Obesity in patients with major depression is related to bipolarity and mixed features: evidence from the BRIDGE-II-MIX study.

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Running head

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Abstract

Objectives: BRIDGE-II-MIX study aimed to estimate the frequency of mixed states in patients with MDE according to different definitions. This post-hoc analysis evaluates the association between obesity and the presence of mixed features and bipolarity. **Methods:** 2811 MDE subjects were enrolled in this multicentre cross-sectional study. In 2744 patients, the body mass index (BMI) has been evaluated. Psychiatric symptoms, socio-demographic and clinical variables were collected, comparing the characteristics of MDE patients with (MDE-OB) and without obesity (MDE-NOB). **Results**: obesity (BMI ≥30) was registered in 493 patients (18%). In the MDE-OB group, 90 patients (20%) fulfilled DSM-IV-TR criteria for BD, 225 patients (50%) fulfilled the criteria for bipolarity specifier, 59 patients (13%) fulfilled DSM-5 criteria for MDE with mixed features and 226 patients (50%) fulfilled Research-Based Diagnostic Criteria for a mixed depressive episode. Older age, history of (hypo)manic switches during antidepressant treatment, the occurrence of three or more MDEs, atypical depressive features, antipsychotic treatment, female gender, depressive mixed state according to DSM-5 criteria, comorbid eating disorders and anxiety disorders were significantly associated with MDE-OB group. Among (hypo)manic symptoms during the current MDE, psychomotor agitation, distractibility, increased energy and risky behaviors were the variables most frequently associated with MDE-OB group. **Conclusions:** In our sample, the presence of obesity in patients with MDE seems to be associated with a lifetime diagnosis of BD. These findings suggest that obesity in patients with MDE could be considered a possible marker of bipolarity.

Key words: Obesity, Major Depressive Episode, Bipolar Disorder, Mixed Features.

1. Introduction

One of the main challenges in the diagnostic assessment of mood disorders is the early detection of bipolarity and mixed features in patients with a major depressive episode (MDE), in order to distinguish unipolar depression from bipolar disorder (BD), with relevant clinical and treatment implications [1, 2]. In fact, several epidemiological and clinical studies reported that almost 40% of BD patients initially receive the incorrect diagnosis of major depressive disorder (MDD) [3-5]. In primary care settings, a careful screening for mixed features allows to the identification of BD in 21% to 26% of unipolar depressed patients [6, 7]. In the Bridge study on 5635 adults with an ongoing MDE, a total of 903 patients fulfilled DSM-IV-TR criteria for BD, whereas 2647 met the bipolarity specifier criteria [8-10]. Growing evidence suggests an increased prevalence of mood disorders and in particular BD among individuals who are overweight or obese compared to those with weight in the normal range [11, 12]. A relationship between depression, especially with atypical features, and obesity has been widely demonstrated [13-15]. Moreover, atypical symptoms in depressed patients have been associated with both obesity and BD [16]. Notably, obese (OB) patients have been shown to have a higher risk of developing MDD and BD [17]. On the other hand, the course of bipolar depression is frequently affected by the development of overweigh and obesity, that could be related to the effects of psychotropic medications or comorbid diagnosis with eating disorders such as binge eating disorder (BED) [12, 18].

A recent meta-analysis of 9 cross-sectional epidemiological studies confirmed that obesity is associated with increased prevalence of BD, however the mechanisms and temporal sequence underlying this relationship are poorly understood [19]. Regarding gender differences, women showed higher rates of atypical features, as well as a

higher body mass index (BMI) than males, especially abdominal obesity [16]. Furthermore, the rate of obesity in women with BD has found to be higher than in men with BD [20]. The co-occurrence of BD and obesity seems to negatively affect the course and the long-term prognosis of BD [21]. Greater number of lifetime depressive and manic episodes, more severe and difficult-to-treat index affective episode, higher affective recurrence, predominantly depressive, and shorter time to relapse were more frequently reported in OB than in non-obese (NOB) BD patients [22]. A recent study sample of 571 consecutive patients with MDE suggested that obesity could be considered as a predictor of bipolarity [23]. However, to our knowledge, the prevalence of mixed features, according to the definition of the DSM-5 and the research based diagnostic criteria (RBDC), and bipolarity, according to the criteria of the specifier for bipolarity and the DSM-IV-R for BD, in OB and NOB patients with MDE has not been systematically investigated.

