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Contrasting genetic burden for bipolar disorder: Early onset versus late onset in an older adult bipolar disorder sample

Laura Montejo [a,b,c], Brisa Sole [a,b,c], Giovanna Fico [a,b], Janos L. Kalman [d,e], Monika Budde [d], Urs Heilbronner [d], Vincenzo Oliva [a,b,f], Michele De Prisco [a,b], Sara Martin-Parra [a,b], Andrea Ruiz [a,b], Anabel Martinez-Aran [a,b,c,f], Kristina Adorjan [d,g], Peter Falkai [e,h,i], Maria Heilbronner [d], Mojtaba Oraki Kohshour [d,j], Daniela Reich-Erkelenz [d,e], Sabrina K. Schaupp [d], Eva C. Schulte [d,e,i,k,l], Fanny Senner [d,e,m], Thomas Vogl [d], Ion-George Anghelescu [n], Volker Arolt [o], Bernhard T. Baune [p,q,r], Udo Dannlowski [o], Detlef E. Dietrich [s,t,u], Andreas J. Fallgatter [v,w], Christian Figge [x], Georg Juckel [y], Carsten Konrad [z], Jens Reimer [aa,ab], Eva Z. Reininghaus [ac], Max Schmauß [ad], Jens Wiltfang [ae,af,ag], Jörg Zimmermann [ah], Eduard Vieta [a,b,c,f,*], Sergi Papiol [d,h,*], Thomas G. Schulze [d,i,ai,aj,1], Carla Torrent [a,b,c,1]

[a] Bipolar and Depressive Disorders Unit, Hospital Clinic de Barcelona, Barcelona, Spain
[b] Fundació Clínic per la Recerca Biomèdica-Institut d'Investigacions Biomèdiques August Pi i Sunyer (FCRB-IDIBAPS), Barcelona, Spain
[c] Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Instituto de Salud Carlos III, Madrid, Spain
[d] Institute of Psychiatric Phenomics and Genomics (IPPG), LMU University Hospital, LMU Munich, Munich, Germany
[e] Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich, Germany
[f] Departament de Medicina, Facultat de Medicina i Ciències de la Salut, Institut de Neurociencies (UBNeuro), Universitat de Barcelona (UB), Barcelona, Spain
[g] University Hospital of Psychiatry and Psychotherapy, University of Bern, Bern, Switzerland
[h] Max Planck Institute of Psychiatry, Munich, Germany
[i] DZPG (German Center for Mental Health), partner site Munich/Augsburg
[j] Department of Immunology, Faculty of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[k] Department of Psychiatry and Psychotherapy, Faculty of Medicine and University Hospital Bonn, University of Bonn, Bonn, Germany
[l] Institute of Human Genetics, University Hospital, Faculty of Medicine, University of Bonn, Bonn, Germany
[m] Centres for Psychiatry Suedwuerttemberg, Ravensburg, Germany
[n] Department of Psychiatry and Psychotherapy, Mental Health Institute Berlin, Berlin, Germany
[o] Institute for Translational Psychiatry, University of Münster, Münster, Germany
[p] Department of Psychiatry, Melbourne Medical School, The University of Melbourne, Melbourne, Australia
[q] The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Parkville, VIC, Australia
[r] Department of Psychiatry, University of Münster, Münster, Germany
[s] AMEOS Clinical Center Hildesheim, Hildesheim, Germany
[t] Center for Systems Neuroscience (ZSN), Hannover, Germany
[u] Department of Psychiatry, Medical School of Hannover, Hannover, Germany
[v] Department of Psychiatry and Psychotherapy, Tübingen Center for Mental Health (TüCMH), University of Tübingen, Tübingen, Germany
[w] German Center for Mental Health (DZPG), Partner Site Tübingen, Tübingen, Germany
[x] Karl-Jaspers Clinic, European Medical School Oldenburg-Groningen, Oldenburg, Germany
[y] Department of Psychiatry, Ruhr University Bochum, LWL University Hospital, Bochum, Germany
[z] Department of Psychiatry and Psychotherapy, Agaplesion Diakonieklinikum, Rotenburg, Germany
[aa] Department of Psychiatry and Psychotherapy, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[ab] Center for Psychosocial Medicine, Academic Teaching Hospital Itzehoe, Itzehoe, Germany
[ac] Division of Psychiatry and Psychotherapeutic Medicine, Research Unit for Bipolar Affective Disorder, Medical University of Graz, Graz, Austria
[ad] Clinic for Psychiatry, Psychotherapy and Psychosomatics, Augsburg University, Medical Faculty, Bezirkskrankenhaus Augsburg, Augsburg, Germany
[ae] Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Göttingen, Germany
[af] German Center for Neurodegenerative Diseases (DZNE), Göttingen, Germany
[ag] Neurosciences and Signaling Group, Institute of Biomedicine (iBiMED), Department of Medical Sciences, University of Aveiro, Aveiro, Portuga
[ah] Psychiatrieverbund Oldenburger Land gGmbH, Karl-Jaspers-Klinik, Bad Zwischenahn, 26160, Germany
[ai] Department of Psychiatry and Behavioral Sciences, SUNY Upstate Medical University, Syracuse, NY, USA

