 6 years of follow-up.

Results: Obesity and bipolar disorder showed a significant effect on cognition in cross-sectional and long-term MANOVA analyses ($F_{7,111} = 2.54$, $P = .018$ and $F_{19,23} = 2.25$, $P = .033$, respectively). In the cross-sectional linear regression model, global cognitive functioning was predicted by the interaction of BMI-factor by group (β = −0.44, SE = 0.14, $P = .002$), current age (β = −0.44, $P < .0001$), and premorbid IQ (β = 0.28, $P = .0002$), which explained 56% of variance ($F_{5,115} = 29.6$, $P < .0001$). Change in cognitive functioning over time was predicted by the interaction of BMI-factor by group (β = −0.8, SE = 0.33, $P = .022$) and cognition at baseline (β = −0.46, SE = 0.15, $P = .004$), which explained 27.65% of variance ($F_{6,40} = 2.548$, $P = .0349$). Generalized estimating equations analysis showed that interaction of group by BMI (Wald $\chi^2_1 = 5.37$, $P = .02$), age (Wald $\chi^2_1 = 22.08$, $P < .0001$), and premorbid IQ (Wald $\chi^2_1 = 25.65$, $P < .0001$) were the significant predictors.

Conclusions: Obesity was significantly associated with cognitive impairment in euthymic bipolar patients, and it also appeared to affect cognition in the long term.

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[a]Psychiatric Service, Hospital Universitari Santa Maria, University of Lleida, IRBLleida (Biomedicine Research Institute), Lleida, Catalonia, Spain
[b]Child and Adolescent Mental Health Centre, Sant Joan de Déu Lleida, Catalonia, Spain
[c]Psychiatric Service, Research Institute, Hospital de Santa Creu i Sant Pau, Autonomous University of Barcelona, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Barcelona, Catalonia, Spain
[d]Biostatistics Unit, University of Lleida, IRBLleida (Biomedicine Research Institute), Lleida, Catalonia, Spain
[e]Bipolar Disorder Program, Hospital Clinic, Institute of Neuroscience, University of Barcelona, L'Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), CIBERSAM, Barcelona, Catalonia, Spain
*Corresponding author: Maria Mur, MD, PhD, Department of Psychiatry, Hospital Santa Maria de Lleida, University of Lleida, Alcalde Rovira Roure Ave, 80, 25198 Lleida, Catalonia, Spain (mmur@gss.scs.es).
Corresponding author for statistical analyses: Maria J. Portella, PhD, Department of Psychiatry, Hospital de Santa Creu i Sant Pau, Autonomous University of Barcelona, St. Antoni M. Claret, 167, 08025 Barcelona, Catalonia, Spain (mportella@santpau.cat).

Obesity can be conceptualized as a neurotoxic phenotype among individuals with neuropsychiatric disorders evidenced by alterations in the structure and function of neural circuits and disseminated networks, diminishing cognitive performance, and adverse effects on illness trajectory.[1] Moreover, strong evidence also indicates that individuals with bipolar disorder exhibit cognitive deficits in attention, verbal memory, and executive functioning during long-term periods of clinical remission.[2–4] However, there are still few studies that focus on both obesity and cognitive impairment and their interaction in bipolar disorder.

Available data further suggest that being overweight is associated with cognitive deficits and numerous pathophysiologic changes such as cardiovascular problems,[5] impaired insulin regulation,[6,7] systemic inflammation,[8,9] abnormal leptin levels in the brain,[10,11] and oxidative stress markers.[12] A growing literature now links obesity to poor adult cognitive functioning in healthy individuals[13–21] and in patients with psychiatric disorders such as schizophrenia[22–24] and bipolar disorder.[25–27]

It is well known that bipolar disorder is associated with roughly twice the risk of obesity compared to nonclinical controls and the prevalence of obesity is approximately 60%.[28] Obesity, type II diabetes, and insulin resistance have been found to be associated with a more advanced stage of bipolar disorder with greater burden of disease, poorer functioning, and greater disability.[29] In addition, poor treatment response, more previous depressive and manic episodes, higher baseline depression scores, and prolonged acute treatment were found in overweight and obese patients compared to normal-weight individuals with bipolar disorder.[30] Obesity and bipolar disorder establish a bidirectional relationship evidenced by alterations in the structure and function of the central nervous system, in addition to greater depressive recurrence risk, cognitive dysfunction, and risk of suicidality.[31,32]

It is proposed that the co-occurrence of bipolar disorder and obesity may exert a toxic

Clinical Points

- The impact of obesity on cognitive impairment in euthymic bipolar patients was addressed in this study. Some questions remain to be answered.
- Overweight or obesity together with some clinical variables (such as age at onset and duration of illness) contributes to worse cognitive functioning in short- and long-term outcome in bipolar patients.
- Preventing obesity in individuals with bipolar disorder may help to prevent cognitive decline.

effect on the structures and connections within the brain that are associated with specific cognitive impairments.[31] A previous study has shown reductions in cortical white matter structures in obese bipolar patients.[33] It is known that clinical factors and pathophysiologic mechanisms may contribute to obesity condition,[26] but it may also be true that difficult-to-treat bipolar patients may be more prone to obesity, as a result of increased depressive and anxious morbidity, sedentary lifestyle, and medication side effects.[34] Currently, there is growing interest in studying the obesity consequences in terms of cognition. To date, bipolar disorder is scarcely studied and only in cross-sectional designs,[27] and there is a lack of long-term studies assessing this issue.