The objective of Bipolar Disorders: Improving Diagnosis, Guidance and Education (BRIDGE)-II-MIX [24-26] naturalistic study was to provide a reliable estimate of the frequency of mixed states in a large international sample of patients diagnosed with MDE according to several sets of criteria.

The aim of the present post-hoc analysis is to compare the characteristics of patients diagnosed with MDE who present a BMI ≥30 (MDE-OB) and patients with BMI <30 (MDE-NOB). We aim to characterize the MDE-OB patients in order to clarify the correlation between mixed features, bipolarity and obesity. We will also discuss the possible clinical and treatment implications of this association.

2. Patients and methods

The BRIDGE-II-Mix Study was a multicentre, international, non-interventional, cross-sectional study. The recruitment procedure and the inclusion criteria have been described in a previous study [24]. From an initial pool of 2811 patients with MDE, BMI has been evaluated in 2744 patients. 493 (18%) patients presented a BMI ≥30.

2.1 Data collection

In a single consultation the participating psychiatrists completed a case report form for each patient, incorporating inclusion criteria, socio-demographic variables (age, gender, marital status), biometrics values (height, weight), in- or out- patient status, history of psychiatric symptoms (mood symptoms, suicide attempts) and previous psychiatric hospitalizations. Features of the MDE, including bipolar symptoms listed in the DSM-IV-TR diagnostic criteria for BD, known risk factors for BD (e.g. family history of BD, early onset depression), previous response to ADs, psychiatric comorbidity, current treatment and functional status determined by the investigator using the Global Assessment of Functioning (GAF) were assessed [27].

The evaluation packet was explicitly structured to use skills that fully trained psychiatrists would have and routinely apply in conducting an initial evaluation of an acutely ill patient. No rating scales requiring calibration with a standard were incorporated. Raters were instructed to follow their usual practice, as training might have altered these practices and been seen as a biasing factor.

The primary objective of the BRIDGE-II-MIX study was to establish the frequency of depressive mixed states by analyzing all the relevant symptoms of either pole. After the publication of DSM-5, this was post-hoc defined as 1) the proportion of patients fulfilling DSM-5 criteria for MDE with mixed features (DSM-5-MXS) [28], and 2)

research based diagnostic criteria for mixed state (RBDC-MXS). RBDC-MXS are defined by the presence of MDE plus 3 out of the following 14 hypomanic symptoms for at least a week: Irritable mood, Emotional/mood lability, Distractibility, Psychomotor agitation, Impulsivity, Aggression (verbal or physical), Racing thoughts, More talkative/pressure to keep talking, Hyperactivity, Increased energy, Risky behavior, Grandiosity, Elation, Hyper-sexuality. The proportion of patients fulfilling criteria for BD according to the DSM-IV-TR and bipolarity specifier proposed by Angst et al. [5, 8, 9] was also identified. The bipolarity specifier attributes a diagnosis of BD to patients who experienced an episode of elevated mood or irritable mood or increased activity with at least three of the symptoms listed under Criterion B of the DSM-IV-TR, associated with at least one of the three following consequences: (i) unequivocal and observable change in functioning uncharacteristic of the person's usual behavior, (ii) marked impairment in social or occupational functioning observable by others or (iii) requiring hospitalization or outpatient treatment. No minimum duration was required and no exclusion criteria were applied.

2.2 Statistical analysis

Chi-square test was used for comparison between groups for categorical variables and Student's t-test for continuous variables. The univariate analysis involved many tests of statistical significance, raising the problem of type I errors. For this reason, we corrected for multiple comparisons and utilized a Bonferroni-corrected threshold for statistical significance. A stepwise backward logistic regression model was then used to identify the predictive value of the 14 current (hypo)manic symptoms on the presence of BMI $\geq$30. The stepwise modeling procedure started with the full model and consisted, for each step, in eliminating the least statistically significant variable

from the model and re-computing the revised model, until all remaining variables were at $p<.1$. Odds ratios with 95% confidence intervals were used for observed associations. We used the statistical routines of SPSS Statistics 22.0 for Mac OS (SPSS Inc., USA).

