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Cognitive performance in older-age bipolar disorder: Investigating psychiatric characteristics, cardiovascular burden and psychotropic medication

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Abstract

Objective: This study aimed to explore a large range of candidate determinants of cognitive performance in older-age bipolar disorder (OABD).

Methods: A cross-sectional study was performed in 172 BD patients aged ≥50 years. Demographics, psychiatric characteristics and psychotropic medication use were collected using self-report questionnaires and structured interviews. The presence of cardiovascular risk factors was determined by combining information from structured interviews, physical examination and laboratory assessments. Cognitive performance was investigated by an extensive neuropsychological assessment of 13 tests, covering the domains of attention, learning/ memory, verbal fluency and executive functioning. The average of 13 neuropsychological test Z-scores resulted in a composite cognitive score. A linear multiple regression model was created using forward selection with the composite cognitive score as outcome variable. Domain cognitive scores were used as secondary outcome variables.

Results: The final multivariable model ($N = 125$), which controlled for age and education level, included number of depressive episodes, number of (hypo)manic episodes, late onset, five or more psychiatric admissions, lifetime smoking, metabolic syndrome and current use of benzodiazepines. Together, these determinants explained 43.0% of the variance in composite cognitive score. Late onset and number of depressive episodes were significantly related to better cognitive performance whereas five or more psychiatric admissions and benzodiazepine use were significantly related to worse cognitive performance.

Conclusion: Psychiatric characteristics, cardiovascular risk and benzodiazepine use are related to cognitive performance in OABD. Cognitive variability in OABD thus seems multifactorial. Strategies aimed at improving cognition in BD should include cardiovascular risk management and minimizing benzodiazepine use.

KEYWORDS
benzodiazepines, bipolar disorder, cognitive dysfunction, heart disease risk factors, neuropsychological tests, psychotropic drugs

1 | INTRODUCTION

Bipolar disorder (BD) is a severe mental illness (SMI), characterized by recurrent episodes of depression and hypomania or mania separated by euthymic intervals.[1] A large number of studies have reported evidence of impaired cognitive functioning in patients with BD compared to healthy controls, not only during depression or mania, but also during remission.[2,3] Cognitive impairment is present in up to 50% of euthymic individuals with older-age bipolar disorder (OABD, defined in international literature as BD patients of ≥50 years or ≥60 years,[4] mainly in the domains of attention, processing speed, memory, verbal fluency and executive functioning.[5-7] The pathophysiological mechanisms of BD-related cognitive dysfunction have not yet been clarified. It is also unclear why some BD patients develop significant cognitive symptoms during the course of illness, whereas others do not seem to become affected.[8] Previous studies primarily focussed on younger adult patients, although older patients may be more likely to have accumulated enough pathophysiological burden to impact cognitive functioning.[9] It is important to identify correlates of cognitive impairment, such that BD patients at risk can be identified at an early stage and can receive adequate monitoring and personalized treatment.[8]

Several mechanisms have been proposed to play a role in BD-related cognitive impairment.[8] One of these is the neuroprogression hypothesis, which states that stressful events, including affective episodes and childhood trauma, may be neurotoxic, possibly through mechanisms including accumulation of allostatic load and bodily 'wear and tear', sensitization, oxidative stress, pro-inflammatory mediators and alteration of neurotrophins.[10,11] In support of this hypothesis, previous studies found associations between the number of manic mood episodes,[12] childhood trauma,[13] history of psychosis[14] and cognitive functioning in BD patients. The neuroprogression hypothesis thus postulates that the observed cognitive impairment is a function of certain psychiatric characteristics, including illness severity, illness duration, and/or burdensome psychiatric comorbidity in BD. However, recent longitudinal studies on cognition in BD suggest that cognitive dysfunction occurs early and remains stable across time.[8,15]

Cardiovascular disease (CVD) may also be involved in the pathogenesis of cognitive impairment in BD. Previously, small studies have shown associations between obesity,[16] metabolic syndrome,[17] triglyceride levels,[18,19] HDL levels,[20] hypertension,[21] cumulative cardiovascular disease risk[22,23] and cognitive functioning in BD patients. Moreover, unhealthy lifestyle habits including dietary saturated fat intake, a sedentary lifestyle, impaired sleep, smoking and problematic alcohol use may lead to the formation of cardiovascular risk and ultimately, to vascular brain damage.[8] However, a recent small study did not show associations between cognitive function and unhealthy dietary choices in BD.[18] In OABD specifically, Schouws et al. (2010) found a relationship between the presence of vascular risk factors and cognitive functioning in the domains of attention and memory.[24]

Third, some research suggests that pharmacological treatment for BD has an impact on cognitive function.[25] In the general population, long-term benzodiazepine use has been

Significant outcomes

- In this sample of patients with Older-Age Bipolar Disorder, psychiatric characteristics, cardiovascular risk factors and benzodiazepine use were associated with cognitive performance.
- Our findings stress the importance for clinicians to prevent psychiatric admissions, metabolic syndrome and incorrect use of benzodiazepines in BD patients, as these factors could negatively impact cognitive functioning.
- Individuals with Older-Age Bipolar Disorder should preferably be treated using an integrated care model. Treatment should include reduction of cardiovascular risk factors, lifestyle interventions and reduction of benzodiazepine use.

Limitations

- As cross-sectional data were used for this study, we cannot draw definite causal inferences from the analyses.
- The forward selection procedure might have produced overfitting and/or suppressor effects. Suppressor effects might occur when a determinant is only significant when another determinant is held constant.
- Some selection bias might have occurred since the subset of respondents with available neuropsychological test data differed in some ways (more lithium use, less cardiovascular risk factors) from the sample that did not undergo a neuropsychological assessment.

found to cause only partly reversible impairments in several cognitive domains, including visuospatial ability, speed of processing and verbal learning.[26] Among BD patients, lithium appears to improve cognition, whereas antipsychotics and valproate are associated with worse cognitive performance.[25] Current evidence regarding medication use and cognition in BD is sparse and of limited methodological quality.[25]

1.1 | Aims of the study

To date, no study has investigated psychiatric characteristics, cardiovascular risk factors and psychotropic medication use at the same time in relation to cognitive functioning in BD. Also, previous studies on cardiovascular risk or medication and cognition were small ($N < 100$) or performed only one or two neuropsychological tests instead of a full neuropsychological assessment (NPA). The aim of this observational study was to explore which patient characteristics are related to cognitive performance in a sample of 172 OABD patients that all completed an extensive NPA. In this study, OABD was defined as individuals with BD of ≥50 years, as recommended by the ISBD Task Force on Older-Age Bipolar Disorder.[4] We hypothesized that cognitive variability in OABD is multifactorial, thus that not only psychiatric characteristics, but also cardiovascular and/or medication use characteristics play a role.