The effect of obesity on cognitive impairment in bipolar patients remains without a clear answer. The aim of the present study was to investigate the role of obesity in the progression of cognition in euthymic bipolar outpatients compared with healthy matched controls in a cross-sectional and longitudinal study. We hypothesized that obesity would impact neuropsychological performance. Furthermore, we hypothesized that euthymic bipolar patients with higher body mass index (BMI) at baseline would display worse cognitive outcome at endpoint.

METHOD

Subjects

The results in the current article are post hoc analyses of data from previous publications.[35,36] For the cross-sectional study, a total of 121 subjects—52 euthymic bipolar patients and 69 healthy matched controls—were admitted into the study and were evaluated with a clinical interview, biochemical tests, and a neuropsychological battery. Patients were recruited from the Outpatient Lithium Clinic at Hospital Santa Maria, Lleida, Catalonia, Spain, from 2003 to 2011. Inclusion criteria included fulfilling *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*) criteria for bipolar disorder, being aged 18 to 65 years, and being in remission for at least 3 months.[37] Following previous studies,[38] patients were characterized as euthymic if they had a total 17-item Hamilton Depression Rating Scale[39] (HDRS) score below 8 and a total Young Mania Rating Scale[40] (YMRS) score below 6 for at least 3 months at the time of assessment. Exclusion criteria were the following: significant physical or neurologic illness, substance abuse or dependence in the last 12 months, and electroconvulsive therapy in the preceding year. Sixty-nine healthy controls, comparable in terms of gender, age, and years of education, were recruited with advertisements and from nonmedical hospital staff. Controls had no current or past psychiatric history, as determined by the Structured Clinical Interview for *DSM-IV* Axis I Disorders.[41] They had no first-degree relatives with bipolar or psychosis diagnoses. Control subjects underwent the same exclusion criteria as the patients and were assessed at the same full clinical and demographics interview by a trained psychiatrist. The local ethics committee approved the study, and written informed consent was obtained from all participants.

After 6 years of follow-up, the final sample comprised 54 subjects (28 euthymic individuals with bipolar disorder and 26 healthy matched controls), which was primarily used to investigate the longitudinal neuropsychological profile of euthymic bipolar outpatients compared with healthy matched controls in a 6-year period of follow-up.[36] On this occasion, participants were assessed again with the previous full study protocol (a clinical interview and a neuropsychological evaluation).

Demographic, Clinical, and Pharmacologic Data

Demographic variables included age, gender, years of education, and current work status. Psychiatric variables were obtained from the sample of bipolar patients, including age at illness onset, number of prior manic episodes and hospitalizations, period of stabilization (years), history of psychotic symptoms, seasonal pattern, suicide attempts, and bipolar subtype (I or II) during the psychiatric interview. Other physical and medical issues (eg, cardiovascular, neurologic, gastrointestinal, hematologic, renal, hepatic, respiratory, or endocrine illnesses) and concurrent psychiatric and nonpsychiatric medications were recorded in the same interview. Biochemical tests were performed in all patients, including for thyroid function, lipid profile, serum lithium levels, and urine drug testing.

With respect to pharmacologic variables, 17 patients were on lithium monotherapy, 32 on combination treatment (plus antidepressant or antipsychotic), and 3 on treatment with another mood stabilizer (ie, valproate; see Table 1).

Body Mass Index

Body mass index was calculated for each participant. Patients and healthy controls were categorized into 2 groups (BMI-factor): normal weight and overweight or obese based on the established criteria of BMI (normal weight, BMI of 18.5–24.9 kg/m^2; overweight, BMI of 25.0–29.9 kg/m^2; and obese, BMI ≥ 30 kg/m^2).[42]

Neuropsychological Assessment

To characterize cognitive functioning, a selected battery that included neuropsychological tasks covering the most impaired cognitive domains in bipolar disorder, ie, executive and memory functioning,[37,43,44] was administered to all participants. The estimated mean intelligence quotient (IQ)

of the subjects was obtained from the weighted scores of the Vocabulary and Block Design subtests of the Wechsler Adult Intelligence Scale-III (WAIS-III),[45] because these 2 scores are highly correlated with total IQ.