3. Results

3.1 Differences in clinical variables between MDE-OB and MDE-NOB

According to the DSM-IV-TR criteria, a diagnosis of BD was detected more frequently in the MDE-OB group (19.9%) compared to the MDE-NOB group (15.8%) ($p = 0.033$). Considering the BD subtypes, a statistically significant difference was found regarding the diagnosis of BD-I, with prevalence rates of 14.1% in the MDE-OB group and 9.3% in the MDE-NOB group ($p = 0.002$). Conversely, there were no significant differences in the prevalence rates of BD-II subtype between the two groups. Regarding the frequency of mixed depression, 59 (13%) patients in the MDE-OB group and 151 (6.6%) in MDE-NOB group fulfilled the DSM-5 criteria for mixed states ($p < 0.001$). In addition, when RBDC criteria for Mixed Episode were applied, MDE-OB patients reported more frequently mixed features than MDE-NOB subjects ($p < .001$). The two groups significantly differed for age, with MDE-OB patients resulting older than MDE-NOB subjects ($p < 0.001$). Female gender was significantly more prevalent in the MDE-OB group than in the MDE-NOB group ($p = 0.001$). MDE-OB patients were more frequently married than MDE-NOB subjects ($p < 0.001$). MDE-OB patients had significantly higher rates of first-degree family history for BD compared to subjects in the MDE-NOB group ($p < 0.001$). MDE-OB patients presented more frequently psychotic features ($p < 0.001$) and atypical features ($p < 0.001$) than MDE-NOB patients. Moreover, MDE-OB patients reported more frequently three or more lifetime depressive episodes ($p < 0.001$), history of suicide attempts ($p = 0.026$) and current episode that lasts more than one month ($p = 0.011$) compared to the MDE-NOB subjects *(Table 2)*. Regarding the psychiatric comorbidity, there were no statistically significant differences between the two groups with respect to the rates of alcohol-substance use disorders, ADHD and borderline personality disorder. Eating

disorders and anxiety disorders were significantly more frequent in the MDE-OB group in comparison to the MDE-NOB group [respectively 11.8% vs 6.1% (p <0.001) and 34.0% vs 27.6% (p =0.006)]. With respect to previous pharmacological treatments, MDE-OB patients were treated with more than three drugs contemporarily more frequently than the MDE-NOB patients (p <0.001). Furthermore, they were more frequently prescribed antipsychotics (p <0.001) and mood stabilizers (p <0.001) than the MDE-NOB subjects. There were no statistically significant differences regarding AD treatment and benzodiazepines prescriptions between the two groups. As concern the past response to treatment with ADs, MDE-OB patients have presented more (hypo)manic switches compared to MDE-NOB subjects (p <0.001). After the multivariate logistic regression analysis, the variables most strongly associated with the presence of obesity were age [p <0.001; OR 1.02 (1.01-1.02)], history of (hypo)manic switches during AD treatment [p =0.005; OR 1.46 (1.12-1.90)], comorbid anxiety disorders [p =0.049; OR 1.26 (1.00-1.60)], antipsychotics treatment [p =0.025 OR 1.29 (1.03-1.62)], marriage [p <0.001; OR 1.48 (1.19-1.84)], female gender [p =0.004; OR 1.43 (1.12-1.82)]; atypical features [p =0.002; OR 1.78 (1.24-2.54)], comorbid eating disorders [p = 0.010; OR 1.61 (1.12-2.32), psychotic features [p =0.39; OR 1.44 (1.02-2.05)], occurrence of three or more MDEs [p =0.003; OR 1.44 (1.13-1.82)], , and depressive mixed state according to DSM-5 criteria [p =0.019; OR 1.52 (1.07-2.15)] *(Table 3)*.

3.2 Differences in the frequency of (hypo)manic symptoms between MDE-OB and MDE-NOB

The MDE-OB patients showed 11 out of the 14 RBDC (hypo)manic symptoms with a significantly higher prevalence compared to the MDE-NOB patients (p <0.001) *(Table 4)*. In multivariate logistic regression analysis, (hypo)manic symptoms most strongly

associated with obesity were psychomotor agitation, distractibility, increased energy and risky behavior *(Table 5)*.