2 | MATERIAL AND METHODS

2.1 | Participants

This cross-sectional study used data from the Dutch Older Bipolars (DOBi) dynamic cohort study.[27] An OABD patient was defined as having a BD diagnosis and being aged 50 years or older. Baseline data were available for 227 individuals (see Figure 1 for a flowchart). The first baseline sample was included in 2010–2012 and consisted of 101 OABD patients aged 60 years or older. In 2017–2018, a new baseline wave was added to the cohort study, consisting of 126 OABD patients. For this second wave, the age limit was lowered to ≥50 years, as recommended by the ISBD Task Force for OABD in 2015, given the shorter life-span and higher medical burden in BD.[4] All patients received treatment at GGZ inGeest, an outpatient mental health facility in Amsterdam, the Netherlands, at the time of inclusion. Exclusion criteria were a dementia diagnosis, intellectual disability (IQ < 70), a language barrier, very poor cognitive functioning (MMSE < 18) or an insufficiently stable psychiatric condition to undergo the assessments (eg involuntary admission). Definite BD diagnosis was established through the MINI-plus, based on the DSM IV-TR.[28] Patients with Bipolar I Disorder (BD-I), Bipolar II Disorder (BD-II) or Bipolar Disorder Not Otherwise Specified (BD-NOS) were included. Of the 227 participants included in the first and

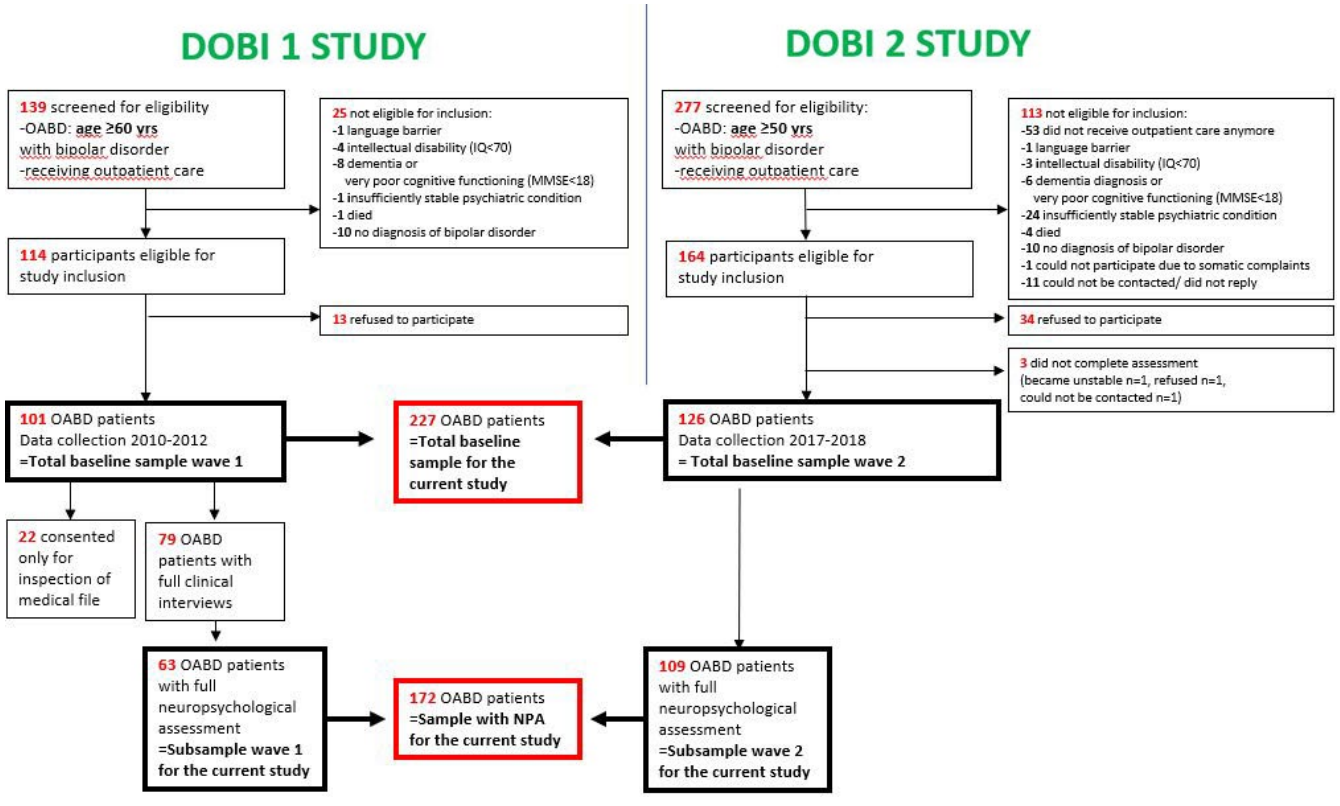

FIGURE 1 Flowchart of the DOBI cohort study, wave 1 and 2.

second wave, 172 agreed to undergo an extensive neuropsychological assessment (NPA) ($N = 63$ or 62.4% in 2012 and $N = 109$ or 86.5% in 2017–2018). The study was approved by the Medical Ethics Committee of VU University Medical Centre, Amsterdam, the Netherlands. The procedures are in accordance with the Helsinki Declaration of 1975.

2.2 | Outcome: cognitive performance

A comprehensive battery of neuropsychological assessments (NPA) was performed by a neuropsychologist or trained psychology students. The NPA consisted of 13 tests: the Trail Making test Part A,[29] Digit Span Forward and Digit Span Backward subtest of the Wechsler Adult Intelligence Scale (WAIS-III),[30] the 10 Word Test: total learning (trials 1 to 5), delayed recall, recognition (modified Rey Auditory Verbal Learning test),[31] Control Oral Word Association Test (COWAT, letters D-A-T),[32] the Animal Naming and Occupation Naming subtest of the Groningen Intelligence Test (GIT),[33] Test III (interference) of the Stroop Color Word Test (modified version),[34] the Trail Making Test Part B,[29] The Mazes (1 to 4) subtest of the Wechsler Intelligence Scale for Children (WISC),[35] and the Rule Shift Cards subtest of Behavioral Assessment of the Dysexecutive Syndrome (BADS).[36] The primary outcome was the composite cognitive score, which was the average score of the 13 neuropsychological test Z-scores. We planned to perform secondary analyses with multiple cognitive domains scores as secondary outcomes.

2.3 | Determinants

Apart from covariates age and education level, we selected 27 candidate determinants which could theoretically influence cognitive performance in patients with BD. This list was created by investigating which factors had previously been described as possible determinants of cognitive functioning in the literature, not only among BD patients, but also in the general population. The following variables were selected:

Psychiatric characteristics: Young Mania Rating Scale (YMRS)[37]; Centre for Epidemiologic Studies Depression Scale (CES-D)[38]; number of (hypo)manic episodes; number of depressive episodes; late onset (first episode ≥50 years); disease duration; BD type; Bipolarity Index[39]; five or more psychiatric admissions, psychotic features; current alcohol use; current problematic alcohol use; current recreational drug use; abuse during childhood or adolescence;
Cardiovascular risk factors: hypertension; obesity; waist circumference; lifetime (current or previous) smoking; diabetes mellitus; history of cardiovascular disease (CVD); dyslipidemia; metabolic syndrome;
Psychotropic medication use: current use of lithium; antipsychotics; anticonvulsants; antidepressants; benzodiazepines.

2.4 | Data collection, data measurement and definitions

Data were derived from a self-report questionnaire (QBP-NL; Questionnaire for Bipolar Illness, Dutch translation, based on[40] and[41]), the MINI-Plus,[28] a structured physical health interview, physical examination (measurement of blood pressure, weight, height and waist circumference), laboratory tests (random serum glucose, triglycerides, HDL-cholesterol), medication lists or a combination of these. All measurements were performed at baseline, around the same time as the neuropsychological assessment. The MINI-Plus[28] was assessed during a clinical interview by the patient's psychiatrist, a trained research assistant or psychology intern. The physical health interview was conducted by a trained doctor or trained research assistant. Detailed information on data collection, measurement and definitions of all investigated variables are available as Supplementary Data.

2.5 | Statistical analysis

2.5.1 | Descriptive statistics

A group comparison of patients with data from a neuropsychological assessment and those without was performed using Fisher's exact tests for dichotomous and categorical variables and Student's T tests for continuous variables.