The instruments administered were (1) Vocabulary, Block Design, and Digits subtests from WAIS-III[45]; (2) Wisconsin Card Sorting Test (WCST),[46] to assess executive function and perseverative behavior; (3) Stroop Color and Word Test,[47] to evaluate selective attention and inhibition capacity; (4) FAS verbal fluency task of the Controlled Oral Word Association Test/Categories,[48] to assess executive function; (5) Trail Making Test (TMT), to evaluate processing speed part A (TMT-A) and cognitive flexibility part B (TMT-B)[49]; (6) Conners' Continuous Performance Test II (CPT-II),[50] to evaluate sustained attention, processing speed, and perseverative behavior; (7) the California Verbal Learning Test (CVLT),[51] to evaluate verbal learning, recall, and recognition; and (8) Rey Complex Figure Test (RCFT),[52] to evaluate visual memory.

Psychosocial Functioning

To obtain information about the global activity, patients were assessed with the Global Assessment of Functioning (GAF) scale.[53] Moreover, occupational functioning was specifically assessed and defined as follows: active (subjects with a full- or part-time job, students, and housewives), inactive (unemployed subjects and those with temporary sick leave), and retired (permanent sick leave or retired subjects) as reported elsewhere.[37]

Statistical Procedures

Data analyses were carried out with the statistical package SPSS for Windows, version 22.0 (IBM Corp, Armonk, New York) and R statistical software (version 3.2.2).[54] Demographic, clinical, and psychosocial characteristics of groups were compared with *t* tests for continuous variables and χ^2 tests for categorical variables as descriptive statistics analyses.

For the cross-sectional analyses, neuropsychological data were analyzed in a 2-way multivariate analysis of variance (MANOVA; patients vs controls and overweight or obese vs normal weight). Those cognitive variables that showed a significant group by BMI-factor effect were *z*-transformed and then summed into a composite score to obtain a global cognitive index.[35] On measures of reaction time (for which low scores indicate good performance), *z* scores were reversed before forming the index.

Afterward, a multivariate linear regression model in which the global cognitive index was the dependent factor was performed to predict the impact of BMI on cognition comparing both groups (bipolar individuals and healthy controls). Subclinical (YMRS score and HDRS score), demographic (age, gender, years of education, and estimated premorbid IQ), and functional (GAF) variables and BMI were included in the model using backward stepwise method in the whole sample, with the exception of significant interaction terms that were included together with the main effects. In order to determine the specific statistical weight of BMI subgroups and bipolar disorder, an interaction factor was created (group × BMI-factor), which was included in the regression model.

Clinical (age at onset, number of hospitalizations, years of stabilization, duration of illness, and lifetime history of psychotic symptoms) variables were also included in another model using the backward stepwise method for the sample of bipolar individuals.

For the longitudinal analyses, the neuropsychological performance at endpoint was analyzed in a 2-way MANOVA with 2 between-subject factors (overweight or obesity vs normal weight at baseline and bipolar individuals vs healthy controls). Those cognitive variables that showed a significant effect of group by BMI-factor were z-transformed and then summed up into a composite score so as to obtain a long-term cognitive index at endpoint. A baseline cognitive index based on the follow-up sample was created using the same neuropsychological variables used for the endpoint cognitive index. Difference between both indexes was used to measure cognitive change over time. Afterward, a general linear regression model was performed using the same backward stepwise method mentioned above to predict the impact of BMI at baseline on cognitive changes after a 6-year period of follow-up.

In order to determine whether changes in weight over time were associated with cognitive performance at follow-up, a linear regression model, based on generalized estimating equations (GEE) analysis, was fitted including the same predictors (group and gender as factors, and BMI, age, years of education, premorbid IQ, YMRS, and HDRS as covariates) and time as the within-subject variable.

RESULTS

Baseline Results

Demographic, clinical, and pharmacologic results. A total of 121 subjects were enrolled in the study. The demographic and clinical characteristics for the euthymic bipolar group and control group are shown in Table 1. Patients and healthy controls were comparable in age and gender. There were statistical differences between groups in terms of years of education, HDRS, and YMRS. A total of 52 euthymic individuals with bipolar disorder were included in the analysis, and they were categorized in 2 groups: 15 of them had a normal BMI, and 37 patients presented overweight or obesity (19 and 18, respectively). There were statistical differences between BMI subgroups in age ($P < .0001$) and in years of education ($P = .013$). However, there were no differences between BMI subgroups in IQ, HDRS, or YMRS. There were no differences in mean cholesterol levels. As expected, there were statistical differences in mean triglyceride ($F_{1,50} = 11.89$, $P = .001$) and fasting glucose ($F_{1,50} = 5.41$, $P = .024$) levels between normal weight and overweight/obese patient groups. Table 1 displays mean scores, standard deviation, and statistical results. From the 69 healthy controls that participated in the current study, 2 groups of BMI were obtained: 34 individuals presented