4. Discussion

In our multinational sample of 2744 patients with MDE, obesity resulted to be relatively common (18%), in line with the results of previous studies, supporting the strong association between depression and obesity [23, 29-31]. Interestingly, we observed a significant association between BD and obesity, similarly to previous findings [19, 32]. In our sample, the frequency of BD varied substantially according to different diagnostic criteria. When bipolar specifier was applied, about half of the MDE-OB subjects presented BD in comparison with approximately 40% of MDE-NOB patients. We found that obesity was significantly associated with the presence of atypical depressive features [14, 33]. Symptoms such as leaden paralysis, increased appetite, overeating, oversleeping and reduced physical activity might explain the weight gain in atypical depressive patients [34]. Atypical features have been associated with both BD and BED [35]. Thus, the specific association between BD and obesity might be partly explained by these overlapping atypical symptoms. Our results also showed a relationship between obesity and female gender in MDE patients, similarly to previous findings [36]. Interestingly, women present more frequently depression with atypical features [16] and this association could represent the link between obesity and female gender. The relationship between obesity and BD has been associated with a predominant depressive polarity of BD [22, 37, 38]. Similarly, in our sample obesity was associated with a history of more than three previous MDEs, supporting the relevant role of depression in developing overweight. MDE-OB patients were more frequently married than MDE-NOB, maybe due to older age of this group of patients. Moreover,the positive relationship that we found between MDE-OB patients and older age, reported also in previous studies [32, 39, 40], could be partially explained by the exposure to psychopharmacological treatment over a longer time

period [41-43]. Noteworthy, in our sample antipsychotic treatment was significantly more frequent in MDE-OB group. Antipsychotics are known to be associated with obesity [44], even if other studies reported that about 40% of drug-naïve BD patients were obese or overweight [37]. Since BD-I patients are more likely to be treated with antipsychotics/mood stabilizers compared to BD-II patients [45], in our sample the higher prevalence of BD-I diagnosis in MDE-OB patients in comparison to BD-II diagnosis could be related to the psychotropic medications. However, there are insufficient data to define how much psychotropic treatment is associated with overweight in BD patients [46]. With regard to lifetime comorbid diagnosis, in accordance with the existing literature [47-49], we found that comorbidity with eating disorders and anxiety disorders was more frequently reported in MDE-OB patients than in MDE-NOB subjects. A recent post-hoc analysis of the BRIDGE-II-mix showed that comorbidities with eating disorders and anxiety disorders were more frequently associated with a BD diagnosis (50). In this sense, a possible association between obesity, eating disorders and bipolar spectrum disorders could be hypothesized, in line with previous findings [49]. This comorbidity has been associated with increased severity of eating behaviors, poorer prognosis for obesity and treatment resistance in BD [22, 49, 51]. In our sample, first-degree family history for BD, antidepressant-induced (hypo)manic switches and psychotic features were more frequent in MDE-OB patients than in MDE-NOB patients. Moreover, regardless of the diagnostic criteria applied, the presence of mixed features was significantly more prevalent in the MDE-OB patients than in MDE-NOB subjects. After the multiple logistic regression, DSM-5 mixed features resulted as the most significantly variable correlated with obesity. Taken together, these results might support the hypothesis of relationship between obesity and the bipolar spectrum. It has been

suggested that the presence of lifetime (hypo)manic symptoms and mood instability may lead to impulsive-addictive behaviors, such as uncontrolled eating [23]. In our sample, most of the RBDC (hypo)manic symptoms were more prevalent in the MDE-OB group compared to the MDE-NOB subjects. This association could represent a possible link between bipolar spectrum disorders and obesity.

The main strengths of the BRIDGE-MIX II study include the large sample size, and the wide range of care settings, both hospital and community, from eight countries across three continents. Narrow exclusion criteria help making the findings more generalizable. The major limitation is that the participating centres were not randomly selected, which may led to a bias through the inclusion of psychiatrists with a particular interest in mixed states. Furthermore, among comorbid eating disorders, the BED subtype was not specified. Moreover, the lack of complete biometric data (waist circumference) might lead to an under-detention of abdominal obesity, especially in women.

5. Conclusion

From the results of our study, MDE-OB seems to show higher rates of bipolarity and mixed features than MDE-NOB individuals, indicating that obesity could be investigated as a possible biomarker of bipolar spectrum disorders. The identification of individuals with MDE and obesity as subset of patients at higher risk of presenting mixed and hypomanic symptoms should lead to a more comprehensive clinical evaluation in order to achieve a prompt detection of bipolar spectrum disorders, with important clinical and treatment implications, such as tailored behavioral psychological interventions [52]. Further longitudinal data on different populations are necessary to better define the burden and the role of the association between obesity

and mood disorders on correct diagnosis, treatment response and clinical outcome.