2.6 | Exploratory factor analysis

First, the neuropsychological test data were explored by visual inspection of histograms, boxplots, stem-and-leaf plots, and Q-Q plots. For the exploratory factor analysis only, extreme raw test scores (≥4 SD or ≤-4 SD) were deleted pairwise per test. The raw test scores of the Trailmaking Test A, Trailmaking Test B, Stroop Test 3 and Mazes test were reversed such that a positive raw score indicated better cognitive performance for all tests. In order to explore which cognitive domains were represented by each neuropsychological test, an exploratory factor analysis was performed on the 13 cognitive measures using the raw test scores and listwise deletion (complete case analysis). We used Principal Component analysis (PCA) with oblique rotation (Direct Oblimin) as the final factors were expected to be intercorrelated. Factors were

extracted on the basis of high primary loadings on one factor, lower loadings on the other factors, eigenvalues (>0.7), observation of the screeplot and theoretical interpretability of the factors.[42]

2.7 | Primary outcome: the composite cognitive score

For each of the 13 neuropsychological tests, raw test scores were transformed into Z-scores by using the sample mean and standard deviation as a reference. The Z-scores of the Digit Span Forward, Digit Span Backward, the 10 Word Test, the COWAT, Animal and Occupation naming, and the BADS Rule Shift Cards subtest were reversed such that a positive Z-score indicated better cognitive performance for all tests. In case of an extreme Z-score, Z-scores were truncated at $z = -4.0$ or $z = +4.0$. The overall composite cognitive score, the main outcome of this study, was calculated by taking the mean of the 13 neuropsychological test Z-scores.

2.8 | Main analysis: a multiple linear regression model for composite cognitive score

All regression analyses were restricted to the study group with data from a neuropsychological assessment. A stepwise multiple linear regression model was built. As a first step, each of the 27 candidate determinants was entered in a separate linear regression model together with age and education level (forced entry) and the composite cognitive score as the outcome variable (covariate-adjusted analyses). From these 27 analyses, determinants with $p < 0.30$ were pre-selected. This was done to reduce the risk of suppressor effects during the forward selection procedure (ie selection of a determinant that is only significant when another determinant is held constant). Second, a forward selection procedure with $p < 0.1$ as entry criterion was performed using the pre-selected variables from the covariate-adjusted analyses with the composite cognitive score as the outcome variable. Multicollinearity among two variables was defined as a high correlation coefficient ($r > 0.7$) or a variance inflation factor (VIF) of >2. In case of multicollinearity among two variables, the weakest determinant of the two was excluded from further analyses.

2.9 | Secondary analyses: multiple linear regression models for cognitive domains

The factors extracted from the exploratory factor analysis represented four theoretical cognitive domains. For each of these, a domain cognitive score was calculated by taking the mean of those neuropsychological test Z-scores that loaded onto the respective cognitive domain. Several multiple linear regression models were created with the pre-selected candidate determinants and domain cognitive scores as outcome variables. For these analyses, the same forward selection procedure was used as in the main analysis. All data analyses were conducted with SPSS v25.[43]

3 | RESULTS

3.1 | Descriptive statistics

A full NPA was completed in 172 participants (75.8%). For most variables (including age, sex, education level) the sample with NPA ($N = 172$) was similar to the sample without NPA ($N = 55$, Table 1). The sample with NPA used lithium more often ($p < 0.001$). On the other hand, those without NPA data used anticonvulsants more often ($p = 0.011$) and had a higher prevalence of a 'very high' waist circumference ($p = 0.043$) and diabetes mellitus ($p = 0.041$).

3.2 | Exploratory factor analysis

Table 2 shows the factor loadings, eigenvalues and explained variances of the exploratory factor analysis on the 13 neuropsychological tests. Initially, the exploratory factor analysis retained five factors. The first four factors clearly represented theoretical cognitive domains. These four factors were interpreted as verbal fluency (Occupation Naming, Animal Naming, COWAT D-A-T test), executive functioning (Mazes, Trailmaking Test A & B, Stroop Test 3), attention (Digit Span Forward and Digit Span Backward) and learning & memory (10 Word Test Total Learning, Delayed Recall, Recognition), respectively. These four factors together explained 68.3% of the total variance. The fifth factor only contained the BADS Rule Shift Cards test, which according to the literature also tests executive function.[36] This test was not selected for a domain cognitive score, as this fifth factor did not provide sufficient additional information (Total Eigenvalue <1, explaining 6.25% of total variance) and theoretically did not cover an additional cognitive domain.

3.3 | Cognitive performance

The composite cognitive score, a composite score reflecting global cognitive functioning based on 13 neuropsychological tests, was calculated from raw group means and standard deviations (Table 3). For a few participants, the analysis of TMT-A, TMT-B, 10 words test recognition, The Mazes, and Stroop test III revealed extreme scores, that is more than four standard deviations (SDs) below the mean, and for this reason,

TABLE 1 Baseline characteristics of the total sample and comparison of the subgroups with and without an extensive neuropsychological assessment (NPA)

	Total sample max $N = 227$	Sample with NPA max $N = 172$	Sample without NPA max $N = 55$	p-value
	Mean (SD), range or % (N)	Mean (SD), range or % (N)	Mean (SD), range or % (N)	Fisher's exact test or Student's t test
Demographics				
Age (at assessment)	66.0 (7.6), 51.3–87.4	65.5 (7.5), 51.3–86.8	67.4 (7.8), 53.5–87.4	0.09
Sex, female	55.1% (125)	54.1% (93)	58.2% (32)	0.64
Level of education, scale 1–5	3.4 (1.2), 1–5	3.4 (1.2), 1–5	3.3 (1.4), 1–5	0.67
Low education level	26.9% (52)	25.6% (42)	34.5% (10)	0.37
High education level	49.7% (96)	49.4% (81)	51.7% (15)	0.84
Psychiatric characteristics				
Bipolar Disorder Type				0.27
Type 1	56.4% (128)	55.8% (96)	58.2% (32)	
Type 2	43.2% (98)	44.2% (76)	40.0% (22)	
NOS	0.4% (1)	0% (0)	1.8% (1)	
YMRS	4.7 (6.2), 0–33	4.3 (5.7), 0–33	7.9 (9.8), 0–31	0.17
CES-D	14.8 (10.2), 0–51	15.1 (10.2), 0–49	13.1 (10.3), 0–51	0.35
Bipolarity Index	65.3 (16.8), 22–100	66.2 (16.6), 34–100	62.6 (17.4), 22–100	0.18
Age of onset	31.3 (15.0), 4–76	31.3 (15.8), 4–76	31.1 (12.2), 12–66	0.90
Late onset, first mood episode ≥50 yrs	15.0% (34)	15.7% (27)	12.7% (7)	0.67
Disease duration, in yrs	34.7 (13.8), 0.8–66.8	34.2 (14.4), 0.8–66.8	35.4 (11.8), 6.1–57.9	0.24
Number of (hypo) manic episodes	7.9 (9.8), 1–50	8.1 (10.0), 1–50	7.2 (9.1), 1–50	0.53
Number of depressive episodes	9.8 (11.4), 0–50	10.5 (11.9), 0–50	7.9 (9.9), 0–50	0.18
Psychiatric admissions, five or more	20.4% (39)	19.1% (31)	27.6% (8)	0.32
History of psychotic features	57.3% (129)	58.1% (100)	54.7% (29)	0.75
Abuse during childhood or adolescence	48.7% (92)	50.3% (81)	39.3% (11)	0.31
Alcohol use, current	71.8% (145)	72.9% (124)	65.6% (21)	0.40
Problematic alcohol use, current	18.5% (35)	20.6% (33)	6.9% (2)	0.12
Lifetime recreative drug use	21.6% (43)	23.4% (39)	12.5% (4)	0.24
Cardiovascular risk factors				
Hypertension	68.7% (156)	69.8% (120)	65.5% (36)	0.62
Obesity, BMI >30	17.2% (27)	16.5% (21)	20.0% (6)	0.60

(Continues)

TABLE 1 (Continued)

	Total sample max $N = 227$	Sample with NPA max $N = 172$	Sample without NPA max $N = 55$	p-value
	Mean (SD), range or % (N)	Mean (SD), range or % (N)	Mean (SD), range or % (N)	Fisher's exact test or Student's t test
Waist circumference, very high	56.3% (111)	52.3% (79)	69.6% (32)	**0.043***
Lifetime smoking	74.0% (168)	73.8% (127)	74.5% (41)	1.000
Diabetes mellitus	17.6% (40)	14.5% (25)	27.3% (15)	**0.041***
History of CVD	23.3% (47)	20.6% (35)	37.5% (12)	0.07
Dyslipidemia	44.9% (102)	43.0% (74)	50.9% (28)	0.35
Metabolic syndrome	33.5% (76)	31.4% (54)	40.0% (22)	0.25
Psychotropic medication use				
Lithium	54.3% (121)	62.1% (105)	29.6% (16)	**<0.001*****
Antipsychotics	40.8% (84)	41.4% (65)	38.8% (19)	0.87
Anticonvulsants	31.8% (70)	26.9% (45)	47.2% (25)	**0.011***
Antidepressants	28.8% (59)	26.3% (41)	36.7% (18)	0.21
Benzodiazepines	40.0% (82)	37.0% (57)	49.0% (25)	0.14

Notes: Bold indicates statistical significance. *$p < 0.05$. **$p < 0.01$. ***$p < 0.001$. Relative percentages, excluding missings, are shown.