Table 1. Demographic, Clinical, and Pharmacologic Variables

Variable	Bipolar Patients (n = 52)			Healthy Controls (n = 69)			Between Bipolar Patient Groups		Between Healthy Control Groups		Between Patients and Controls	
	Normal Weight BMI = 18.5–24.9 kg/m^2 (n = 15)	Overweight BMI ≥ 25 kg/m^2 (n = 37)	All Bipolar Patients	Normal Weight BMI = 18.5–24.9 kg/m^2 (n = 34)	Overweight BMI ≥ 25 kg/m^2 (n = 35)	All Healthy Controls	*F*	*P*	*F*	*P*	*F*	*P*
Age, mean (SD), y	35.20 (10.4)	48.19 (11.2)	44.44 (12.4)	39.06 (12.0)	49.6 (11.1)	44.41 (12.6)	14.9	<.0001	14.4	<.0001	0.0	.9
Education, mean (SD), y	12.20 (2.7)	10.11 (2.7)	10.71 (2.8)	13.29 (3.1)	12.14 (3.2)	12.71 (3.2)	6.6	.013	2.3	.1	13.1	<.0001
Estimated premorbid IQ, mean (SD)	104.2 (11.9)	98.8 (11.0)	100.3 (11.5)	111.0 (11.5)	112.9 (9.4)	112.0 (10.4)	2.4	.1	0.5	.5	33.8	<.0001
YMRS score, mean (SD)	1.40 (1.8)	2.19 (2.4)	1.67 (0.3)	0.65 (1.0)	0.80 (1.1)	0.72 (1.0)	0.4	.5	0.4	.5	12.3	.001
HDRS score, mean (SD)	1.80 (1.7)	1.78 (2.0)	2.08 (2.2)	1.06 (1.3)	1.57 (1.5)	1.32 (1.4)	0.3	.6	2.3	.1	5.4	.022
GAF score, mean (SD)	78.00 (8.6)	70.57 (9.4)	72.71 (9.7)	85.2 (5.1)	84.69 (5.1)	84.91 (5.0)	6.9	.011	0.1	.8	32.2	<.0001
BMI, mean (SD)	22.82 (1.6)	31.00 (3.9)	28.65 (5.0)	22.47 (1.5)	29.07 (4.6)	25.82 (4.8)	62.3	<.0001	64.3	<.0001	10.0	.002
Age at onset, mean (SD), y	22.67 (9.0)	25.24 (10.7)	24.50 (10.3)				0.7	.4				
No. of hospitalizations, mean (SD)	1.40 (1.2)	3.37 (2.8)	2.42 (2.4)				4	.050				
Total no. of manic episodes, mean (SD)	1.60 (0.9)	2.84 (2.7)	2.33 (2.3)				2.2	.1				
Years of stabilization, mean (SD)	1.92 (2.0)	4.48 (5.6)	3.74 (4.9)				3	.1				
Duration of illness, mean (SD), y	12.47 (9.1)	22.65 (12.5)	19.71 (12.4)				8.2	.006				
Years of lithium treatment, mean (SD)	2.72 (2.3)	7.93 (7.2)	6.45 (6.6)				7	.011				
Serum lithium levels, mean (SD), mmol/L	0.58 (0.2)	0.70 (0.2)	0.67 (0.2)				4.5	.039				
Lithium dosage, mean (SD), mg/d	1,014 (199.0)	1,148 (316.0)	1,110 (292.0)				2.2	.1				
Cholesterol, mean (SD), mg/dL	186.50 (42.2)	193.38 (36.0)	191.49 (37.5)				0.3	.6				
Triglycerides, mean (SD), mg/dL	91.33 (36.9)	172.50 (87.5)	148.18 (84.4)				11.9	.001				
Fasting glucose, mean (SD), mg/dL	87.6 (8.9)	110.0 (36.7)	103.54 (32.8)				5.4	.024				
							χ^2		χ^2		χ^2	
Gender, male, n (%)	8 (53.3)	18 (48.6)	26 (50.0)	12 (35.3)	20 (57.1)	32 (46.4)	0.92	.8	3.3	.1	0.2	.7
Current work status, n (%)												
Active	10 (66.7)	12 (32.4)	22 (42.3)	31 (91.2)	26 (74.3)	57 (82.6)	10.9	.001	6.0	.014	13.9	<.0001
Inactive	5 (33.3)	5 (13.5)	10 (19.2)	2 (5.9)	2 (5.7)	4 (5.8)						
Retired/disabled	0 (0.0)	20 (54.0)	20 (38.5)	1 (2.9)	7 (20.0)	8 (11.6)						
Positive family history of mental illness, n (%)	13 (86.7)	28 (75.7)	41 (78.8)	13 (38.2)	13 (37.1)	26 (37.7)	0.8	.4	0.01	.9	20.2	<.0001
Lifetime history of psychotic symptoms, n (%)	12 (80.0)	29 (78.4)	41 (78.8)				0.02	.9				
Lifetime history of seasonal pattern, n (%)	8 (53.3)	21 (56.8)	29 (55.8)									
Personal history of suicide attempts, n (%)	6 (40.0)	12 (32.4)	18 (34.6)				0.05	.8				
Suicidal thoughts, n (%)	11 (73.3)	30 (81.1)	41 (78.8)				0.3	.6				
Diagnosis, n (%)												
Bipolar I disorder	11 (73.3)	25 (67.6)	36 (69.2)				0.4	.5				
Bipolar II disorder	4 (26.7)	12 (32.4)	16 (30.8)				0.2	.7				
Type of current medication, n (%)							2.6	.6				
Lithium monotherapy	8 (53.3)	9 (24.3)	17 (32.7)									
Lithium + combination	6 (40.0)	26 (70.2)	32 (61.5)									
Other mood stabilizers	1 (6.7)	2 (5.4)	3 (5.8)									
Concomitant treatment, n (%)							1.2	.3				
Antidepressants	4 (26.7)	14 (37.8)	18 (34.6)									
Antipsychotics	5 (33.3)	16 (43.2)	21 (40.4)									
Benzodiazepines as hypnotic	0 (0.0)	3 (8.1)	3 (5.8)									
BMI subgroup, n (%)	15 (28.8)	37 (71.2)		34 (49.3)	35 (50.7)						5.1	.024

