The Effect of Body Mass Index on Cognitive Functioning in Euthymic Bipolar I Disorder

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Abstract

Objective. The aim of this study was to determine the influence of Body Mass Index (BMI) on cognitive functioning in bipolar disorder type I (BD-I). A previous study suggested that BMI contributes to cognitive decline in BD (Yim et al., 2012). In the present study, this suggestion was tested on a big homogenous group of Dutch patients, while controlled for factors that are known to influence cognitive functioning in BD: medication use, age at onset, and socioeconomic status.

Method. A sample of 258 euthymic BD-I patients was recruited from the 'Bipolar Genetics' project. Participation included a three hour hospital visit and an 1,5 hour internet survey. For diagnosis and clinical characteristics, the SCID-1 interview for the DSM-IV-TR and QBP-NL were administered. Four subtasks of the WAIS-III were used to measure cognitive functioning.

Results. After controlling for the relevant confounders and potential gender- and age effects, negative effects of BMI on cognitive functioning were found. Significance was reached on the WAIS subtasks Digit Symbol-Coding, Information, and Block Design.

Conclusion. Results of the present study indicate that BMI independently influences cognitive functioning in BD I patients. This finding implies that weight monitoring is of great importance in clinical practice.

Keywords: bipolar disorder, body mass index, cognitive functioning

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Overweight (BMI 25-29.9) and obesity (BMI≥30) are common in bipolar disorder (BD). In a sample of 644 bipolar patients of European and American origin, 58% was overweight and 21% was obese (McElroy et al., 2002). These high percentages are worrisome because obesity is associated with major medical illnesses such as cardiovascular disease, diabetes mellitus type 2, and metabolic syndrome. It is found that obesity-related diseases occur more often and manifest relatively earlier in patients who are suffering from a mood

disorder (Kilbourne et al., 2004; McIntyre et al., 2006).

The relationship between obesity and mood disorders is bidirectional. Obesity is a risk factor for depression and suicide attempts, and vice versa: depression in adolescence has significant negative influence on adult BMI (Carpenter, Hasin, Allison, & Faith, 2000; Pine, Cohen, Brook, & Coplan, 1997; McElroy et al., 2004; Roberts, Deleger, Strawbridge, & Kaplan, 2003). Results from imaging studies indicate that overlapping pathophysiology contributes to the co-occurrence of obesity and mood disorders (McElroy & Keck, 2012; McIntyre et al., 2010; Soczynska et al., 2011).

Obesity in BD is associated with medication use. Lithium, the most prescribed mood stabilizer in BD, can cause weight gain (Burgess et al., 2001). Lithium is often combined with atypical antipsychotics, which are also known to induce weight gain in bipolar patients as well (Elmsie, Silverstone, Mann, Williams, & Romans, 2000; McElroy et al., 2002).

Overweight or obese BD patients are at higher risk of poor functional outcome, a greater number of affective episodes, and rapid recurrence of depressive episodes (Fagiolini, Kupfer, Houck, Novick, & Frank, 2003; Rosa et al., 2009). Furthermore, the burden of BD in obese patients is increased because of low physical fitness and socioeconomic inferiority (Devlin, Yanovski, & Wilson, 2000; Gortmaker, Must, Perrin, Sobal, & Dietz, 1993; Wolf & Colditz, 1996).

Cognitive Functioning in Bipolar Disorder

A common problem among BD patients is cognitive impairment. During the last decade a great deal of research was performed in this field. Nearly two thirds of euthymic BD patients report problems with functioning in different cognitive domains such as concentration, psychomotor performance, working memory, processing speed, and executive functioning (Martinez-Arán et al., 2005; Torres, Boudreau, & Yatham, 2007; Yates, Dittman, Kapczinski, & Trentini, 2011).

Bora, Yucel, & Pantelis (2009) labeled some cognitive deficits as endophenotypes, hereditary characteristics that are associated with a certain disorder. According to this study, response inhibition deficit is the most prominent endophenotype for BD. However, Bora et al. (2009) conclude that impairments in most cognitive domains are likely caused by confounding factors rather than by heredity characteristics.

Factors that predict performance on the Wechsler Adult Intelligence Scale (WAIS-III) are the number of hospitalizations, use of mood stabilizer, age at onset, and duration of disease (Yates, Dittman, Kapczinski, & Trentini, 2011). Also, a greater number of episodes, residual depressive symptomatology, psychosis, and long-term medication use can influence cognitive performance (Dias et al., 2012; Fagiolini et al., 2005; Kessing, 1998; MacQueen, Young, Robb, Cooke, & Joffe, 1997; Macqueen et al., 2000; Rosa et al., 2009; Savits, Solms, & Ramesar, 2005; Van Gorp, Altshuler, Theberge, Wilkins, & Dixon, 1998).

In summary, a severe course of disease is associated with impaired cognitive performance (Denicoff et al., 1999). Additionally, low socioeconomic status, comorbidity with substance use disorder, and older age can induce poor functional outcome in BD, which is linked to cognitive impairment (Cacilhas et al., 2008; Keck et al., 1998; MacQueen, Yount, & Joffe, 2001; Martinez-Aran et al., 2007).

Medication Use and Cognitive Decline

A lot of research on cognitive performance in BD focuses on medication use. A recent meta-analysis summarizes the varying impact of medication use on cognitive functioning in BD (Dias et al., 2012). This article uses the metaphor of a ‘two edged sword’, because medication use improves cognition by targeting psychotic and mood symptoms, but can also induce cognitive side effects. In their meta-analysis, Dias et al. tried to clarify the effects of frequently used medicines on cognition in BD: lithium, anticonvulsants, antidepressants, antipsychotics, and anxiolytics (benzodiazepines). The researchers conclude that variability in

doses, polypharmacy, individual sensitivity to medication, and family risk factors make it difficult to draw precise conclusions. With this in mind, we will summarize which medication can contribute to cognitive decline in BD.