See supplementary table for information on data collection and definition for each of the determinants.

Abbreviations: NPA, neuropsychological assessment; SD, standard deviation; *N*, Number of participants; NOS, Not otherwise specified; YMRS, Young Mania Rating Scale; CES-D, Centre for Epidemiologic Studies Depression Scale; BMI, Body Mass Index; CVD, cardiovascular disease.

TABLE 2 Factor loadings, eigenvalues and explained variances of the exploratory factor analysis on the 13 neuropsychological tests.

	Factors				
	1	2	3	4	5
Neuropsychological tests					
Occupation Naming	**0.880**	0.039	0.026	−0.016	−0.037
Animal Naming	**0.826**	0.047	−0.045	0.077	0.048
Control Oral Word Association Test (D-A-T)	**0.773**	−0.030	0.063	0.012	0.031
Mazes	0.092	**0.926**	−0.113	−0.087	−0.188
Trailmaking Test B	0.082	**0.738**	0.017	0.067	0.114
Trailmaking Test A	−0.037	**0.653**	0.243	0.085	0.141
Stroop Test 3	−0.065	**0.549**	0.099	0.120	0.296
Digit Span Forward	0.063	−0.077	**0.925**	−0.069	−0.073
Digit Span Backward	−0.009	0.096	**0.790**	0.083	0.010
10 Word Test - Recognition	−0.088	−0.018	−0.030	**0.929**	−0.100
10 Word Test - Delayed Recall	0.170	0.004	0.020	**0.787**	0.005
10 Word Test - Total Learning	0.179	0.050	0.067	**0.647**	0.172
BADS Rule Shift Cards	0.069	0.002	−0.064	−0.049	**0.962**
Total Eigenvalues	5.199	1.505	1.142	1.027	0.812
% of variance	40.00	11.58	8.79	7.90	6.25
Cumulative %	40.00	51.57	60.36	68.26	74.50

Notes: Bold indicates the primary loading for each item.

these Z-scores were truncated at $z = -4.0$. The Z-scores for Digit Span Forward and Animal Naming were truncated at $z = +4.0$. Significant variation in cognitive performance was observed in our sample, with the composite cognitive score ranging from −1.61 to +1.12 and a standard deviation of 0.64. The domain cognitive scores were calculated by taking

the average of the individual tests Z- scores covering that domain (Table 3). The BADS Rule Shift Cards test was not used for formation of the domain cognitive scores.

3.4 | Main analysis: determinants of cognitive performance

3.4.1 | Covariate-adjusted analyses

First, all 27 possible determinants were analysed individually, controlling for age and education level (Table 4). From these analyses, 14 determinants were pre-selected ($p < 0.30$): number of (hypo)manic episodes ($B = 0.005$, $p = 0.29$), number of depressive episodes ($B = 0.008$, $p = 0.05$), late onset ($B = 0.34$, $p = 0.006$), disease duration ($B = -0.005$, $p = 0.07$), BD type 1 ($B = -0.12$, $p = 0.18$), Bipolarity Index ($B = -0.004$, $p = 0.12$), five or more psychiatric admissions ($B = -0.34$, $p = 0.002$), history of psychotic features ($B = -0.12$, $p = 0.19$), very high waist circumference ($B = -0.11$, $p = 0.24$), lifetime smoking ($B = 0.20$, $p = 0.04$), dyslipidemia ($B = -0.21$, $p = 0.02$), metabolic syndrome ($B = -0.23$, $p = 0.01$), use of antipsychotics ($B = -0.18$, $p = 0.05$) and use of benzodiazepines ($B = -0.23$, $p = 0.01$). The variables dyslipidemia and metabolic syndrome were multicollinear. Dyslipidemia was excluded from further analyses as this was the weakest determinant of the two (smallest Beta). Disease duration was not pre-selected due to multicollinearity with the variable late onset. This resulted in 12 pre-selected variables.

3.4.2 | Multiple linear regression model

A forward stepwise selection procedure was performed on the 12 pre-selected variables. In addition to age and education level, the final model included number of (hypo) manic episodes ($B = 0.010$, $p = 0.065$), number of depressive episodes ($B = 0.009$, $p = 0.044$), late onset ($B = 0.30$, $p = 0.036$), five or more psychiatric admissions ($B = -0.33$, $p = 0.010$), lifetime smoking ($B = 0.18$, $p = 0.10$), metabolic syndrome ($B = -0.18$, $p = 0.077$) and use of benzodiazepines ($B = -0.25$, $p = 0.014$). Late onset and number of depressive episodes were significantly related to a higher composite cognitive score, indicating better overall cognition. Five or more psychiatric admissions and benzodiazepine use were significantly related to a lower composite cognitive score, indicating worse cognitive performance. The final multiple regression model included 125 individuals and explained 43.0% of the variance in composite cognitive score.

TABLE 3 Cognitive performance: raw test scores, domain cognitive scores and composite cognitive scores for the total sample.

		N	Mean	Standard deviation	Range
1	Digit Span Forward (nr. of digits)	169	5.8	1.6	2–14
2	Digit Span Backward (nr. of digits)	167	4.1	1.3	2–9
	Domain cognitive score: Attention	**169**	**−0.0001**	**0.88**	**−1.94 – 3.47**
3	10 Word Test - Total learning (total nr. of words correct, trial 1–5)	170	30.6	8.2	11–48
4	10 Word Test - Delayed recall (nr. of words correct out of 10)	171	4.9	2.5	0–10
5	10 Word Test - Recognition (nr. correct out of 20)	170	18.2	2.2	5–20
	Domain cognitive score: Learning and memory	**171**	**0.003**	**0.82**	**−2.62 – 1.58**
6	Control Oral Word Association Test (D-A-T) (Total nr. of words)	168	32.2	12.5	8–60
7	Animal Naming (Total nr. of words)	172	20.6	6.3	8–49
8	Occupation Naming (Total nr. of words)	172	15.8	5.3	4–30
	Domain cognitive score: Verbal fluency	**172**	**−0.002**	**0.87**	**−2.00 – 2.20**
9	Trail Making Test A (in sec)	171	53.5	29.1	19–255
10	Trail Making Test B (in sec)	166	137.0	95.6	43–564
11	Modified Stroop Test, Test 3 (in sec)	166	56.4	36.6	19–406
12	Mazes (total of 4 mazes, in sec)	164	113.3	90.9	27–500
	Domain cognitive score: Executive functioning	**172**	**−0.011**	**0.77**	**−3.35 – 0.89**
13	BADS Rule Shift Cards (score 0–4)	170	3.1	1.0	0–4
	Composite cognitive score	**172**	**−0.003**	**0.64**	**−1.61 – 1.12**

TABLE 4 Main analyses: Determinants of the composite cognitive score.