Abbreviations: BMI = body mass index, GAF = Global Assessment of Functioning, HDRS = Hamilton Depression Rating Scale, IQ = intelligence quotient, YMRS = Young Mania Rating Scale.

normal weight, and 35 exhibited overweight or obesity (25 and 10, respectively). There was a statistical difference between groups in terms of age (see Table 1), but there were no differences between groups in years of education, IQ, HDRS, or YMRS. In terms of medical issues, participants with higher BMI had more cardiovascular and endocrinal problems in both groups ($\chi^2_6 = 6.9$, $P = .33$).

Neuropsychological performance. All neuropsychological variables and univariate effects at baseline are listed in Table 2. MANOVA showed a significant association between bipolar disorder and BMI-factor ($F_{7,111} = 2.54$, $P = .018$). In order to study the impact of obesity on cognitive functioning, a global cognitive index was created using the neuropsychological test scores that displayed group by BMI-factor significant interactions in the 2-way MANOVA: FAS, Stroop Inhibition subscore, TMT-A, TMT-B, WCST number of categories, perseverative errors, and detectability of CPT.

Impact of BMI and demographic and clinical variables on cognitive functioning. The regression linear model with cross-sectional data, including demographic, subclinical, and functional variables to predict the global cognitive index, showed that the interaction factor (group × BMI-factor) was significantly associated with cognitive functioning ($\beta = -0.44$, SE = 0.14, $P = .002$), as well as current age ($\beta = -0.44$, $P < .0001$) and premorbid IQ ($\beta = 0.28$, $P = .0002$). The model explained 56% of variance ($F_{5,115} = 29.6$, $P < .0001$) (see Figure 1). It is noteworthy that group and BMI scores were not significant factors when entered separately in the model.

A similar model was run for the bipolar individuals group including clinical variables. The model showed a significant association with age at onset ($\beta = -0.39$, $P = .004$), duration of illness ($\beta = -0.34$, $P = .017$), and BMI-factor ($\beta = -0.42$, SE = 0.16, $P = .009$), and it explained 40% of variance ($F_{3,48} = 10.71$, $P < .00009$).

Longitudinal Results

Long-term effects of overweight on cognitive functioning. The dropout rate after 6 years was 55.4%; however, there were no differences at baseline between dropouts and those patients who were followed up in terms of BMI, illness severity, or other relevant clinical variables (data not shown). Within the whole sample of 54 retested individuals, 7 (5 healthy controls and 2 euthymic bipolar patients) refused to perform the neuropsychological evaluation again and were considered missing values. There were no significant effects of time by group nor group in BMI ($F_{1,52} = 0.90$, $P = .77$; and $F_{1,53} = 1.65$, $P = .2$, respectively).

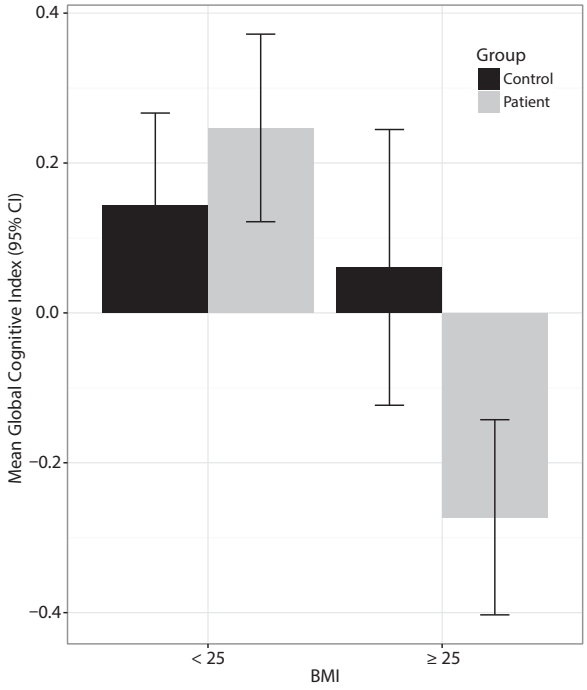
The results of 2-way MANOVA again showed a significant main effect of group by BMI-factor at baseline (n = 54; $F_{19,23} = 2.25$, $P = .033$). The cognitive variables that displayed significant differences in the