* Corresponding authors.
E-mail addresses: evieta@clinic.cat (E. Vieta), sergi.papiol@med.uni-muenchen.de (S. Papiol).

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[aj] Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA

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ABSTRACT

Older Adults with Bipolar Disorder (OABD) represent a heterogeneous group, including those with early and late onset of the disorder. Recent evidence shows both groups have distinct clinical, cognitive, and medical features, tied to different neurobiological profiles. This study explored the link between polygenic risk scores (PRS) for bipolar disorder (PRS-BD), schizophrenia (PRS-SCZ), and major depressive disorder (PRS-MDD) with age of onset in OABD. PRS-SCZ, PRS-BD, and PRS-MDD among early vs late onset were calculated. PRS was used to infer posterior SNP effect sizes using a fully Bayesian approach. Demographic, clinical, and cognitive variables were also analyzed. Logistic regression analysis was used to estimate the amount of variation of each group explained by standardized PRS-SCZ, PRS-MDD, and PRS-BD. A total of 207 OABD subjects were included (144 EOBD; 63 LOBD). EOBD showed higher PRS-BD compared to LOBD ($p = 0.005$), while no association was found between age of onset and PRS-SCZ or PRS-MDD. Compared to LOBD, EOBD individuals also showed a higher likelihood for suicide attempts ($p = 0.01$), higher presence of psychotic symptoms ($p = 0.003$), higher prevalence of BD-I ($p = 0.002$), higher rates of familiarity for any psychiatric disorder ($p = 0.004$), and lower processing speed measured with Trail-Making Test part A ($p = 0.03$). OABD subjects with an early onset showed a greater genetic burden for BD compared to subjects with a late onset. These findings contribute to the notion that EOBD and LOBD may represent different forms of OABD, particularly regarding the genetic predisposition to BD.

1. Introduction

Bipolar disorder (BD) is a severe mental illness, characterized by recurrent episodes of depression and hypomania or mania alternated with intervals of absent or reduced affective symptomatology. Older adults with BD (OABD) are defined as individuals with BD over the age of 50 according to the last consensus by the International Society for Bipolar Disorders Task Force (Sajatovic et al., 2015). Several evidence supports the idea of considering this subgroup of individuals as a differentiated population based on the significant differences observed in clinical, social, cognitive, and medical particularities when compared to younger patients (Almeida et al., 2022; Beunders et al., 2021; Dols and Sajatovic, 2024; Eyler et al., 2022; Sajatovic et al., 2021). Thus, the OABD population requires more specific clinical investigations and management (Sajatovic et al., 2019). OABD also represents a heterogeneous population, where age at onset is considered a potential differentiating factor. Within OABD, it can be distinguished between early onset BD (EOBD; i.e., individuals who have the first disorder's episode under 50 years old), and late onset of BD (LOBD; i.e., individuals who have the first disorder's episode at the age of 50 years old or older (Vasudev and Thomas, 2010).