	Covariate-adjusted models		Final multivariable model $N = 125$, adjusted $R^2 = 0.430$			
	Composite cognitive score		Composite cognitive score			
	Beta	***p*-value**	**Beta**	**SE_b**	**95% CI**	***p*-value**
Covariates						
Age (in years)			−0.039	0.007	−0.052 to −0.026	<0.001***
Education level (continuous, scale 1–5)			0.11	0.040	0.034 to 0.19	<0.005**
Psychiatric characteristics						
1. YMRS	−0.003	0.73				
2. CES-D	−0.004	0.38				
3. Number of (hypo)manic episodes	**0.005**	**0.29**	0.010	0.005	<0.001 to 0.022	0.065
4. Number of depressive episodes	**0.008**	**0.05***	0.009	0.005	<0.001 to 0.019	0.044*
5. Late Onset (first mood episode ≥50 yrs)	**0.34**	**0.006****	0.30	0.14	0.019 to 0.58	0.036*
6. Disease duration (in years)	−0.005	0.07†				
7. BD type, type 1 (vs. type 2 and NOS)	**−0.12**	**0.18**				
8. Bipolarity Index (scale 0–100)	**−0.004**	**0.12**				
9. Psychiatric admissions, five or more	**−0.34**	**0.002****	−0.33	0.12	−0.57 to −0.080	0.010*
10. History of psychotic features	**−0.12**	**0.19**				
11. Alcohol use, current	0.081	0.40				
12. Problematic alcohol use, current	−0.039	0.72				
13. Lifetime recreational drug use	0.11	0.31				
14. Abuse during childhood or adolescence	<0.001	1.00				
Cardiovascular risk factors						
15. Hypertension	0.022	0.82				
16. Obesity (BMI >30)	0.013	0.91				
17. Waist circumference, very high	**−0.11**	**0.24**				
18. Lifetime smoking	**0.20**	**0.04***	0.18	0.11	−0.035 to 0.39	0.10
19. Diabetes mellitus	−0.001	1.00				
20. History of CVD	−0.030	0.78				
21. Dyslipidemia	−0.21	0.02*†				
22. Metabolic syndrome	**−0.23**	**0.01***	−0.18	0.10	−0.39 to 0.020	0.077
Psychotropic medication use						
23. Lithium use	−0.023	0.80				
24. Use of antipsychotics	**−0.18**	**0.05**				
25. Use of benzodiazepines	**−0.23**	**0.01***	−0.25	0.098	−0.44 to −0.051	0.014*
26. Use of anticonvulsants	−0.070	0.50				
27. Use of antidepressants	−0.073	0.47				

Notes: Bold indicates that the determinant was pre-selected for the forward selection procedure ($p < 0.30$).

Abbreviations: SE_b, Standard Error of Beta; 95% CI, 95% Confidence Interval; YMRS, Young Mania Rating Scale; CES-D, Centre for Epidemiologic Studies Depression Scale; BD, Bipolar Disorder; NOS, Not Otherwise Specified; BMI, Body Mass Index; CVD, cardiovascular disease.

*$p < 0.05$ **$p < 0.01$ ***$p < 0.001$. See supplementary table for information on data collection and definition for each of the determinants.

†Disease duration was not pre-selected due to multicollinearity with Late Onset. Dyslipidemia was not pre-selected due to multicollinearity with Metabolic Syndrome.

3.5 | Secondary analyses: determinants of four cognitive domain cognitive scores

Together with age and education level, the 12 pre-selected determinants were also explored in multiple linear regression models with the cognitive domain cognitive scores as outcome variables using a forward selection procedure (Table 5). Number of depressive episodes was associated with better verbal fluency ($B = 0.017$, $p = 0.004$). Late onset was associated with better learning and memory ($B = 0.51$, $p = 0.004$).

TABLE 5 Secondary analyses: Multiple linear regression models with the cognitive domain cognitive scores as outcome variables.

	Attention		Learning and memory		Verbal fluency		Executive functioning	
	$N = 131$, adjusted $R^2 = 0.202$		$N = 153$, adjusted $R^2 = 0.227$		$N = 144$, adjusted $R^2 = 0.229$		$N = 127$, adjusted $R^2 = 0.318$	
	Beta	*p*-value	Beta	*p*-value	Beta	*p*-value	Beta	*p*-value
Covariates								
Age (in years)	−0.024	0.012*	−0.043	<0.001***	−0.032	<0.001***	−0.041	<0.001***
Education level (continuous, scale 1–5)	0.15	0.006**	0.15	0.003**	0.20	<0.001***	0.096	0.076
Psychiatric characteristics								
Number of (hypo)manic episodes							0.011	0.062
Number of depressive episodes	0.009	0.095			0.017	0.004**		
Late Onset (first mood episode ≥50 yrs)			0.51	0.004**				
BD type, type 1 (vs. type 2 and NOS)								
Bipolarity Index (scale 0–100)								
Psychiatric admissions, five or more							−0.47	0.003**
History of psychotic features	−0.38	0.008**						
Cardiovascular risk factors								
Waist circumference, very high							−0.25	0.051
Lifetime smoking							0.28	0.046*
Metabolic syndrome			−0.22	0.093	−0.31	0.031*		
Psychotropic medication use								
Use of antipsychotics			−0.22	0.077				
Use of benzodiazepines	−0.41	0.004**					−0.34	0.008**

See supplementary table for information on data collection and definition for each of the determinants.

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

Five or more psychiatric admissions were associated with worse executive functioning ($B = -0.47$, $p = 0.003$). A history of psychotic features was associated with worse attention ($B = -0.38$, $p = 0.008$). Lifetime smoking was related to better executive functioning ($B = 0.28$, $p = 0.046$). Metabolic syndrome was significantly associated with worse verbal fluency ($B = -0.31$, $p = 0.031$). Use of benzodiazepines was associated with decreased attention ($B = -0.41$, $p = 0.004$) and worse executive functioning ($B = -0.34$, $p = 0.008$). BD type 1 and Bipolarity Index were not significantly associated with any of the cognitive domain cognitive scores.

4 | DISCUSSION

In this sample of 172 individuals with Older-Age Bipolar Disorder (OABD), we investigated a large range of candidate determinants of cognitive performance by creating a multiple linear regression model. The main outcome was a composite cognitive score, which represents overall cognitive functioning based on 13 neuropsychological tests. The final model explained 43.0% of the variance in composite cognitive score and included demographics (age, education level), psychiatric characteristics (number of depressive episodes, number of (hypo)manic episodes, late onset, five or more psychiatric admissions), cardiovascular risk factors (lifetime smoking, metabolic syndrome) and psychotropic medication use (current use of benzodiazepines). The strongest determinants (largest Beta's) were late-onset (associated with better cognitive performance), five or more psychiatric admissions, and benzodiazepine use (both related to worse performance). Cognitive variability in OABD thus seems multifactorial: not only psychiatric factors, but also the presence of cardiovascular risk factors and psychotropic medication use play a role.