6. Funding source

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Table 1. Diagnostic distribution and frequency of mixed states and bipolarity according to different definition in 2744 patients with a Major Depressive Episode with (MDE-OB) and without (MDE-NOB) BMI ≥30.				
	MDE-NOB (n = 2291)	**MDE-OB (n = 493)**	**OR (95% CI)**	**p**
Diagnostic Distribution of Bipolar Disorder				
DSM-IV Bipolar	362 (15.8%)	90 (19.9%)	1.32 (1.02-1.71)	.033
- DSM-IV Bipolar I	213 (9.3%)	64 (14.1%)	1.61 (1.19-2.17)	.002
- DSM-IV Bipolar II	149 (6.5%)	26 (5.7%)	0.88 (0.57-1.35)	ns
Bipolar Specifier	920 (40.1%)	225 (49.7%)	1.47 (1.20-1.80)	<.001
- Bipolar I Specifier	526 (22.9%)	164 (36.2%)	1.90 (1.54-2.36)	<.001
- Bipolar II Specifier	394 (17.2%)	61 (13.5%)	0.75 (0.56-1.00)	ns
Depressive Mixed State				
DSM-5 criteria[a]	151(6.6%)	59 (13.0%)	2.12 (1.54-2.92)	<.001
RBDC Mixed Depression[b]	929 (40.5%)	226 (49.9%)	1.46 (1.19-1.79)	<.001

Legend. [a] MDE + three non-overlapping hypomanic criteria; [b] MDE + three or more hypomanic symptoms.

Abbreviations. BMI: body mass index; RBDC: research based diagnostic criteria.

Table 2. Clinical Features in 2744 patients with a Major Depressive Episode with (MDE-OB) and without (MDE-NOB) BMI ≥30.				
	MDE-NOB (n = 2291)	**MDE-OB (n = 493)**	**OR (95% CI)**	**p**
Age, mean (S.D.)	43.4 (13.9)	47.1 (12.4)	t=5.38	<0.001
Gender, Female	1547 (67.5%)	342 (75.5%)	1.48 (1.18-1.87)	.001
Marital status, Married	1186 (51.7%)	281 (62.0%)	1.52 (1.24-1.87)	<0.001
First-Degree Family History of BD	317 (14.0%)	93 (20.7%)	1.60 (1.25-2.07)	<.001
(Hypo)manic switches with ADs	340 (14.8%)	117 (25.8%)	1.99 (1.57-2.54)	<.001
Psychotic Features	564 (24.6%)	157 (34.7%)	1.63 (1.31-2.01)	<.001
Atypical Features	132 (5.8%)	57 (12.6%)	2.36 (1.70-3.27)	<.001
Suicide Attempts	490 (21.4%)	119 (26.3%)	1.31 (1.04-1.65)	.026
≥3 MDE	1242 (54.2%)	316 (69.8%)	1.95 (1.57-2.42)	<.001
Current Episode >1 month	779 (34.0%)	183 (40.4%)	1.31 (1.07-1.61)	.011
First MDE <30 Years	1119 (52.2%)	231 (51.0%)	0.95 (0.78-1.17)	ns
Psychiatric comorbidity				
Anxiety Disorders	632 (27.6%)	154 (34.0%)	1.35 (1.09-1.68)	.006
Eating Disorders	138 (6.1%)	53 (11.8%)	2.07 (1.48-2.89)	<.001
Alcohol-Substance Use Dis.	199 (8.7%)	32 (7.1%)	0.80 (0.54-1.78)	Ns
ADHD	49 (2.2%)	12 (2.7%)	1.25 (0.66-2.36)	Ns
Borderline Personality Disorder	143 (6.2%)	39 (8.6%)	1.42 (0.98-2.05)	Ns
Previous treatments				
Antidepressants	1874 (81.8%)	374 (82.6%)	1.06 (0.81-1.38)	ns
Antipsychotics	748 (32.6%)	199 (43.9%)	1.62 (1.32-1.99)	<.001
Mood-Stabilizers	606 (26.4%)	168 (37.1%)	1.64 (1.32-2.02)	<.001
More than 3 drugs	707 (30.8%)	190 (41.9%)	1.62 (1.32-1.99)	<.001
Benzodiazepines	1046 (45.6%)	212 (46.8%)	1.05 (0.85-1.28)	ns

Abbreviations. ADs: antidepressants; ADHD: attention deficit and hyperactivity disorders; BD: bipolar disorder; BMI: body mass index.