There is a need to better understand the underlying factors explaining the differences between EOBD and LOBD. Differences in illness course, prognosis, severity, comorbidity, cognitive performance, neuroanatomic, and neuropathological factors based on the age at onset in later-life have been identified. For instance, it seems that EOBD represents a more severe form of the disorder, more psychotic symptoms, mixed episodes, and worse treatment response (Joslyn et al., 2016; Schürhoff et al., 2000). On the contrary, some reports indicate that LOBD shows a worse course of the disorder, higher cerebrovascular risk (Ramírez-Bermúdez et al., 2021; Subramaniam et al., 2007), and more cognitive impairment (Martino et al., 2013; Schouws et al., 2009). Likewise, age at onset has been associated with genetic disease burden in OABD (Thesing et al., 2015). Thus, while EOBD is strongly associated with a higher prevalence of family history of psychiatric disorders, especially mood disorders (Depp and Jeste, 2004; Thesing et al., 2015), LOBD is associated with a higher cerebrovascular risk (Subramaniam et al., 2007). These differences could suggest a higher genetic burden in those patients with an early onset. Altogether, these differences prompt the belief among many researchers that EOBD and LOBD might represent distinct forms of BD or even differentiated clinical entities with similar phenotypic expression (Schürhoff et al., 2000). Age at onset could be a potential differentiator of homogeneous subgroups of BD and these distinctions could be useful in the identification of genetic vulnerability factors and other pathogenic components (Leboyer et al., 2005). The study of the potential association between genetic burden and age of onset in OABD may help to clarify whether the two groups constitute two different clinical and biological entities. Therefore, the main aim of the present study is to investigate the association between the genetic load of major psychiatric disorders and the age of onset in OABD.

2. Methods

2.1. Participants

This is a cross-sectional study using data of the transdiagnostic PsyCourse Study that is a longitudinal, multicenter and deep-phenotyping study, conducted by a network of 20 clinical sites in Germany and Austria. The design and other properties of the PsyCourse Study are well-described elsewhere (Budde et al., 2019). We used data from the baseline assessment (time point 1) for our analyses, with the exception of the Verbal Learning and Memory Test that was assessed at visit 2 (six months after baseline). Data were extracted from the PsyCourse dataset Version 5.0 (https://data.ub.uni-muenchen.de/251/) (Heilbronner et al., 2021). The diagnosis of BD was made according to DSM-IV criteria using an adapted version of the German version of the Structured Clinical Interview for DSM-IV; Axis I Disorders (SCID-I) (Wittchen et al., 1997).

2.2. Assessment

Age, sex, history of psychotic symptoms, illness duration, number of episodes, diagnosis subtype, psychiatric family history, lifetime history of suicide attempts, and cognitive performance as sociodemographic and clinical variables were included in this study. Depressive symptoms were evaluated using the Inventory of Depressive Symptomatology scale (IDS-C_{30}) (Rush et al., 1996). The Young Mania Rating Scale (YMRS) (Young et al., 1978) was used for assessing the presence of (hypo)manic symptoms, and the Global Assessment of Functioning Scale (GAF) (Endicott et al., 1976) assesses the psychosocial functioning. The IDS-C_{30}, the YMRS, and the GAF all represent the state of symptoms and functioning at the time of the study interview. Participants were categorized according to their highest educational attainment based on the German educational system.

[1] Thomas G. Schulze and Carla Torrent should be considered senior authors.

The neuropsychological battery includes measures that assess cognitive domains, including attention, processing speed, working memory, verbal memory, executive functions, and intelligence. Trail-Making Test (TMT) (Reitan, 1958) part A and the Digit-Symbol Test (DST) (Wechsler, 1997) assess processing speed. The forward verbal digit span assesses short-term memory, and the backward verbal digit span was used to measure working memory (Wechsler, 1997). TMT-B and TMT-AB interference calculations address executive functions. The values of TMT-A and TMT-B each represent the total time taken to finish the respective task. For the calculation of the estimation of the switching process (TMT-AB) the time taken to complete TMT-A was subtracted from the time taken to complete TMT-B. Learning and memory were assessed by the Verbal Learning and Memory Test (Deutsch: "Verbaler Lern- und Merkfähigkeitstest") (VLMT) (Helmstaedter et al., 2001). The measures we used for assessing verbal memory were: 1) Total recall: the sum of correctly recalled words across all five presentations of the main list (list 1); 2) Immediate loss: the difference between the number of words recalled of list 1 after the presentation of the interference list (list 2) and the number of words recalled in the last presentation of list 1; 3) Delayed loss: the difference between the number of words recalled in the last presentation of list 1 and the number of words recalled after time interval (25–30 min.); 4) Recognition: the number of correct words of list 1 by presenting 50 words (including word from list 1, list 2 and completely new words). Crystalized intelligence was measured by means of Multiple-Choice Vocabulary Intelligence Test (Deutsch: Mehrfach-wahl–Wortschatz–Intelligenz: MWT-B) (Lehrl et al., 1995).