Table 2. Neuropsychological Results in All Individuals[a]

	Bipolar Patients (n = 52)			Healthy Controls (n = 69)			Bipolar Patients (overweight vs normal weight)		Healthy Controls (overweight vs normal weight)		Between Patients and Controls		Interaction	
Test	Normal Weight BMI = 18.5–24.9 kg/m² (n = 15)	Overweight BMI ≥ 25 kg/m² (n = 37)	All Bipolar Patients	Normal Weight BMI = 18.5–24.9 kg/m² (n = 34)	Overweight BMI ≥ 25 kg/m² (n = 35)	All Healthy Controls	*F*	*P*	*F*	*P*	*F*	*P*	*F*	*P*
TMT part B	74.13 (31.6)	124.97 (73.9)	110.31 (68.4)	61.26 (26.2)	65.40 (24.1)	63.56 (25.1)	6.5	.014	0.5	.5	27.7	<.0001	6.5	.012
FAS	40.93 (11.7)	32.35 (10.5)	34.83 (11.4)	44.38 (9.7)	44.71 (10.1)	44.55 (9.8)	6.7	.013	0.0	.9	25.2	<.0001	5.0	.027
Digit span backward	5.60 (1.7)	5.03 (1.9)	5.19 (1.9)	6.56 (2.0)	6.03 (1.8)	6.29 (1.9)	1.0	.3	1.3	.3	9.9	.002	0.0	.9
No. of categories WCST	4.73 (1.3)	2.57 (1.8)	3.19 (1.9)	4.82 (1.8)	4.06 (2.0)	4.43 (1.9)	17.1	<.0001	2.8	.1	12.1	.001	4.4	.037
Stroop Inhibition	43.73 (10.2)	32.95 (9.9)	36.06 (11.0)	46.65 (9.0)	45.69 (8.4)	46.16 (8.7)	12.5	.001	0.2	.6	31.8	<.0001	7.4	.008
No. Persev errors WCST	14.33 (14.2)	20.95 (18.3)	19.04 (17.3)	12.82 (9.0)	14.71 (11.6)	13.78 (10.4)	1.6	.2	0.6	.4	4.3	.04	0.7	.4
No. Persev errors CPT	0.33 (0.7)	2.19 (2.8)	1.65 (2.5)	0.12 (0.4)	0.20 (0.4)	0.16 (0.4)	6.3	.015	0.7	.4	23.3	<.0001	7.9	.006
Stroop Interference	3.53 (6.6)	1.06 (11.6)	1.77 (10.4)	2.99 (6.2)	2.59 (7.1)	2.78 (6.6)	0.6	.4	0.1	.8	0.4	.5	0.4	.5
Digit span forward	8.20 (2.0)	8.03 (2.3)	8.08 (2.2)	8.82 (2.0)	8.94 (1.5)	8.88 (1.7)	0.1	.8	0.1	.8	5.2	.025	0.2	.7
CPT detectability, d'	0.97 (0.4)	0.67 (0.5)	0.76 (0.5)	0.89 (0.4)	0.97 (0.4)	0.93 (0.4)	4.3	.043	0.6	.4	4.3	.04	4.3	.04
TMT part A	33.80 (11.1)	60.81 (32.2)	53.02 (30.3)	30.47 (13.2)	34.74 (14.3)	32.64 (13.8)	10.0	.003	1.6	.2	24.5	<.0001	7.5	.007
CPT-II hit RT, ms	438.16 (76.0)	475.84 (80.4)	464.97 (80.3)	400.30 (47.8)	455.81 (67.3)	428.45 (64.5)	2.4	.1	15.5	<.0001	7.7	.006	0.3	.6
CVLT first trial	6.93 (2.0)	5.95 (2.2)	6.23 (2.0)	6.71 (1.9)	6.77 (1.7)	6.74 (1.8)	2.7	.1	0.0	.9	2.2	.1	2.0	.2
CVLT total words	54.93 (8.1)	46.76 (11.6)	49.12 (11.3)	57.47 (8.2)	55.14 (7.8)	56.29 (8.0)	6.2	.016	1.5	.2	16.7	<.0001	2.4	.1
CVLT immediate recall	11.40 (3.2)	9.68 (3.5)	10.17 (3.5)	12.62 (2.6)	12.46 (2.7)	12.54 (2.6)	2.7	.1	0.1	.8	17.9	<.0001	1.6	.2
CVLT delayed recall	12.27 (2.8)	10.57 (3.6)	11.06 (3.5)	13.32 (2.4)	13.37 (2.3)	13.35 (2.3)	2.6	.1	0.0	.9	18.9	<.0001	2.3	.1
CVLT recognition	14.73 (1.5)	14.11 (1.9)	14.29 (1.8)	15.35 (1.1)	15.26 (1.3)	15.30 (1.2)	1.3	.3	0.1	.7	13.9	<.0001	0.8	.4
RFCT immediate recall	20.67 (6.0)	17.16 (6.6)	18.17 (6.7)	24.15 (5.1)	24.40 (5.2)	24.27 (5.1)	3.0	.1	0.0	.8	31.9	<.0001	2.7	.1
RFCT delayed recall	20.57 (6.0)	16.84 (7.1)	17.91 (7.0)	23.82 (5.8)	24.04 (5.6)	23.93 (5.7)	3.2	.1	0.0	.8	27.5	<.0001	2.4	.1