Table 3. Multiple logistic regression backward procedure of clinical features, bipolarity and mixed state diagnosis on the presence of BMI ≥30 in 2744 subjects with Major Depressive Episode (MDE).			
Variables in equation	**Wald**	**p-value**	**OR (95% CI)**
Age	14.525	<.001	1.02 (1.01-1.02)
(Hypo)manic switches with Ads	7.848	.005	1.46 (1.12-1.90)
Anxiety Disorders	3.860	.049	1.26 (1.00-1.60)
Antipsychotics	5.045	.025	1.29 (1.03-1.62)
Marital status, Married	12.310	.000	1.48 (1.19-1.84)
Gender, Female	8.453	.004	1.43 (1.12-1.82)
Atypical Features	9.993	.002	1.78 (1.24-2.54)
Eating Disorders	6.580	.010	1.61 (1.12-2.32)
Psychotic Features	4.251	.039	1.44 (1.02-2.05)
≥3 MDE	8.99	.003	1.44 (1.13-1.82)
Depressive mixed state (DSM-5)	5.467	.019	1.52 (1.07-2.15)

Legend. Wald = 227.909, df = 1, p <.001. Variables not included in the equation: more than 3 drugs, current episode >1 month, first-degree family history of BD, suicide attempts, mood-stabilizers.

Abbreviations. ADs: antidepressants; BMI: body mass index.

Table 4: Distribution of 14 current (hypo)manic symptoms in 2744 patients with a Major Depressive Episode with (MDE-OB) and without (MDE-NOB) BMI ≥30.				
	MDE-NOB (n = 2291)	**MDE-OB (n = 493)**	**OR (95% CI)**	**p**
Irritable mood	720 (31.4%)	181 (40.0%)	1.45 (1.18-1.79)	<.001
Emotional/mood lability	674 (29.4%)	153 (33.8%)	1.22 (0.99-1.52)	ns
Distractibility	525 (22.9%)	151 (33.3%)	1.68 (1.35-2.09)	<.001
Psychomotor agitation	330 (14.4%)	111 (24.5%)	1.93 (1.51-2.46)	<.001
Impulsivity	306 (13.4%)	98 (21.6%)	1.72 (1.39-2.31)	<.001
Aggression (verbal or physical)	298 (13.0%)	91 (21.0%)	1.78 (1.37-2.29)	<.001
Racing thoughts	246 (10.7%)	81 (17.9%)	1.81 (1.38-2.38)	<.001
More talkative/pressure to keep talking	238 (10.4%)	79 (17.4%)	1.82 (1.38-2.40)	<.001
Risky behaviour	147 (6.4%)	56 (12.4%)	2.06 (1.49-2.85)	<.001
Hyperactivity	164 (7.2%)	60 (13.2%)	1.98 (1.45-2.71)	<.001
Increased energy	137 (6.0%)	52 (11.5%)	2.04 (1.46-2.86)	<.001
Grandiosity	82 (3.6%)	23 (5.1%)	1.44 (0.89-2.32)	ns
Euphoria	97 (4.2%)	32 (7.1%)	1.72 (1.14-2.59)	.013
Hyper-sexuality	57 (2.5%)	17 (3.8%)	1.53 (0.88-2.65)	ns

Abbreviations. BMI: body mass index.

Table 5. Multiple logistic regression backward procedure of 14 current (hypo)manic symptoms on the presence of BMI ≥30 in 2744 subjects with Major Depressive Episode (MDE).			
Variables in equation	**Wald**	**p-value**	**OR (95% CI)**
Psychomotor agitation	8.180	.004	1.50 (1.13-1.97)
Distractibility	5.693	.017	1.34 (1.05-1.71)
Increased energy	3.897	.048	1.44 (1.00-2.08)
Risky behaviour	2.845	.092	1.37 (0.95-1.97)

Legend. Wald = 801.99, df = 1, p <.001. Variables not included in the equation: irritable mood, mood lability, impulsivity, racing thoughts, hyper-sexuality, aggression, more talkative/pressure to keep talking, hyperactivity, grandiosity, euphoria.

Abbreviations. BMI: body mass index.