2.3. Genotyping and PRS calculation

For investigating the genetic burden among early vs late onset in OABD, we calculated the Schizophrenia-Polygenic Risk Score (PRS-SCZ), Major Depression PRS (PRS-MDD), and PRS-BD in a selected subsample of OABD defined as $\geq$ 50 years old (Sajatovic et al., 2015), from the entire sample of 511 BD patients with available genomic data. Early onset was defined as patients who develop the disorder before 50 years old, and LOBD by those who had their first episode after 50 years old (Vasudev and Thomas, 2010).

In addition, as a secondary analysis to investigate differences in genetic burden between young and older patients, we also performed a PRS analysis by including young and late-life patients establishing also the cut-off of 50 years old for the age at onset. As well, we also wanted to explore the genetic burden and age at onset in younger patients (< 50 years old) establishing a cut-off of 30 for the age at onset.

DNA was extracted from venous blood samples. All individuals included in this study were genotyped using Illumina's Global Screening Array (GSA) v3.0 at the Helmholtz Center in Munich, Germany. Quality Control steps were carried out as described in other studies (Boudriot et al., 2024). Genetic imputation was carried out in the Michigan Imputation Server using Minimac4 and individuals from the Haplotype Reference Consortium (HRC; Version r1.1) as the reference dataset. Genetic variants with MAF>0.01 were kept. The PRS-CS tool was used to infer posterior SNP effect sizes under continuous shrinkage priors and estimate the global shrinkage parameter (φ) using a fully Bayesian approach (Ge et al., 2019) using imputed genotypes based on their respective GWAS summary stats (Mullins et al., 2021; Trubetskoy et al., 2022; Wray et al., 2018). PRS-SZ, PRS-MDD, and PRS-BD were scored with PLINK 1.90 (Chang et al., 2015) (www.cog-genomics.org/plink/1.9). Ancestry principal components analyses showed all the samples overlapped with European reference population of the 1000 Genomes project.

2.4. Statistical analysis

Descriptive analyses were conducted using independent *t*-tests for continuous variables and chi-square tests for categorical variables to examine differences in sociodemographic and clinical characteristics between EOBD and LOBD. Neuropsychological variables were log-transformed to normalize their distribution and reducing the impact of the outliers. Specific variables (i.e., TMT-A, TMT-B, VLMT immediate loss, and VLMT delayed loss) were multiplied by −1 due to their inverse interpretation. To assess the impact of age at onset on neuropsychological outcomes, multiple linear regression analyses were conducted, adjusting for potential confounders, including age, sex, center, and education status. The distribution of residuals from the regression models was evaluated by inspecting Q-Q plots and performing the Shapiro-Wilk test to assess normality. If the residuals did not follow a normal distribution, the neuropsychological variable in question was dichotomized at the median, and a logistic regression analysis was performed instead. Model fit and explanatory power were evaluated using R^2 for linear regression models and Nagelkerke R^2 for logistic regression models. Logistic regression analyses were used to estimate the amount of variation (EOBD vs LOBD) explained by z-standardized PRS-SCZ, PRS-MDD, and PRS-BD. Specifically, the amount of variance explained by the PRSs was estimated by calculating the incremental Nagelkerke's pseudo-R2, which is the difference Nagelkerke's pseudo-R2 between the full model and the baseline model (i.e., including all variables except the PRSs). This model was adjusted for sex, recruitment site, and the first two ancestry principal components. Statistical significance was set at p-value < 0.05. All the analyses were conducted with R, version 4.3.1. Statistical significance was set at p-value < 0.05.

3. Results

A total of 207 OABD subjects were included in this study. Of those, 144 had EOBD and 63 had LOBD. Demographic data showed differences in age between EOBD and LOBD,), but not in sex distribution ($p = 0.34$). Regarding clinical variables, the presence of psychotic symptoms across the lifetime (67.2 % in EOBD and 38.9 % in LOBD; $p < 0.001$) and lifetime history of suicide attempts (42.6 % in EOBD and 22.4 % in LOBD; $p = 0.01$) were also significantly higher in EOBD compared with LOBD. A diagnosis of BD type I was more prevalent in EOBD (77.3 % of EOBD and 22.7 % in LOBD; $p = 0.002$). Finally, a significantly greater presence of a family history of psychiatric illness was found in EOBD (84.7 % vs 66.7 %; $p = 0.004$) (Table 1).