Lithium has few and minor negative effects on cognition (Tsaltas, Kontis, Boulougouris, & Papadimitriou, 2009; Wingo, Wingo, Harvey, & Baldessarini, 2009). Of all mood stabilizers, the anticonvulsant valproate causes the worst cognitive decline (Gualtieri & Johnson, 2006). As to antipsychotics, it is reported that both conventional and atypical antipsychotics influence cognition negatively (Ramaekers et al., 1999; Torrent et al., 2011). The use of antidepressants and benzodiazepines in BD is not studied properly. Symptoms of benzodiazepine use in general include numerous dysfunctions in cognitive domains, such as memory, psychomotor speed, and attention (Barker, Jackson, Greenwood, & Crowe, 2003).

The Role of Body Mass Index

The influence of medication use and clinical characteristics on cognitive performance are both extensively studied in BD. Less attention is paid to the possible contribution of Body Mass Index (BMI), despite the strong co-occurrence of obesity and BD (McElroy et al., 2002). Emerging evidence indicates that obesity is associated with reduced cognitive functioning in otherwise healthy individuals (Brook, Zhang, Saar, & Brook, 2009; Nilsson & Nilsson, 2009). Cross-sectionally, a higher Body Mass Index (BMI) is associated with lower cognitive performance after adjustment for age, sex, educational level, and other relevant covariates (Cournot et al., 2006; Gunstad et al., 2007). The relationship between obesity and cognitive functioning is probably bidirectional. Obese individuals tend to have poorer cognitive functions, but people with impaired executive functioning are more likely to become overweight or obese, because of disturbances in impulse control, self-monitoring, and goal-directed behavior, which can cause overeating (Smith, Hay, Campbell, & Trollor, 2011).

To our knowledge, only one previous study has examined the effect of BMI on

cognitive functioning in BD (Yim et al., 2012). In this study a total of 67 euthymic individuals with BD type I and II were included. The researchers found that BMI is significantly and negatively correlated with scores on the Digit Symbol-Coding subtask, an indication of processing speed. This result needs further extensive examination because of the many shortcomings of the study of Yim et al. (2012). For example, the confounding effects of possible confounders as medication use and severity of disease course on cognitive abilities were not clearly examined. It was only stated that there were no significant differences between normal and overweight groups in clinical characteristics and number and types of medication.

The Present Study

In the present study, we will take a closer look at the possible influence of BMI on cognitive performance in BD. We will use tasks that measure several cognitive domains and will check if the results of Yim et al. (2012) remain intact in a larger sample. Instead of comparing two groups (normal weight and overweight/obese), we will look for a linear relation. Thereafter, we will add confounding factors to the analysis. We chose the confounders: age at onset, socioeconomic status, current age, gender, and medication use. Figure 1 gives a summary of the variables.

We hypothesize that (1) the relation between BMI and the performance on the WAIS subtasks is negative. We will analyze the confounders separately, before adding them to the analysis. For the confounders, we propose the following hypotheses: (2) the relation between socio-economic status and the performance on all WAIS subtasks is positive and (3) the relation between age at onset and the performance on all subtasks of the WAIS is positive. As to medication use, we propose two general hypotheses: (4) the use of lithium and antidepressants does not influence the performance on the WAIS subtasks and (5) the use of anticonvulsants, conventional and atypical antipsychotics, and benzodiazepines influences the

performance on the WAIS subtasks negatively.

For the main analysis, we expect that (6) the relation between BMI and the performance on all WAIS subtasks is negative, if controlled for the confounders age at onset, SES, current age, gender, and medication.