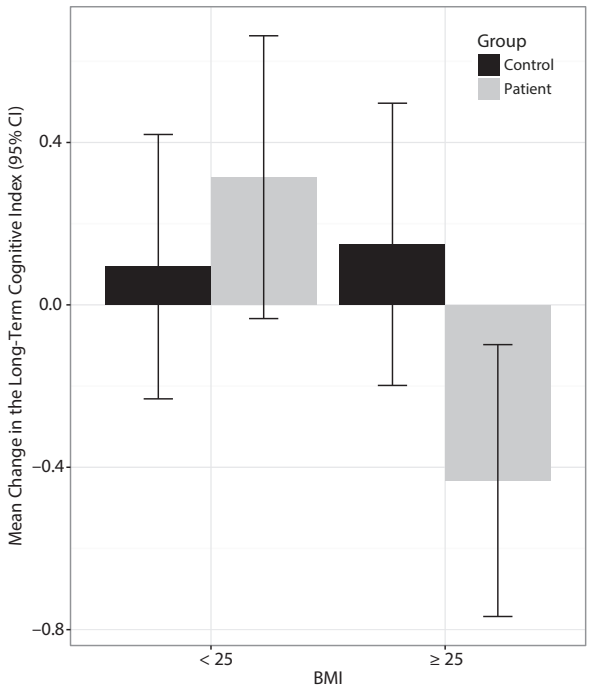
[a]Results are shown as mean (SD).
Abbreviations: CPT = Continuous Performance Test, CVLT = California Verbal Learning Test, FAS = verbal fluency task of the controlled oral word association test, Persev = perseverative, RFCT = Rey Complex Figure Test, RT = reaction time, TMT = Trail Making Test, WCST = Wisconsin Card Sorting Test.

Figure 1. Prediction of Global Cognitive Index by Body Mass Index (BMI-Factor) (BMI < 25 and BMI ≥ 25) and Groups of Participants (Healthy Controls and Bipolar Individuals)[a]



[a]This figure shows the significant interaction effect between group and BMI-factor on the global cognitive index (likelihood ratio test for the interaction with $P = .0088$), adjusted by age and premorbid intelligence quotient (IQ).

Figure 2. Prediction of Long-Term Cognitive Index Changes by Body Mass Index (BMI-Factor) (BMI < 25 and BMI ≥ 25) and Groups of Participants (Healthy Controls and Bipolar Individuals)[a]



[a]This figure shows the significant interaction effect between group and BMI-factor measured at baseline, on the change in the long-term cognitive index (likelihood ratio test for the interaction with $P = .01726$), adjusted by age, premorbid intelligence quotient (IQ), and long-term cognitive index, all of them at baseline.

2-way MANOVA analysis comparing patients and controls and BMI-factor were FAS ($F_{1,43} = 10.47$, $P = .002$), TMT-B ($F_{1,43} = 4.38$, $P = .042$), and WCST number of categories ($F_{1,43} = 7.53$, $P = .009$). These variables were used to create the baseline and endpoint cognitive indexes. Thus, a new long-term cognitive index was created to capture the cognitive change over time calculating the difference between these 2 indexes. The regression linear model showed that cognitive changes were predicted by the interaction factor between group and BMI-factor ($\beta = -0.8$, SE = 0.33, $P = .022$) and baseline cognitive index ($\beta = -0.46$; SE = 0.15, $P = .004$) and explained 27.65% of variance ($F_{6,40} = 2.548$, $P = .0349$; see Figure 2). The linear model based on GEE showed that group by BMI (Wald $\chi^2_1 = 5.37$, $P = .02$), age (Wald $\chi^2_1 = 22.08$, $P < .0001$), and premorbid IQ (Wald $\chi^2_1 = 25.65$, $P < .0001$) were the significant predictors of the cognitive changes along time. The rest of the predictors or interactions were not significant.

DISCUSSION

The results of the current study show that bipolar individuals with overweight or obesity exhibit worse cognitive functioning compared to healthy controls and still display worse cognitive performance than normal weight bipolar individuals after a 6-year follow-up period. These findings are consistent with the few available cross-sectional studies,[25–27] but, by adding the long-term results and using a global cognitive index, the present study may contribute to expand knowledge on how overweight or obesity affect cognition over a follow-up period, particularly in bipolar patients. This represents a highly relevant finding as there are no studies that have considered the role of obesity on the longitudinal trajectory of cognitive deficits in bipolar disorder.