Concerning neuropsychological performance (Table 2), after correcting by age, sex, center and educational level, we found significant differences only in processing speed assessed with the TMT-A (total time) in which the EOBD group had lower performance than LOBD ($p < 0.001$). No statistically significant differences between both groups were found in the other cognitive variables.

The logistic regression analyses for the associations of PRS-SCZ, PRS-BD, and PRS-MDD with the age at onset between EOBD and LOBD in the OABD group showed a strong association between PRS-BD and age at onset status (z-value = −2.84; $p = 0.0045$), in which the amount of variance explained by the PRS-BD regarding early or late onset was 6.0 % (Nagelkerke's Pseudo R2). Specifically, EOBD had a higher genetic burden for BD with respect to LOBD. No association has been found between age at onset (EOBD vs LOBD) and PRS-SCZ ($p = 0.27$) and PRS-MDD ($p = 0.66$). Fig. 1 shows the polygenic load between early and late onset for the investigated psychiatric diagnoses.

In addition, the analysis on young and older patients to differentiate genetic burden based on age at onset (50 years old), showed significant (z-value= −2.75; $p = 0.006$) higher polygenic load for BD in EOBD, after correcting for sex, center, and the first two ancestry principal components. The percentage of variance explained by the PRS-BD regarding EOBD and LOBD was 3.0 %. Furthermore, we also conducted a PRS analysis including only the young sample (<50 years all, $N = 258$), defining the early and late onset by using the cut-off of 30 years old. In this analysis, no differences were found after correcting for sex, center, and the first two ancestry principal components (z-value= 0.535, $p = 0.59$).

Table 1
Demographic and clinical comparisons between EOBD and LOBD groups.

	EOBD (n = 144)	LOBD (n = 63)		
	Mean (SD)/ N(%)	**Mean (SD)/ N(%)**	***t*-test/ X^2**	***p***
Sex (males)	72 (50 %)	36 (57.1 %)	0.89	0.34
Educational level			3.02	0.221
General secondary school	29 (14.3 %)	14 (6.9 %)		
Graduation after 10 years of school	36 (17.7 %)	21 (10.3 %)		
University entrance qualification	78 (38.4 %)	25 (12.3 %)		
Age	57.02 (5.75)	60.54 (6.54)	3.77	**<0.001**
IDS-C30	11.98 (10.03)	12.62 (11.43)	0.66	0.51
YMRS	3.52 (5.42)	3.79 (5.34)	0.27	0.79
GAF	60.67 (11.44)	63.75 (12.03)	1.65	0.10
Age at onset	33.18 (9.45)	55.98 (5.90)	21.06	**<0.001**
Psychotic symptoms (yes)	86 (67.2 %)	21 (38.9 %)	12.55	**<0.001**
Suicide attempts (yes)	58 (42.6 %)	13 (22.4 %)	7.17	**0.01**
Illness duration (years)	23.82 (11.46)	4.64 (5.06)	12.23	**<0.001**
Number of episodes	12.99 (16.97)	8.83 (14.81)	1.79	0.07
Diagnosis (BD I)	120 (77.3 %)	47 (22.7 %)	9.83	**0.002**
Psychiatric family history (yes)	116 (84.7 %)	40 (66.7 %)	8.20	**0.004**

GAF: Global Assessment of Functioning; IDS-C_{30}C30: Inventory of Depressive Symptomatology; YMRS: Young Mania Rating Scale.

Table 2
Multivariate regression analyses using neuropsychological measures as dependent variables.

	EOBD (n = 144)	LOBD (n = 63)				
	Mean (SD)	**Mean (SD)**	**b**	**R^2**	**Pseudo R^2**	**p-value**
TMT-A *	44.83 (22.18)	43.08 (12.60)	−0.13	**0.22**	0.02	**0.03**
TMT-B *	102.96 (46.17)	105.54 (41.71)	−0.08	0.2	0.01	0.25
DGT-SP-FRW *	9.13 (2.09)	9.41 (2.25)	−0.05	0.053	0.01	0.18
DGT-SP-BCK *	6.02 (2.16)	5.73 (1.81)	0.00	0.068	0.00	0.95
VLMT total recall *	44.00 (10.71)	42.37 (9.83)	−0.06	0.254	0.01	0.22
TMT-AB	58.98 (34.18)	63.52 (36.84)	0.50	0.11	0.01	0.17
DST	54.12 (16.16)	51.40 (13.45)	−0.53	0.24	0.01	0.17
MWT-B	30.39 (4.75)	29.65 (4.46)	0.72	0.29	0.02	0.09
VLMT loss immediate	1.72 (2.07)	2.47 (2.00)	0.57	0.06	0.02	0.19
VLMT loss delayed	2.11 (2.17)	2.78 (2.10)	0.51	0.05	0.02	0.24
VLMT recognition	10.56 (4.02)	9.31 (3.93)	0.48	0.11	0.01	0.30