To our knowledge, this is the first study that has explored several psychiatric characteristics, cardiovascular risk factors

and psychotropic medication use factors together in relation to cognitive performance in OABD patients. Barbosa et al. (2018) measured several determinants, including clinical factors, comorbidities, medication use and inflammatory markers, but could not investigate all of them together in a multivariate model due to a small sample size ($N = 20$).[44] Schouws et al. (2010) also described associations between vascular burden and cognitive functioning in OABD, but the current study measured cardiovascular risk factors in more detail using physical examination and laboratory assessment instead of self-report.[24] Also, the current study assessed cognitive performance based on an extensive neuropsychological assessment and investigated overall cognitive performance as well as performance on specific cognitive domains. This is in contrast to several previous studies on cognition in OABD, which used one or two neuropsychological tests, a clinical cognitive rating scale or an ICD dementia diagnosis instead of a full NPA.[22,45,46]

4.1 | The final multivariable model

Together with age and education level, the variables number of depressive episodes, number of (hypo)manic episodes, late-onset, five or more psychiatric admissions, lifetime smoking, metabolic syndrome and current use of benzodiazepines explained 43.0% of the variance in composite cognitive score. We compared our results to studies that also examined combinations of determinants in relation to cognitive functioning in BD. In a cross-sectional linear regression model by Mora et al. (2017), BMI group (normal/overweight/obese), age and premorbid IQ together explained 56% of variance in global cognitive functioning.[47] Barbosa et al. (2018) reported that MMSE, years of study and IL6 plasma levels explained 72% of a global cognitive performance score.[44] Forcada et al. (2015) found that a combination of age at onset, duration of illness and a cognitive reserve score explained 55.2% of the variance in executive functioning.[48] The current study is line with these previous studies in showing that combinations of premorbid, psychiatric and cardiovascular characteristics together explain a high percentage of the variance in cognitive performance. Our study provides additional insight into which determinants have the strongest relationship with cognitive functioning. In particular, our data show that metabolic syndrome is a stronger determinant than BMI, whereas five or more psychiatric admissions seems a stronger determinant than disease duration, number of episodes, childhood trauma or history of psychosis. Also, we show that these determinants influence different cognitive domains. Future prospective studies could evaluate which combination of determinants has most predictive value and try to create a multifactorial risk score for cognitive dysfunction in BD.

We speculate that the determinants identified in this study influence cognitive performance in OABD in distinct ways. Some risk factors may cause permanent and irreversible brain damage leading to cognitive dysfunction, whereas others only influence short-term performance on a neuropsychological test. Although we cannot draw causal inferences from our cross-sectional data, we will describe below potential mechanisms for each identified risk factor based on previously published literature.

4.2 | Psychiatric characteristics

In the final multiple regression model, five or more psychiatric hospital admissions were associated with worse cognitive performance. More specifically, five or more psychiatric admissions were strongly related to worse executive functioning. This finding is in line with Schouws et al. (2010), who found an independent association between the number of psychiatric admissions and poorer cognitive performance in OABD.[24] The finding is also consistent with the large retrospective study by Lin et al. (2020), who found that higher frequency of psychiatric admissions for manic/mixed and depressive episodes increased the risk of incident dementia in more than 20,000 individuals aged 45–80 years with BD.[46]

In our final model, the number of depressive and (hypo) manic episodes were weakly related with better cognitive functioning. Previous literature postulates that each affective episode is accompanied by the accumulation of allostatic load, oxidative stress, pro-inflammatory mediators and alteration of neurotrophins,[10,11] which may lead to structural and/or functional changes and ultimately to brain damage and cognitive decline. Our data do not provide evidence for the hypothesis that each affective episode is neurotoxic. Rather, we speculate that BD severity is indeed related to cognitive functioning, but that the number of psychiatric admissions is a better measure for BD disease severity than the overall number of episodes. For example, some BD patients experience several hypomanic episodes a year, leading to a high total number of episodes but no admissions, whereas others have a history of only a few, very severe manic episodes for which admission was necessary each time. In the Netherlands, a psychiatric hospital admission represents a very severe affective episode, as extensive outpatient care is readily available. Future studies should investigate which is more deleterious for cognitive functioning: number, duration or severity of episodes. Alternatively, there is a possibility that not the psychiatric admission itself is deleterious for cognitive performance, but other factors connected to a psychiatric hospital admission, such as psychotropic polypharmacy, more benzodiazepine use or a sedentary lifestyle.

We identified an association between late-onset and better cognitive performance, which is in contrast with a study

by Schouws et al. (2009), which found that late onset was related to more severe cognitive impairment.[5] Possibly, the descrepencies could be explained by differences in sampling. Schouws et al. (2009) studied 119 individuals, of which 60 (50.4%) with late onset.5 Our sample of 172 BD patients included 27 individuals with late onset (15.7%). Schouws et al. (2009) used a definition of ≥40 years for late onset, whereas we used ≥50 years.5 Late-onset BD patients are a heterogeneous group, including individuals with preclinical dementia as well as individuals with a mild subclinical course of the disease that only manifests later in life.[49] In our sample, the late-onset group was significantly older ($M = 71.5$) than the early-onset group ($M = 65.0$, $p = <0.001$) and had a lower education level ($M = 3.5$ vs. $M = 3.0$, $p = 0.04$). As we excluded patients with dementia diagnosis, a MMSE < 18, or IQ < 70, we think our late-onset group could be 'healthy survivors'. This is also reflected by the finding that late onset was associated with better learning and memory in our secondary analyses. Longitudinal studies with a large, diverse sample of individuals with late-onset BD are necessary to draw definite conclusions on the relationship between age of onset and cognitive functioning.

4.3 | Cardiovascular risk factors

It is striking that in our study lifetime smoking was related to a higher composite cognitive score, indicating a better cognitive performance. This finding is counterintuitive, as previous literature has consistently shown that smokers have an increased risk of any type of dementia.[50,51] We believe that the positive effect of smoking on cognition in this study could be a spurious 'survival effect'. Life expectancy in individuals with BD is about 9–20 years shorter than the general population,[52-54] so it is possible that we selected for healthy OABD respondents in our sample, that in some way were resilient to ('survived') the deleterious effects of smoking. A previous review also suggests that less somatic comorbidity is observed in OABD than in the younger adult BD population due to this 'survivor phenomenon'.[55] Also in the early 1990s, results from case-control and family studies wrongly suggested a protective effect of smoking on dementia due to biased study populations.[56]

Metabolic syndrome was associated with worse cognitive performance in the final multivariable model, although not statistically significant. In the covariate-adjusted models, both dyslipidemia and metabolic syndrome were significantly associated with a poorer cognitive functioning. These results are in line with Gildengers et al. (2010), who described a relationship between vascular burden and a lower MMSE score in OABD.[22] Also, Schouws et al. (2010) found a relationship between the presence of vascular risk factors and cognitive functioning in the domains of attention and memory.[24] Moreover, a recent systematic review by Bora et al. (2019) reported that obesity and related cardiovascular risk factors were significantly associated with more severe cognitive and brain imaging abnormalities in BD.[16] In non-BD communities, cardiovascular disease is an important risk factor for Mild Cognitive Impairment and dementia, due to formation of small vessel disease, including plaque formation, cerebral hypoperfusion, lacunar infarcts, white matter lesions, haemorrhages and microbleeds.[57,58] This is a process of years, if not decades. We suggest that comorbid cardiovascular risk factors can play an important role in the development of cognitive dysfunction in BD patients, similarly to non-BD individuals.

4.4 | Psychotropic medication use

In our final multiple regression model, current use of benzodiazepines was strongly related to poorer cognitive function. It is possible that the use of benzodiazepines only had a short-term negative effect on test performance. Our secondary analyses showed that benzodiazepine use was associated with poorer attention and executive functioning, a well-known side effect of these drugs. Thus, these effects on cognitive performance may be (partly) reversible. In the general population, long-term benzodiazepine use causes impairments in several cognitive domains, including visuospatial ability, speed of processing and verbal learning.[26] Future longitudinal studies could investigate the reversibility of these effects. Also, it could be interesting to evaluate if sleep problems, for which benzodiazepines are often prescribed, are related to cognitive performance in OABD.

4.5 | Strengths and limitations

To our knowledge, this is the first study that examined a large range of potential candidate determinants, including psychiatric characteristics, cardiovascular risk factors and psychotropic medication use in relation to cognitive functioning and in relation to each other. Also, cognitive functioning was assessed by an extensive NPA, resulting in precise information on general cognitive functioning as well as performance per cognitive domain. Cardiovascular risk factors were thoroughly assessed by integration of information from laboratory measurements, physical measurements, self-report and medication use. The most important limitation of this study is that we could not create a true prediction model as our data are cross-sectional. Thus, we cannot ensure that the temporality assumption (that the dependent variable has occurred after the independent variables) has been met in our models. However, this seems rather straightforward for the variables age and education level. Yet, a possibility exists

that decreased cognitive performance is the cause rather than the consequence of psychiatric admissions, benzodiazepine use and metabolic syndrome. In addition, the forward selection procedure might have produced overfitting and/or suppressor effects. These suppressor effects occur when a determinant is only significant when another determinant is held constant. To reduce the risk of this form of bias, we pre-selected 12 potentially important determinants out of the 27 initially investigated for the forward selection procedure. Finally, some selection bias might have occurred since the sample with an NPA differed in some ways from the sample without NPA data (more lithium use, less cardiovascular risk factors). However, we believe the sample with NPA data was large enough ($N = 172$) and included sufficient cognitive heterogeneity.