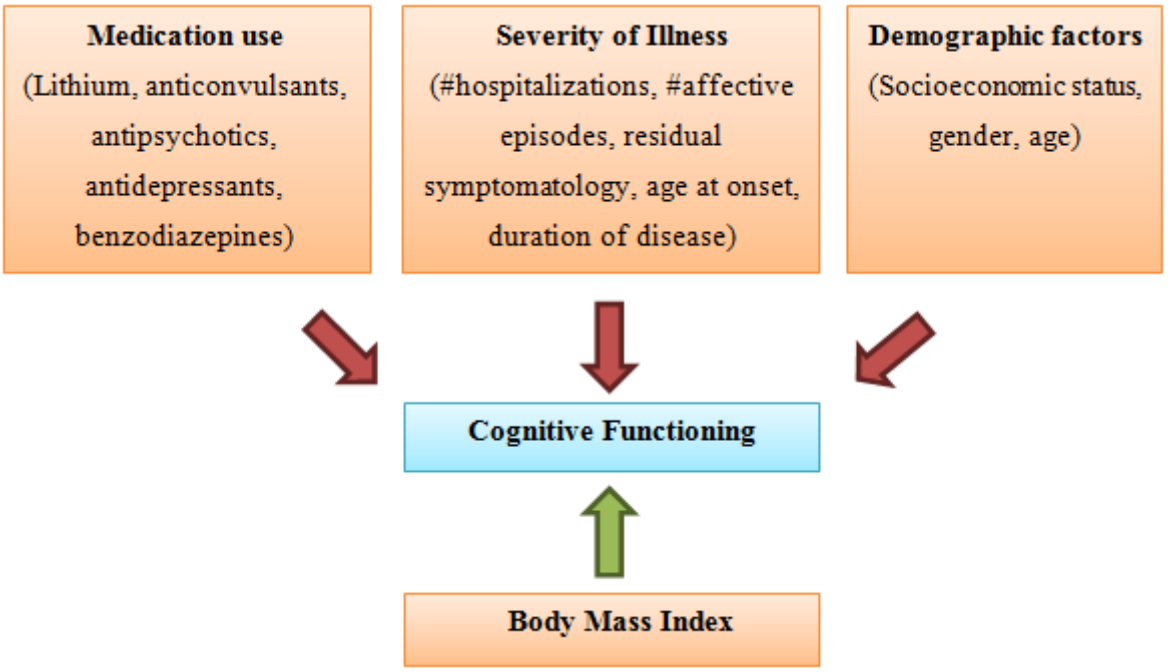

Figure 1. A simplification of the dynamics of factors that influence cognitive functioning and Body Mass Index in bipolar disorder. In the main analysis, we will examine the effect that is marked with the green arrow and control for the effects that are marked with red arrows.

Methods

Participants

Participants were recruited from the 'Bipolar Genetics' project, a cross-sectional study that tries to unravel the genetic profile of Bipolar I Disorder. The study was performed at the University Medical Centre Utrecht (UMCU), in association with the University of California in Los Angeles (UCLA). The Medical Research Ethics Committee (MREC) approved the study. In the main study, data from patients, family members, and controls were obtained. In

the present study, only the data regarding the patients were used. Exclusion criteria in the main study were: no diagnosis of BD-I according to DSM-IV-TR (only for patients), no Dutch ancestry (less than 3 out of 4 grandparents of Dutch origin), age younger than 18 and premorbid IQ lower than 80. In the sample that is used in the present study, patients that were diagnosed with a present mood episode according to the DSM-IV-TR were excluded, because presence of mood symptoms can influence neuropsychological performance (Yates, Dittman, Kapczinski, & Trentini, 2011). Patients were also excluded when data was missing or when WAIS data was not accounted reliable, because of severe fatigue or tremor. The latter could have influenced the score on the Digit Symbol-Coding- and Block Design subtasks.

Procedure

At first, participants completed an online questionnaire, which contained i.a. the Family Affluence Scale and the Inventory of Medication Use. This part took about 1,5 hours. The second part of the study took place in the UMC Utrecht and occasionally in another hospital. At this point, the participants signed an informed consent. Then, a psychiatric interview (SCID-I), some additional questionnaires about family, substance (ab)use, and the four subtests of the WAIS-III were administered by (neuro)psychologists in training. Furthermore, blood- and hair samples were taken and blood pressure, weight, and height were measured. All in all, the second part took about three hours. For completing the internet questionnaires patients received a 15 euro internet voucher and for their visit to the hospital a 30 euro fee was provided.

Measures

SCID-1 interview for the DSM-IV-TR . The Dutch adaptation of the patient edition of the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, fourth version text revision (SCID-1 for the DSM-IV-TR) was used to obtain a current and extensive diagnosis (First, Spitzer, Gibbon, & Williams, 1996; Van Groenestijn,

Akkerhuis, Kupka, Schneider, & Nolen, 1999). Psychometric analysis of the Dutch version of the SCID-I showed moderate to excellent inter-rater agreement on the axis I disorders, with a mean kappa value of .71 (Lobbestael, Leurgans, & Arntz, 2010).

WAIS-III. For cognitive performance measures, a shortened version of the Wechsler adult intelligence scale-III (WAIS-III) was used, which contained the following subtasks: Block Design (visuoconstructive ability), Digit Symbol-Coding (processing speed) Information (degree of general information acquired from culture), and Arithmetic (working memory) (Wechsler, Steene, & Vertommen, 2002). The sum of the four scaled subtest scores is also an indication of IQ, if multiplied by eleven and divided by four. This short version of the WAIS-III accounted best for the variance in full-scale IQ in both patients with schizophrenia (R^2 =.90) and healthy controls (R^2 =.86) (Blyler, Gold, Iannone, & Buchanan, 2000).

FAS. The Family Affluence Scale (FAS) is a four-item measure to determine the Socioeconomic Status (SES), which is developed in the WHO Health Behaviour in School-aged Children Study . Several studies conclude that FAS is a valid, and easy to answer SES measure (Boudreau & Poulin, 2009; Boyce, Torsheim, Currie, & Zambon, 2006).

QBP-NL part B. The Questionnaire for Bipolar Illness (QBP-NL, translation: Akkerhuis, Groenesteijn, & Nolen, 2005) is a patient self-report questionnaire for demographical and social characteristics (Leverich et al.,2001). This questionnaire was administered to determine the age at onset, which was operationalized as the age at which the patient took medication for mood symptoms for the first time.

Statistical Analyses

For analyses, Statistical Package for Social Sciences (SPSS) 20.0 was used. All the hypotheses were tested with regression analysis.

(1) The relation between BMI and the performance on the WAIS subtasks is negative.

(2) The relation between socio-economic status and the performance on the WAIS subtasks is positive.

(3) The relation between age at onset and the performance on the WAIS subtasks is positive.

Hypothesis 1-3 are tested with simple linear regression analysis.

(4) The use of lithium and antidepressants does not influence the performance on the WAIS subtasks.

(5) The use of anticonvulsants, conventional and atypical antipsychotics, and benzodiazepines influences the performance on the WAIS subtasks negatively.