DGT-SP-BCK: Verbal digit span backward; DGT-SP-FRW Verbal digit span forward; DST: Digit Symbol Test; MWT: Multiple-Choice Vocabulary Intelligence Test; TMT: Trail Making Test; VLMT: Verbal Learning and Memory Test.
*These variables were normally distributed.

4. Discussion

This study examined the genetic burden related to age at onset in a sample of OABD. We analysed the association of PRS-SCZ, PRS-BD, and PRS-MDD with EOBD and LOBD. To our knowledge, this is the first study to investigate the relationship between age at onset and PRS for psychiatric disorders in an OABD sample. As the main result, we identified a higher genetic burden of BD in the sample of EOBD compared with LOBD group while no significant associations have been found with PRS-SCZ and PRS-MDD. As mentioned before, an earlier age at onset in OABD has been associated with a higher family history of psychiatric diagnoses, but this association had not been demonstrated using biomarkers of genetic burden for psychiatric disorders until now. In contrast, other factors such as negative life stressors or cerebrovascular conditions would represent a main role in the expression of LOBD (Alves et al., 2018; Chu et al., 2010; Subramaniam et al., 2007; Thesing et al., 2015). Thus, EOBD appears to be more strongly influenced by genetic predispositions, while LOBD may involve interactions with environmental factors or age-related neurodegenerative changes. Our findings show that early and late onset are characterized by different genetic loads, with EOBD probands presenting a higher genetic burden for BD as measured by PRS-BD. This supports the notion that EOBD and LOBD may represent distinct subgroups, at least in terms of genetic component. In middle-aged BD patients, a family history of psychiatric disorders has been related to an earlier onset (Post et al., 2016), a relationship further supported by the significant association between PRS-BD and an earlier age at onset found in other studies (Park et al., 2020). However, some research has failed to identify the association between the genetic factors and earlier onset, suggesting that the genetic variable may not contribute to differentiating between early and late-onset presentations (Kennedy et al., 2015). Nonetheless, although PRS provides valuable insights into genetic predispositions, gene-environment interactions play a central role in disease onset and progression of psychiatric disorders. Factors such as lifestyle, environmental exposures, and psychosocial stressors significantly influence the observed differences between EOBD and LOBD. For instance, early exposure to adverse environmental conditions or traumatic experiences may exacerbate genetic vulnerabilities, leading to an earlier onset, suggesting that genetic predisposition to mental illness, as measured by polygenic scores, may be less significant in the presence of such severe environmental risk factors (Anand et al., 2015; Lake et al., 2024). In contrast, maintaining healthy lifestyle habits may help mitigate the disease's progression or reduce the risk of developing BD (Li et al., 2024; Simjanoski et al., 2023). Moreover, PRS developed in one population may not be fully generalizable due to differences in genetic architecture and environmental exposures across populations (culture, lifestyle factors, climate environment, etc.) (Martin et al., 2019; Radua et al., 2024).

Building on our results, the weak association observed between genetic load and age of onset in younger BD patients (<50 years old), could support the hypothesis of greater genetic differentiation as the age of onset is delayed, especially in OABD. This aligns with the idea that OABD is a differentiated population with unique characteristics. Furthermore, PRS-BD does not appear to distinguish between earlier age at onset such as the cut-off of 18 years (Kalman et al., 2019).