4.6 | Implications

This study has important clinical implications. Our results suggest that cognitive dysfunction in BD patients may be the result of an accumulation of several distinct risk factors. Our data stress the importance for clinicians to prevent severe episodes requiring psychiatric admissions in BD patients. Treatment of cardiovascular risk factors and lifestyle intervention programmes should be offered using integrated care models, preferably already from the moment of BD diagnosis.[59] Also, it is important to reduce or stop benzodiazepine use in periods of euthymia, since this may aggravate cognitive performance. Future research should study (combinations of) determinants of cognitive functioning in further detail. For example, it is important to study these relationships in different phases of BD and in different age groups. Also, the influence of the dosing of psychotropic medication on cognition could be a topic of further (longitudinal) studies.

4.7 | Concluding remarks

This cross-sectional study examined determinants of cognitive performance in 172 patients with Older-Age Bipolar Disorder (OABD). The final model explained 43.0% of the variance in composite cognitive score and included demographics (age, education level), psychiatric characteristics (number of depressive episodes, number of (hypo)manic episodes, late-onset, five or more psychiatric admissions), cardiovascular risk factors (lifetime smoking, metabolic syndrome) and psychotropic medication use (current use of benzodiazepines). Cognitive variability in OABD thus seems multifactorial. Strategies aimed at improving cognition in BD should include cardiovascular risk management and minimizing benzodiazepine use.

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CONFLICT OF INTEREST

All authors declare no competing interests.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data concerning the present study are available upon reasonable request.

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REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th edn. Washington, DC: American Psychiatric Publishing; 2013.
2. Martínez-Arán A, Vieta E, Reinares M, et al. Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder. Am J Psychiatry. 2004;161(2):262-270. https://doi.org/10.1176/appi.ajp.161.2.262.
3. Cipriani G, Danti S, Carlesi C, Cammisuli DM, Di Fiorino M. Bipolar disorder and cognitive dysfunction: a complex link. J Nerv Ment Dis. 2017;205(10):743-756. https://doi.org/10.1097/NMD.0000000000000720.
4. Sajatovic M, Strejilevich SA, Gildengers AG, et al. A report on older-age bipolar disorder from the International Society for Bipolar Disorders Task Force. Bipolar Disord. 2015;17(7):689-704. https://doi.org/10.1111/bdi.12331.
5. Schouws SNTM, Comijs HC, Stek ML, et al. Cognitive impairment in early and late bipolar disorder. Am J Geriatr Psychiatry. 2009;17(6):508-515. https://doi.org/10.1097/JGP.0b013e31819e2d50.
6. Bourne C, Aydemir Ö, Balanzá-Martínez V, et al. Neuropsychological testing of cognitive impairment in euthymic bipolar disorder: An individual patient data meta-analysis. Acta Psychiatr Scand. 2013;128(3):149-162. https://doi.org/10.1111/acps.12133.
7. Rubinsztein JS, Sahakian BJ, O'Brien JT. Understanding and managing cognitive impairment in bipolar disorder in older people. BJPsych Adv. 2019;25(3):150-156. https://doi.org/10.1192/bja.2018.74.
8. Van Rheenen TE, Lewandowski KE, Bauer IE, et al. Current understandings of the trajectory and emerging correlates of cognitive impairment in bipolar disorder: An overview of evidence. Bipolar Disord. 2020;22(1):13-27. https://doi.org/10.1111/bdi.12821.
9. Samamé C, Martino DJ, Strejilevich SA. A quantitative review of neurocognition in euthymic late-life bipolar disorder. Bipolar Disord. 2013;15(6):633-644. https://doi.org/10.1111/bdi.12077.
10. Berk M, Kapczinski F, Andreazza AC, et al. Pathways underlying neuroprogression in bipolar disorder: Focus on inflammation, oxidative stress and neurotrophic factors. Neurosci Biobehav Rev. 2011;35(3):804-817. https://doi.org/10.1016/j.neubiorev.2010.10.001.