To test hypothesis 4 and 5, medication use was categorized in six groups, which were coded into 6 dummy variables (lithium/ conventional antipsychotics/atypical antipsychotics/ anticonvulsants/ antidepressants/ benzodiazepines). After this, multiple regression was conducted.

(6) The relation between BMI and the performance on the WAIS subtasks is negative, if controlled for the confounders medication, age at onset, SES, gender, and current age.

The sixth hypothesis was tested with a hierarchical multiple regression analysis, in order to determine the additional R^2-change of BMI after adding the confounders.

Results

Sample

The sample consisted of 399 BD-1 patients. WAIS data of 98 patients was not obtained. The most common reasons to skip the WAIS were severe fatigue, a current mood episode or lack of time due to an extended psychiatric interview. From 14 patients WAIS data was not accounted reliable due to diagnosis with a current mood episode according to the SCID-I. Furthermore, WAIS scores from 6 patients were excluded, because of reports of fatigue (1), dyscalculia (1), and severe tremor (4), which could have influenced the results on Digit Symbol-Coding and Block Design. In addition, patients were excluded because data of

medication use (3), socio-economic status (16), and age at onset (4) were missing. Consequently, analysis was conducted over a dataset of 258 patients. For descriptive statistics see table 1.

Table 1

Sample characteristics

Sex, n (%)	
Male	127 (49.2)
Female	131 (50.8)
Age, mean (SD)	48.44 (12.28)
Age at onset, mean (SD)	31.92 (10.96)
Socio-economic status (1-9), mean (SD)	3.31(1.78)
BMI, mean (SD)	26.6 (4.28)
Normal weight (BMI<25), n (%)	92 (35.7)
Overweight (BMI 25-29.9), n (%)	107 (41.5)
Obese (BMI ≥30), n (%)	59 (22.9)
Medication Use, **n** (%)	
Lithium	178 (69.0)
Anticonvulsants	75 (29.1)
Antidepressants	46 (17.8)
Conventional antipsychotics	9 (3.5)
Atypical antipsychotics	80 (31.0)
Benzodiazepines	57 (22.1)

Exploratory Analysis: Confounders

Initial analysis of the confounder socio-economic status (SES) confirmed largely our hypothesis that the relation between socio-economic status and the performance on all WAIS subtasks would be positive. The hypothesis was confirmed for Digit Symbol-Coding (β =.125, p=.046), Block Design (β =.170, p=.006), Information (β =.199, p=.001), and the total IQ score (β =.190, p=.002). Socio-economic status was not a significant predictor for performance on the Arithmetic subtask (β =.070, p=.260).

For age at onset, it was expected that the relation between age at onset and the performance on all subtasks of the WAIS would be positive. This hypothesis was not confirmed (Digit Symbol-Coding (β =.017, p=.780), Block Design (β =.002, p=.977), Arithmetic (β =.045, p= .468), Information (β = -.064, p=.304), and total IQ (β = -.005, p=.938)).

As to medication use, we proposed two general hypotheses. We expected that the use of lithium and antidepressants would not influence the performance on the WAIS subtasks. However, we did expect that the use of anticonvulsants, conventional and atypical antipsychotics, and benzodiazepines would influence the performance on the WAIS subtasks negatively.

In our hypotheses we did not differentiate between the WAIS subtasks. However, we found that only specific tasks were influenced by specific types of medication. Lithium use influenced the performance on Digit Symbol-Coding negatively (β =-.197 p= .004) and approached significant influence on performance on Arithmetic (β = -.124, p= .066). Use of benzodiazepines did also influence performance on Arithmetic negatively (β =-.131, p= .036) and approached significant influence on the total IQ score (β =-.117, p= .065). Antidepressant use influenced performance on Arithmetic positively (β =.170, p= .006). Derived from these effects, specific types of medication were taken into account as confounders in the main

analysis.

Furthermore, we found that women scored significantly lower than men on Arithmetic, Information, and total IQ. Current age only had small, but significant influence on the performance on the Information subtask (β =.165, p=.040).

Body Mass Index

For BMI, we expected that the relation between BMI and the performance on all WAIS subtasks would be negative. In our initial analysis, we found a small but significant negative influence on Digit Symbol-Coding (β = -.143, p=.022), Block Design (β = -.141, p=.023), Information (β = -.145, p=.011), and total IQ (β = -.140, p=.020). The performance on Arithmetic (β =.014, p=.821) was not influenced significantly by BMI.

Hierarchical multiple regression analysis was conducted to examine if these effects would hold up after adding the confounders. The confounders gender, current age, socio-economic status, and age at onset were entered in the first blocks and BMI was entered in the last block. After controlling for these confounders, the significant negative effects of BMI on cognitive functioning remained intact, although the effect sizes were very small (see table 2).

The positive relation between cognitive performance and gender/socio-economic status also held up after adding the other predictors.

Table 2

Results of the main analysis

	Arithmetic		Information		Block Design		Digit Symbol-Coding		Total IQ	
	ΔR^2	β	ΔR^2	β	ΔR^2	β	ΔR^2	β	ΔR^2	β
Benzodiazepine	.017	-.095							.015	-.098
Antidepressant	.028	***.201								
Lithium							.022	**-.173		
SES	.006	.082	.040	***.232	.029	*.180	.017	**. 222	.037	**.233
Age at onset	.004	.033	.000	-.101	.004	.054	.006	.038	.003	-.005
Gender	.119	***-.351	.164	***-.395	.008	-.093	.008	.102	.055	***-.229
Age	.000	.008	.015	*.165	.000	.018	.012	.143	.008	.112
BMI	.000	.007	.013	*-.116	.015	*-.123	.017	*-.131	.014	*-.120

*P<0.05, **P<.01 ***P≤.001

Discussion

In the present study, the effect of BMI on cognitive functioning in BD was examined. The importance of BMI-related research in BD is highlighted by a the strong co-occurrence of BD and overweight. The mean BMI (26.6) of this sample was above healthy range (18-25). 41.5% of the patients was overweight and 22.9% was obese. These percentages are similar to other bipolar populations (McElroy et al., 2002).