Regarding cognitive performance, we found significantly lower performance of EOBD group in one measure of processing speed, TMT-A, while no differences were found in the other measure of processing speed (DST) or in other cognitive domains. On the one hand, the fact that we only found differences in one test (TMT-A) may be attributed to the specific characteristics of the population studied, such as their demographic or clinical profiles, which might not be fully accounted for by the other variables. Additionally, the high cognitive heterogeneity frequently observed in BD (Ehrlich et al., 2022; Lima et al., 2019) and also in OABD (Montejo et al., 2022a), in terms of severity and specific cognitive domains, could also explain this finding. It is also possible that TMT- A may be a more sensitive factor for identifying differences based in age at onset in OABD, while other factors remain largely comparable (Luperdi et al., 2021; Montejo et al., 2022b). Moreover, processing speed is particularly susceptible to the effects of greater clinical severity which might explain its prominence in differentiating our EOBD group (Cardoso et al., 2015; Ko et al., 2022). Contrary to our findings, previous

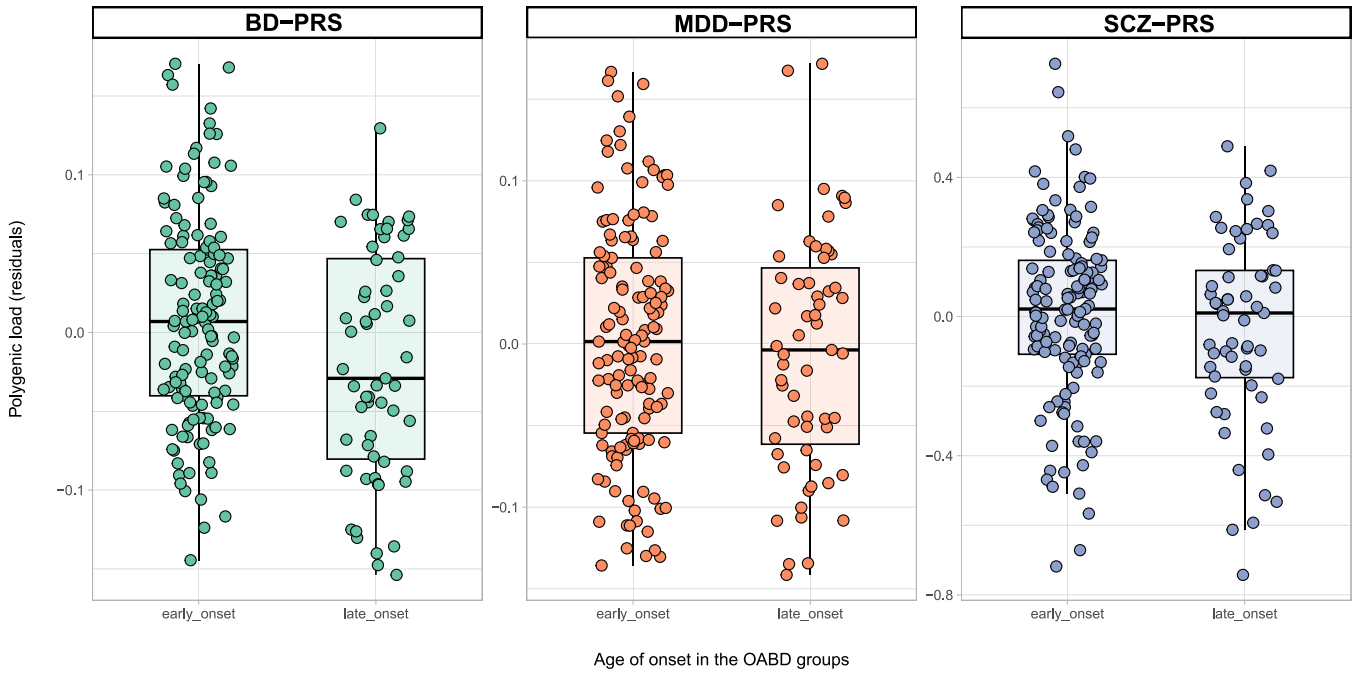

Fig. 1. Polygenic risk scores for psychiatric diagnoses between early and late onset.