This study shows that a global cognitive index composed by executive functioning, inhibition, processing speed, and attention is impaired in bipolar patients with overweight or obesity. Previous works have already found that higher BMI is associated with worse cognitive performance cross-sectionally, but each study shows different cognitive domains to be affected and they used different cognitive tests and different comparison groups. In particular, Lackner and colleagues[27] found that overweight patients with bipolar disorder exhibit lower performance in the TMT-A/B as well as in the free recall performance of the CVLT compared to normal-weight patients with bipolar disorder and controls. In another recent study,[26] comparing outpatients with either bipolar disorder or schizophrenia, obesity was associated with worse global cognitive ability only in bipolar disorder,

as well as with poorer performance on individual tests of processing speed, sustained attention, verbal memory, and reasoning/problem-solving. Previously, Yim et al[25] found that BMI was negatively correlated with attention and psychomotor processing speed as measured by the Digit Symbol Substitution Test in patients with bipolar disorder. Furthermore, overweight or obese bipolar individuals had a significantly lower score on the Verbal Fluency Test when compared to normal-weight subjects with bipolar disorder. None showed a long-term effect of obesity on cognitive outcome, while in our study obesity affected cognition after 6-year follow-up, suggesting that overweight might be a neurotoxic factor of bipolar disorder.

Indeed, the relationship between obesity and mental illness is bidirectional and surrounded by many confounding factors. Possible factors contributing to obesity in bipolar disorder include lifestyle, medication exposure, neuroendocrine and neurotransmitter dysfunctions, genetic predisposition, immune dysfunction,[55] and comorbid conditions such as binge-eating disorder.[56,57] A severe course of illness[34] and symptoms such as disorganization and depression are themselves associated with overeating and subsequent weight gain.[21] Moreover, greater cognitive impairment may result in placement in treatment facilities that might alter access to health-promoting diets and lifestyle activities.[58] Selective impairments in cognitive functioning can be predicting factors for obesity or play an according mediating role.[27] Our data were unable to determine whether obesity occurred prior to the onset of bipolar disorder or as a consequence of multiepisode/chronic illness and treatment. In any case, overweight or obese bipolar individuals displayed cognitive worsening after a 6-year follow-up period, while normal-weight bipolar individuals did not. Therefore, our findings may shed some new light on the neuroprogression model in bipolar disorder.[59] In our study, some clinical variables (such as age at onset and duration of illness) together with overweight or obesity contribute to worse cognitive functioning in short- and long-term outcomes.

The linkage between obesity and mood disorders may be due to a pathophysiologic nexus that includes abnormalities in hypothalamus-pituitary-adrenal axis function[60]; immune,[55] inflammatory, and metabolic systems[59]; insulin resistance[29]; and disruption of brain circuitry,[61] all of which are potential mediators of cognitive function.[62] More studies on inflammatory biomarkers (proinflammatory cytokines, anti-inflammatory agents including TNF-α inhibitors)[55,63] and peripheral markers of oxidative stress[64,65] may shed more light on this field.

Some limitations warrant acknowledgment in the current study. First, the sample size of the long-term study is relatively small, even though 6-year follow-up is quite a long time and more than half of the bipolar disorder sample could be reevaluated. Second, another anthropometric measure such as waist circumference, hip circumference, waist-to-hip ratio, waist-to-height ratio, or subcutaneous fat measurement should have been included. Third, individuals with bipolar disorder did not receive the same medication, even though most of them were on lithium treatment (94.2%), which might have influenced BMI and cognition similarly, although it cannot be disentangled whether obesity is a consequence of the illness or of the medication. In any case, the interaction of BMI and group was significant in all regression models, indicating that both conditions impact cognitive performance. Fourth, glycemic control, cholesterol, and triglyceride levels from the healthy control group were not available. Hence, it was not possible to study the role of metabolic dysfunction in the relationship between obesity and cognition. However, it is important to mention that more endocrinal and cardiovascular issues were registered in participants with higher BMI regardless of whether they were patients or healthy controls. So the synergistic effect of bipolar disorder and obesity might be a better explanation of the cognitive dysfunction in euthymic bipolar individuals.

CONCLUSIONS

The prevalence of obesity was higher in individuals with bipolar disorder than in healthy controls in the current sample. The presence of obesity explains worse cognitive performance mainly in executive functioning over nonobese bipolar subjects, and this cognitive dysfunction is maintained over time. Hence, overweight bipolar disorder constitutes a neurotoxic phenotype, which may adversely impact cognitive outcome. Better understanding of the mechanisms and management of obesity may aid in efforts to preserve cognitive[26] and general health[66] in bipolar disorder. Early intervention programs aimed at preventing neuroprogression[67] may benefit from including healthy habits modules focused on diet and preserving normal weight, as a way to prevent cognitive and functional decline.

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