A previous study suggested that BMI contributes to cognitive decline in BD (Yim et al., 2012). This suggestion, combined with the finding that in non-psychiatric samples a higher BMI is associated with lower cognitive performance, resulted in the hypothesis that the

relation between BMI and cognitive performance would be negative (Brook, Zhang, Saar, & Brook, 2009; Cournot et al., 2006; Gunstad et al., 2007; Nilsson & Nilsson, 2009). For three of the four WAIS subtasks, this hypothesis is confirmed. A small, but significant negative relation between BMI and performance on Digit Symbol-Coding, Information, and Block Design is found.

It would be useful to discuss some notable findings in the exploratory analyses of the confounders. This will put our findings in a wider perspective, because BMI is only one of the factors that plays a role in cognitive decline in BD.

Analyses of the Confounders

Medication. As to medication, negative influence on cognitive performance was significant for specific subtasks only. No firm conclusions can be drawn from these results because in this study it has not been possible to take some important confounding factors into account, such as the dose, polypharmacy, and the history of medication use. We would plead for a study that takes all these factors into account and is specifically designed to examine the effects on cognitive functioning of frequently used medication in BD. The possibility that BMI is a mediator in medication-related cognitive decline should be considered, because most frequently used medicines in BD are known to induce weight gain (Burgess et al., 2001, Elmsie, Silverstone, Mann, Williams, & Romans, 2000; McElroy et al., 2002).

Socioeconomic Status. The finding that the relation between socioeconomic status and cognitive functioning is positive, is consistent with previous findings that a higher SES is associated with a more rapid onset of recovery and preservation of cognitive functioning (Keck et al., 1998). The reason for this association is unclear. Keck et al. (1998) suggested that a better understanding of psychiatric illness and the availability of more social and financial support in higher socioeconomic brackets results in better recovery.

Gender. In the present sample, males performed significantly better on the Arithmetic

and Information subtasks than females. These findings can possibly be attributed to the Dutch adaptation of the WAIS. In a healthy Dutch population, it is found that males outperform females on the Information and Arithmetic subtasks (Van der Sluis, Posthuma, Dolan, de Geus, Colom, & Boomsma, 2006). Van der Sluis et al. (2006) also found that females outperform males on Digit Symbol-Coding. In the present study, this was the only subtask in which women outperformed men, although this result was not significant (p= .08).

Another explanation for the gender effect, is the mediating role of differences in clinical characteristics. It is found that women with BD experience relatively more depressive episodes, which seem to have greater negative influence on cognitive functioning than manic episodes (Robb, Young, Cooke, & Joffe, 1998; Kessing, 1998). However, this explanation is far-fetched and does not explain why cognitive functioning is impaired on only two subtasks. We are conservative to draw a conclusion on these findings, but a gender specific cognitive effect in BD could be an interesting topic for future research.

Main Analysis

The findings in the exploratory analyses are consistent with results in previous studies, that cognitive decline in BD is caused by interaction of demographic factors, medication use, and clinical characteristics (Denicoff et al., 1998; Dias et al., 2012; Macqueen et al., 2000; MacQueen, Yount, & Joffe, 2001; Van Gorp, Altshuler, Theberge, Wilkins, & Dixon, 1998; Yates, Dittman, Kapczinski, & Trentini, 2011). In contrast to the only previous study on BMI-related cognitive decline in BD (Yim et al. (2012), we controlled for these relevant confounders. In the main analysis, the relation of BMI and cognitive functioning remained intact. This indicates that BMI independently influences cognitive functioning in BD-I patients.

No significant negative relation was found between BMI and performance on the Arithmetic subtask, an indication of working memory. This finding is in contrast to non-

psychiatric samples, where obesity is linked to Alzheimer disease and reduced performance on memory tasks (Cournot et al., 2006; Gonzales et al., 2010; Gunstad et al., 2007). We recommend to administer a more extensive neuropsychological test battery in future research, to compare the results of the present study to other cognitive measures. Then, more concrete conclusions on specific cognitive domains can be drawn.

Longitudinal studies have to provide more insight in the possible causal relationship between overweight/obesity and cognitive functioning in BD. The relationship is probably bidirectional, because overeating can also be caused by impaired executive functioning and disturbances in impulse control (Smith, Hay, Campbell, & Trollor, 2011).

Clinical implications

In the present study, BMI is identified as one of the factors that influences cognitive functioning in BD. This result is an important addition to reports in previous literature that overweight/obese BD patients are at higher risk of poor functional outcome, a greater number of affective episodes, and rapid recurrence of depressive episodes (Fagiolini, Kupfer, Houck, Novick, & Frank, 2003; Rosa et al., 2009). Also, mortality by obesity-related diseases is relatively high in BD patients (Sharma & Markar, 1994).

These findings have some important clinical implications. Preventing obesity in BD could possibly improve cognitive functioning, the course of disease, and mortality. In pharmacological treatment, it is a challenge to limit BMI without worsening of mood symptoms. Early intervention is the key for preventing obesity, since losing weight is particularly a challenge for psychiatric patients (Devlin, Yanovski, & Wilson, 2000). At patient intake, family history of binge eating and obesity should be administered. Monitoring of BMI and related metabolic factors as blood lipid and glucose levels should be standard in the treatment of BD. We advise to provide diet and exercise counseling at an early stage.