studies have reported poorer cognitive function in LOBD across several cognitive domains including verbal memory, executive functions, working memory and attention (Martino et al., 2013; Samamé et al., 2013; Schouws et al., 2009). In this context, although later onset has sometimes been related to more severe cognitive impairment, other reports have not identified such differences. For instance, differences in cognitive performance may not be attributable to the higher cerebrovascular risk typically associated with LOBD as some studies have found no differences in cognitive function (Subramaniam et al., 2007). Conversely, it is possible that EOBD patients have been more exposed to neuroprogression (Vieta, 2024; Yatham et al., 2024). Other efforts made to distinguish both groups found no differences across cognitive domains, with higher levels of homocysteine emerging as better predictors of cognitive function in OABD rather than the age of onset (Chen et al., 2019). The age of onset has significant clinical implications on the course and prognosis of BD. Earlier onset is often associated with a greater illness burden and a more severe form of the disease, potentially leading to different clinical trajectories (Kalman et al., 2021; Propper et al., 2015). In our study, EOBD was represented by higher rates of BD type I, a greater likelihood of suicide attempts, and a higher prevalence of psychotic symptoms. This aligns with findings that an earlier onset is frequently associated with a more severe long-term impact of the disorder (Joslyn et al., 2016). The worse clinical profile associated with EOBD patients, combined with a higher genetic load could contribute to the manifestation of a more severe form of the disease. Similarly, the more severe form of the disease in EOBD could potentially lead to a greater number of suicide attempts due to a more significant long-term negative impact, in addition to a higher probability of psychotic symptoms and BD type I (Kalman et al., 2021). Furthermore, later onset has been described as a protective factor against suicide attempts (Su et al., 2022). The higher presence of psychotic symptoms in our EOBD sample could be explained by the higher representation of BD type I. Similar to our results, it has been reported that patients with a family history of affective disorder exhibit an earlier onset and a worse clinical profile, defined as an increased number of episodes, more severe depressive symptoms, higher suicide attempts, and a lower overall quality of life (Antypa and Serretti, 2014; Berutti et al., 2014).

Notwithstanding, other authors suggest that categorizing OABD based on its age of onset has limited clinical implications, as few differences have been evidenced, which can be attributed to other clinical factors (Almeida and Fenner, 2002; Chu et al., 2010; Depp et al., 2004). A recent study using a large dataset of patients similarly found no differences in clinical manifestations, functionality, or comorbid physical conditions, further supporting the hypothesis that LOBD may manifest similar phenotype as EOBD (Lavin et al., 2022). Despite the waning strength of distinguishing OABD based on age of onset in past decades, as most results do not show substantial evidence for distinct clinical presentations (Vasudev and Thomas, 2010), this study does contribute to the differentiation between both groups, particularly regarding the genetic predisposition to BD.

This study is not exempt from limitations. Firstly, the interpretation of these findings should be approached with caution given the limited sample size (De Prisco and Vieta, 2024). So that, we cannot rule out an overestimation of the effects due to the limited statistical power. These results need to be replicated in independent and larger samples to ensure the robustness, interpretation, and generalizability of the conclusions. Further research is required to include a greater number of individuals aged 50 years and older to gain more knowledge about potential etiological variables and processes that impact health outcomes of late-life BD, helping to corroborate the validity of EOBD and LOBD as distinct subtypes. Furthermore, considering other criteria that are sometimes included in the literature for the age of onset cut-off (e.g., 40 years) could have modified our results. Moreover, many of the subjects were medicated, and this might have influenced the results (Ilzarbe and Vieta, 2023). Finally, the high variability in depressive symptom scores and the absence of a standardized battery for assessing BD may have impacted the cognitive outcomes, thereby limiting the robustness of the findings in this area.

To conclude, our findings offer valuable insights into the genetic architecture of OABD in both EOBD and LOBD subpopulations highlighting potential etiological variables and processes that differentiate these groups. Validating LOBD and EOBD as distinct subtypes is crucial for enhancing our knowledge of the disorder and refining clinical and treatment approaches. By delineating the unique features and risk factors associated with each subtype, clinicians can tailor interventions and care strategies to better address the specific needs and challenges faced by individuals according to their age at onset. This will not only deepen our understanding of the disorder but also provide valuable guidance for

clinical practice, ultimately improving the quality of life for individuals affected by this condition.

Contributions

Conceptualization and study design: LM, CT, BS, SP; Data analysis: CT, SP.; Writing—original draft: LM; Writing—review and editing: all authors; Supervision, formal and accurate revision: MB, UH, CT, SP, EV, TS.; Acquisition and/or processing and/or managing of data (phenotype data and/or biological data): JK, MB, UH, KA, PF, MH, MO, DRE, SKS, ECS, FS, TV, IGA, VA, BTB, UD, DED, AJF, CF, GJ, CC, JR, EZR, MS, JW, JZ

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Declaration of competing interest

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