11. Kapczinski NS, Mwangi B, Cassidy RM, et al. Neuroprogression and illness trajectories in bipolar disorder. Expert Rev Neurother. 2017;17(3):277-285. https://doi.org/10.1080/14737175.2017.1240615.
12. Sánchez-Morla EM, López-Villarreal A, Jiménez-López E, et al. Impact of number of episodes on neurocognitive trajectory in bipolar disorder patients: A 5-year follow-up study. Psychol Med. 2019;49(8):1299-1307. https://doi.org/10.1017/S0033291718001885.
13. Jiménez E, Solé B, Arias B, et al. Impact of childhood trauma on cognitive profile in bipolar disorder. Bipolar Disord. 2017;19(5):363-374. https://doi.org/10.1111/bdi.12514.
14. Bora E. Neurocognitive features in clinical subgroups of bipolar disorder: A meta-analysis. J Affect Disord. 2018;229:125-134. https://doi.org/10.1016/j.jad.2017.12.057.
15. Schouws SNTM, Comijs HC, Dols A, Beekman ATF, Stek ML. Five-year follow-up of cognitive impairment in older adults with bipolar disorder. Bipolar Disord. 2016;18(2):148-154. https://doi.org/10.1111/bdi.12374.
16. Bora E, McIntyre RS, Ozerdem A. Neurococognitive and neuroimaging correlates of obesity and components of metabolic syndrome in bipolar disorder: A systematic review. Psychol Med. 2019;49(5):738-749. https://doi.org/10.1017/S0033291718003008.
17. Bai YM, Li CT, Tsai SJ, Tu PC, Chen MH, Su TP. Metabolic syndrome and adverse clinical outcomes in patients with bipolar disorder. BMC Psychiatry. 2016;16(1):448. https://doi.org/10.1186/s12888-016-1143-8.
18. Van Rheenen TE, McIntyre RS, Balanzá-Martínez V, Berk M, Rossell SL. Cumulative cardiovascular disease risk and triglycerides differentially relate to subdomains of executive function in bipolar disorder; preliminary findings. J Affect Disord. 2021;278:556-562. https://doi.org/10.1016/j.jad.2020.09.104.
19. Naiberg MR, Newton DF, Collins JE, Dickstein DP, Bowie CR, Goldstein BI. Elevated triglycerides are associated with decreased executive function among adolescents with bipolar disorder. Acta Psychiatr Scand. 2016;134(3):241-248. https://doi.org/10.1111/acps.12603.
20. Hui L, Yin XL, Chen J, et al. Association between decreased HDL levels and cognitive deficits in patients with bipolar disorder: a pilot study. Int J Bipolar Disord. 2019;7(1). https://doi.org/10.1186/s40345-019-0159-7.
21. Hubenak J, Tuma I, Bazant J. Association of arterial hypertension and cognitive impairment in euthymic bipolar disorder. Neuro Endocrinol Lett. 2015;36(3):294-300.
22. Gildengers AG, Mulsant BH, Al Jurdi RK, et al. The relationship of bipolar disorder lifetime duration and vascular burden to cognition in older adults. Bipolar Disord. 2010;12(8):851-858. https://doi.org/10.1111/j.1399-5618.2010.00877.x.
23. Dev SI, Eyler LT. Bipolar patients with vascular risk display a steeper age-related negative slope in inhibitory performance but not processing speed: a preliminary study. Am J Geriatr Psychiatry. 2017;25(3):272-276. https://doi.org/10.1016/j.jagp.2016.12.002.
24. Schouws SNTM, Stek ML, Comijs HC, Beekman ATF. Risk factors for cognitive impairment in elderly bipolar patients. J Affect Disord. 2010;125(1–3):330-335. https://doi.org/10.1016/j.jad.2009.12.004.
25. Xu N, Huggon B, Saunders K. Cognitive impairment in patients with bipolar disorder: impact of pharmacological treatment. CNS Drugs. 2020;34(1):29-46. https://doi.org/10.1007/s40263-019-00688-2.
26. Stewart SA. The effects of benzodiazepines on cognition. J Clin Psychiatry. 2005;66(Suppl 2):9-13.
27. Dols A, Rhebergen D, Beekman A, Kupka R, Sajatovic M, Stek ML. Psychiatric and medical comorbidities: results from a bipolar elderly cohort study. Am J Geriatr Psychiatry. 2014;22(11):1066-1074. https://doi.org/10.1016/j.jagp.2013.12.176.
28. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59(Suppl 20):22-33;quiz 34–57.
29. Reitan RM. Validity of the Trail Making Test as an Indicator of Organic Brain Damage. Percept Mot Skills. 1958;8:271-276. https://doi.org/10.2466/pms.1958.8.3.271.
30. Wechsler D. Manual for the Wechsler Adult Intelligence Scale – Revised. Cleveland OH: Psychological Corporation; 1981.
31. Rey A. L'Examen Clinique En Psychologie [Clinical Examination in Psychology]. Paris: Presses Universitaires de France; 1964.
32. Benton A, Hamsher K. Multilangual Aphasia Examination. Iowa City, Iowa: University of Iowa; 1976.
33. Luteijn F, van der Ploeg F. Handleiding Groninger Intelligentietest (GIT) [Manual Groningen Intelligence Test]. Lisse, The Netherlands: Swets & Zeitlinger; 1983.
34. Golden C. Stroop Color and Word Test: A Manual for Clinical and Experimental Uses. Wood Dale, IL: Stoelting Company; 1978.
35. Wechsler D. WISC-R Manual: Wechsler Intelligence Scale for Children-Revised. , UK edn. Windsor: NFER-Nelson; 1976.
36. Wilson B, Alderman N, Burgess P, Emslie H, Evan J. Behavioural Assessment of the Dysexecutive Syndrome. Bury St. Edmunds, England: Thames Valley Test Company; 1966.
37. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: Reliability, validity and sensitivity. Br J Psychiatry. 1978;133:429-435. https://doi.org/10.1192/bjp.133.5.429.
38. Radloff LS. The CES-D Scale: A self-report depression scale for research in the general population. Appl Psychol Measures. 1977;1:385-401. https://doi.org/10.1177/014662167700100306.
39. Sachs G. Strategies for improving treatment of bipolar disorder: Integration of measurement and management. Acta Psychiatr Scand Suppl. 2004;422:7-17. https://doi.org/10.1111/j.1600-0447.2004.00409.x.
40. Leverich GS, Nolen WA, Rush AJ, et al. The Stanley Foundation Bipolar Treatment Outcome Network: I. Longitudinal methodology. J Affect Disord. 2001;67(1–3):33-44. https://doi.org/10.1016/s0165-0327(01)00430-x.
41. Suppes T, Leverich GS, Keck PE, et al. The Stanley Foundation Bipolar Treatment Outcome Network – II. Demographics and illness characteristics of the first 261 patients. J Affect Disord. 2001;67(1–3):45-59. https://doi.org/10.1016/s0165-0327(01)00432-3.
42. Jolliffe IT. Discarding variables in a principal component analysis. I: artificial data. Appl Stat. 1972;21(2):160. https://doi.org/10.2307/2346488.
43. IBM SPSS Statistics Software for Windows, Version 25. IBM; 2017.
44. Barbosa IG, Ferreira RA, Rocha NP, et al. Predictors of cognitive performance in bipolar disorder: the role of educational degree and inflammatory markers. J Psychiatr Res. 2018;106:31-37. https://doi.org/10.1016/j.jpsychires.2018.09.003.
45. Belvederi Murri M, Respino M, Proietti L, et al. Cognitive impairment in late life bipolar disorder: Risk factors and clinical outcomes. J Affect Disord. 2019;257:166-172. https://doi.org/10.1016/j.jad.2019.07.052.
46. Lin S-H, Cheng C-M, Tsai S-J, et al. A population-based, nationwide longitudinal study of bipolar disorder with incident dementia

in Taiwan. Am J Geriatr Psychiatry. 2020;28(5):530-541. https://doi.org/10.1016/j.jagp.2019.10.016.
47. Mora E, Portella MJ, Martinez-Alonso M, et al. The impact of obesity on cognitive functioning in euthymic bipolar patients: A cross-sectional and longitudinal study. J Clin Psychiatry. 2017;78(8):e924-e932. https://doi.org/10.4088/JCP.16m10968.
48. Forcada I, Mur M, Mora E, Vieta E, Bartrés-Faz D, Portella MJ. The influence of cognitive reserve on psychosocial and neuropsychological functioning in bipolar disorder. Eur Neuropsychopharmacol. 2015;25(2):214-222. https://doi.org/10.1016/j.euroneuro.2014.07.018.
49. Depp CA, Jeste DV. Bipolar disorder in older adults: a critical review. Bipolar Disord. 2004;6(5):343-367. https://doi.org/10.1111/j.1399-5618.2004.00139.x.
50. Anstey KJ, Von Sanden C, Salim A, O'Kearney R. Smoking as a risk factor for dementia and cognitive decline: A meta-analysis of prospective studies. Am J Epidemiol. 2007;166(4):367-378. https://doi.org/10.1093/aje/kwm116.
51. Reitz C, Den Heijer T, Van Duijn C, Hofman A, Breteler MMB. Relation between smoking and risk of dementia and Alzheimer disease: The Rotterdam Study. Neurology. 2007;69(10):998-1005.
52. Crump C, Sundquist K, Winkleby MA, Sundquist J. Comorbidities and mortality in bipolar disorder: A Swedish national cohort study. JAMA Psychiatry. 2013;70(9):931-939. https://doi.org/10.1001/jamapsychiatry.2013.1394.
53. Kessing LV, Vradi E, McIntyre RS, Andersen PK. Causes of decreased life expectancy over the life span in bipolar disorder. J Affect Disord. 2015;180:142-147. https://doi.org/10.1016/j.jad.2015.03.027.
54. Laursen TM. Life expectancy among persons with schizophrenia or bipolar affective disorder. Schizophr Res. 2011;131(1–3):101-104. https://doi.org/10.1016/j.schres.2011.06.008.
55. Lala SV, Sajatovic M. Medical and psychiatric comorbidities among elderly individuals with bipolar disorder: A literature review. J Geriatr Psychiatry Neurol. 2012;25(1):20-25. https://doi.org/10.1177/0891988712436683.
56. Brayne C. Smoking and the brain. BMJ. 2000;320(7242):1087-1088. https://doi.org/10.1136/bmj.320.7242.1087.
57. Smith EE. Clinical presentations and epidemiology of vascular dementia. Clin Sci. 2017;131(11):1059-1068. https://doi.org/10.1042/CS20160607.
58. Wanleenuwat P, Iwanowski P, Kozubski W. Alzheimer's dementia: pathogenesis and impact of cardiovascular risk factors on cognitive decline. Postgrad Med. 2019;131(7):415-422. https://doi.org/10.1080/00325481.2019.1657776.
59. Firth J, Siddiqi N, Koyanagi AI, et al. The Lancet Psychiatry Commission: a blueprint for protecting physical health in people with mental illness. Lancet Psychiatry. 2019;6(8):675-712. https://doi.org/10.1016/S2215-0366(19)30132-4.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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