In schizophrenic populations, cognitive–behavioral therapy and nutritional counseling

were effective in reducing antipsychotic-induced weight gain (Alvarez-Jimenez, Hetrick, Gonzalex-Blanch, Gleeson, & McGorry, 2008). Similar research in BD is limited. One trial found promising results of a multimodal lifestyle intervention for BD (Gillhoff et al., 2010). It should be noted that the long-lasting effect was only found in females, indicating the need for gender-specific interventions.

Ideally, changes in lifestyle, diet or exercise, should be combined with mood stabilizers that are associated with minimal weight gain, like lamotrigine or carbamazepine (Malhotra & McElroy, 2002). Randomized trials are needed to define the ideal combination of pharmacological and non-pharmacological treatment. Limiting of cognitive decline and keeping BMI on a healthy level should be pillars in future treatment.

In summary, the present study highlights the importance of BMI-related research in bipolar disorder and gives a strong indication for the need for weight monitoring during treatment of bipolar patients.

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References

Alvarez-Jimenez, M., Hetrick, S.E., Gonzalez-Blanch, C., Gleeson, J.F., & McGorry, P.D. (2008). Non-pharmacological management of antipsychotic-induced weight gain: systematic review and meta-analysis of randomized controlled trials. *British Journal of Psychiatry, 193,* 101–107.

Barker, M.J., Jackson, M., Greenwood, K.M., & Crowe, S.F. (2003). Cognitive effects of benzodiazepine use: a review. *Australian Psychologist 38*(3), 202–213.

Blyler, C. R., Gold, J. M., Iannone, V. N., & Buchanan, R. W. (2000). Short form of the WAIS-III for use with patients with schizophrenia. *Schizophrenia Research, 46,* 209-215.

Bora, E., Yucel, M., & Pantelis, C. (2009). Cognitive endophenotypes of bipolar disorder: A meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. *Journal of affective disorders, 113,* 1-20.

Boudreau, B. & Poulin, C. (2009). An examination of the validity of the Family Affluence Scale II (FAS II) in a general adolescent population of Canada. *Social Indicators Research, 94*(1), 29–42.

Boyce, W., Torsheim, T., Currie, C., & Zambon, A. (2006). The family affluence scale as a measure of national wealth: validation of an adolescent self-report measure. *Social Indicators Research, 78,* 473–487.

Brook, J.S., Zhang, C., Saar, N.S., & Brook, D.W. (2009). Psychosocial predictors, higher body mass index, and aspects of neurocognitive dysfunction. *Perceptual & Motor Skills, 108,* 181-195.

Burgess, S.S.A., Geddes, J., Hawton, K.K.E., Taylor, M.J., Townsend, E., Jamison, K., & Goodwin, G. (2001). Lithium for maintenance treatment of mood disorders. *Cochrane Database of Systematic Reviews,* Issue 2: CD003013.

Cacilhas, A.A., Da Silva Magalhães, P.P., Ceresér, K.M., Walz, J.C., Weyne, F. Rosa, A.R., . . . Kapczinski, F. (2009). Bipolar disorder and age-related functional impairment. *Revista Brasileira de Psiquiatria, 31*(4), 354-357.

Carpenter, K.M., Hasin, D.S., Allison, D.B., & Faith, M.S. (2000). Relationships between obesity and DSM-IV major depressive disorder, suicide ideation, and suicide attempts: results from a general population study. *American Journal of Public Health, 90,* 251-257.

Cournot, M., Marquie, J.C., Ansiau, D., Martinaud, C., Fonds, H., Ferrières, J., & Ruidavets, J.B. (2006). Relation between body mass index and cognitive function in healthy middle-aged men and women. *Neurology, 67,* 1208-1214.

Denicoff, K.D., Ali, S.O., Mirsky, A.F., Smith-Jackson, E.E., Leverich, G.S., Duncan, C.C., . . . Post, R.M. (1999). Relationship between prior course of illness and neuropsychological functioning in patients with bipolar disorder. *Journal of Affective Disorders, 56,* 67-73.

Devlin, M.J., Yanovski, S.Z., & Wilson, G.T. (2000). Obesity: what mental health professionals need to know. *American Journal of Psychiatry, 157,* 854–866.

Dias, V.V., Balanzá-Martinez, V., Soeiro-de-Souza M.G., Moreno, R.A., Figueira, M.L., Machado- Vieira, R., & Vieta, E. (2012). Pharmacological approaches in bipolar disorders and the impact on cognition: a critical overview. *Acta Psychiatrica Scandinavia, 126,* 315–331.

Elmslie, J.L., Silverstone, J.T., Mann, J.I., Williams, S.M., & Romans, S.E. (2000). Prevalence of overweight and obesity in bipolar patients. *Journal of Clinical Psychiatry, 61,* 179–184.

Fagiolini, A., Kupfer, D.J., Houck, P.R., Novick, D.M., & Frank, E. (2003). Obesity as a correlate of outcome in patients with bipolar I disorder. *American Journal of*

Psychiatry, 160, 112–117.

Fagiolini, A., Kupfer, D.J., Masalehdan, A., Scott, J.A., Houck, P.R., & Frank E. (2005). Functional impairment in the remission phase of bipolar disorder. *Bipolar Disorders, 7,* 281–285.

First, M.B., Spitzer, R.L., Gibbon, M., & Williams, J.B.W.: Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition (SCID-I/P). New York: Biometrics Research, New York State Psychiatric Institute, November 2002.

Gillhoff, K., Gaab, J., Emini, L., Maroni, C., Tholuck, J., & Greil, W. (2010). Effects of a multimodal lifestyle intervention on body mass index in patients with bipolar disorder: a randomized controlled trial. *Primary Care Companion to the Journal of Clinical Psychiatry, 12* (5), PCC.09m00906.

Gonzales, M.M., Tarumi, T., Miles, S.C., Tanaka, H., Shah, F., & Haley, A.P. (2010). Insulin sensitivity as a mediator of the relationship between BMI and working memory-related brain activation. *Obesity, 18,* 2131–2137.

Gortmaker, S.L., Must, A., Perrin, J.M., Sobol, A.M., & Dietz, W.H. (1993). Social and economic consequences of overweight in adolescence and young adulthood. *New England Journal of Medicine, 329,* 1008–1012.

Gorp, W.G. van, Altshuler, L., Theberge, D.C., Wilkins, J., & Dixon, W. (1998). Cognitive impairment in euthymic bipolar patients with and without prior alcohol dependence. A preliminary study. *Archives of General Psychiatry, 55,* 41-46.

Groenestijn, M.A.C. van, Akkerhuis, G.W., Kupka, R.W., Schneider, N., & Nolen, W.A. (1999). *Gestructureerd klinisch interview voor de vaststelling van DSM-IV As-I stoornissen.* Lisse: Swets en Zeitlinger.

Gualtieri, C.T. & Johnson, L.G. (2006). Comparative neurocognitive effects of 5 psychotropic anticonvulsants and lithium. *MedGenMed, 8,* 46.

Gunstad, J., Paul, R.H., Cohen, R.A., Tate, D.F., Spitznagel, M.B., & Gordon, E. (2007). Elevated body mass index is associated with executive dysfunction in otherwise healthy adults. *Comprehensive Psychiatry, 48,* 57-61.

Kawa, I., Carter, J.D., Joyce, P.R., Doughty, C.J., Frampton, C.M., Wells, J.E., . . . Olds, R.J. (2005). Gender differences in bipolar disorder: age of onset, course, comorbidity, and symptom presentation. *Bipolar Disorders, 7,* 119–125.

Keck, P.E., Jr., McElroy, S.L., Strakowski, S.M., West, S.A., Sax, K.W., Hawkins, J.M., . . . Haggard, P. (1998). 12-month outcome of patients with bipolar disorder following hospitalization for a manic or mixed episode. *American Journal of Psychiatry, 155,* 646–652.

Kessing, L.V. (1998). Cognitive impairment in the euthymic phase of affective disorder. (1998). *Psychological Medicine, 28,* 1027-1038.

Kilbourne, A. M., Cornelius, J. R., Han, X., Pincus, H.A., Shad, M., Salloum, I., . . . Haas, G.L. (2004). Burden of general medical conditions among individuals with bipolar disorder. *Bipolar Disorders, 6* (5), 368–373.

Leverich, G.S., Nolen, W.A., Rush, A.J., McElroy, S.L., Keck, P.E., Jr., Denicoff, K.D., . . . Post, R.M. (2001). The Stanley Foundation Bipolar Treatment Outcome Network: I. Longitudinal methodology. *Journal of affective disorders, 67,* 33-44.

Lobbestael, J., Leurgans, M., & Arntz, A. (2011). Inter-rater reliability of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I) and Axis II Disorders (SCID II). *Clinical Psychology & Psychotherapy, 18,* 75-79.

MacQueen, G.M., Young, L.T., & Joffe, R.T. (2001). A review of psychosocial outcome in patients with bipolar disorder. *Acta Psychiatrica Sandinavia, 103,* 163–170.

MacQueen, G.M., Young, L.T., Robb, J.C., Cooke, R.G., & Joffe, R.T. (1997). Levels of functioning and well-being in recovered psychotic versus nonpsychotic mania. *Journal*

of Affective Disorders, 46, 69–72.

MacQueen, G.M., Young, L.T., Robb, J.C., Mariott, M., Cooke, R.G., & Joffe, R.T. (2000). Effect of number of episodes on wellbeing and functioning of patients with bipolar disorder. *Acta Psychiatrica Scandinavica, 101,* 374-381.

Malhotra, S. & McElroy, S.L. (2002). Medical management of obesity associated with mental disorders. *Journal of Clinical Psychiatry, 63,* 24-32.

Martinez-Arán, A., Vieta, E., Colom, F., Torrent, C., Reinares, M., Goikolea, J.M., . . . Sánchez-Moreno, J. (2005). Do cognitive complaints in euthymic bipolar patients reflect objective cognitive impairment? *Psychotherapy and Psychosomatics, 74*(5), 295-302.

Martinez-Aran, A., Vieta, E., Torrent, C., Sanchez-Moreno, J.,Goikolea, J.M., Salamero, M., . . . Ayuso-Mateos, J.L. (2007). Functional outcome in bipolar disorder: the role of clinical and cognitive factors. *Bipolar Disorders, 9,* 103–113.

McElroy, S.L., Frye, M.A., Suppes, T., Dhavale, D., Keck, P.E., Jr., Leverich, G.S., . . . Post, R.M. (2002). Correlates of overweight and obesity in 644 patients with bipolar disorder. *Journal of Clinical Psychiatry,63,* 207–213.

McElroy, S.L. & Keck, P.E, Jr. (2012). Obesity in bipolar disorder: an overview. *Current Psychiatry Reports, 14,* 650-658.

McElroy, S.L., Kotwal, R., Malhotra, S, Nelson, E.B., Keck, P.E., Jr., & Nemeroff, C.B. (2004). Are mood disorders and obesity related? A review for the mental health professional. *Journal of Clinical Psychiatry, 65,* 634–651.

McIntyre, R.S., Kenna, H.A., Nguyen, H.T., Law, C.W., Sultan, F., Woldeyohannes, H.O., . . . Rasgon, N. L. (2010). Brain volume abnormalities and neurocognitive deficits in diabetes mellitus: Points of pathophysiological commonality with mood disorders? *Advances in Therapy, 27*(2), 63-80.

McIntyre, R.S., Konarski, J.Z., Soczynska, J.K., Wilkins, K., Panjwani, G., Bouffard, B., . . . Kennedy, S.H. (2006). Medical comorbidity in bipolar disorder: Implications for functional outcomes and health service utilization. *Psychiatric Services, 57*(8), 1140–1144.

Nilsson, L.G. & Nilsson, E. (2009). Overweight and cognition. *Scandinavian Journal of Psychology, 50,* 660-667.

Pine, D.S., Cohen, P., Brook, J., & Coplan, J. D. (1997). Psychiatric symptoms in adolescence as predictors of obesity in early adulthood: A longitudinal study. *American Journal of Public Health, 87*(8), 1303–1310.

Ramaekers, J.G., Louwerens, J.W., Muntjewerff, N.D., Milius, H., de Bie, A., Rosenzweig, P., . . . O'Hanlon, J. F. (1999). Psychomotor, cognitive, extrapiramidal, and affective functions of healthy volunteers during treatment with an atypical (amisulpride) and a classic (haloperidol) antipsychotic. *Journal of Clinical Psychopharmacology, 19,* 209–221.

Robb, J.C., Young, L.T., Cooke, R.G. , & Joffe, R.T. (1998). Gender differences in patients with bipolar disorder influence outcome in the medical outcomes survey (SF-20) subscale scores. *Journal of Affective Disorders, 49,* 189–193.

Roberts, R.E., Deleger, S., Strawbridge, W.J., & Kaplan, G.A. (2003). Prospective association between obesity and depression: Evidence from the Alameda County Study. *International Journal of Obesity and Related Metabolism Disorders, 27*(4), 514–521.

Rosa, A.R., Reinares, M., Franco, C., Comes, M., Torrent, C., Sanchez-Moreno, J., . . . Vieta, E. (2009). Clinical Predictors of Functional outcome of bipolar patients in remission. *Bipolar Disorders, 11,* 401–409.

Savitz, J., Solms, M., & Ramesar., R. (2005). Neuropsychological dysfunction in bipolar affective disorder: a critical opinion. *Bipolar Disorders, 7,* 216–235.

Sharma, R. & Markar, H.R. (1994). Mortality in affective disorders. *Journal of Affective Disorder, 31,* 91-96.

Smith, E., Hay, P., Campbell, L., & Trollor, J.N. (2011). A review of the association between obesity and cognitive function across the lifespan: implications for novel approaches to prevention and treatment. *Obesity reviews, 12,* 740-755.

Soczynska, J.K., Kennedy, S.H., Woldeyohannes, H.O., Liauw, S.S., Alsuwaidan, M., Yim, C.Y., & McIntyre, R.S. (2011). Mood disorders and obesity: understanding inflammation as a pathophysiological nexus. *Neuromolecular Medicine, 13,* 93–116.

Torrent, C., Martinez-Arán, A., Daban, C., Amann, B., Balanzá-Martínez, V., Del Mar Bonnín, C., . . . Vieta, E. (2011). Effects of atypical antipsychotics on neurocognition in euthymic bipolar patients. *Comprehensive Psychiatry, 52,* 613–622.

Torres, I.J., Boudreau, V.G., & Yatham, L.N. (2007). Neuropsychological functioning in euthymic bipolar disorder: a meta-analysis. *Acta Psychiatrica Sandinavia, 116*(434), 17-26.

Tsaltas, E., Kontis, D., Boulougouris, V., & Papadimitriou, G.N. (2009). Lithium and cognitive enhancement: leave it or take it? *Psychopharmacology, 202,* 457–476.

Van der Sluis, S., Posthuma, D., Dolan, D.V., de Geus, E.J.C., Colom, R., & Boomsma, D.I. (2006). Sex differences on the Dutch WAIS-III. *Intelligence, 34,* 273−289.

Wechsler, D., Steene, G. van der, & Vertommen, H. (2002). *Manual for the Wechsler adult intelligence scale.* Psychological Corp.: New York.

Wingo, A.P., Wingo, T.S., Harvey, P.D., & Baldessarini, R.J. (2009). Effects of lithium on cognitive performance: a meta-analysis. *Journal of Clinical Psychiatry,70,* 1588–1597.

Wolf, A.M. & Colditz, G.A. (1996). Social and economic effects of body weight in the United States. *American Journal of Clinical Nutrition, 63*(3), 466–469.

Yates, D.B., Dittmann, S., Kapczinski, F., & Trentini, C.M. (2011). Cognitive abilities and clinical variables in bipolar I depressed and euthymic patients and controls. *Journal of Psychiatric research, 45,* 495-504.

Yim, C.Y., Soczynska, J.K., Kennedy, S.H., Woldeyohannes, H.O., Brietzke., E., & McIntyre., R.S. (2012). The effect of overweight/obesity on cognitive function in euthymic individuals with bipolar disorder. *European Psychiatry,27,* 223–228.