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Unravelling the link between body mass index and cognitive performance in individuals with bipolar disorder and exploration of PRS moderation effect: Findings from the PsyCourse Study.

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Additional Information

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Files for peer review

All files submitted by the author for peer review are listed below. Files that could not be converted to PDF are indicated; reviewers are able to access them online.

Name	Type of File	Size	Page
BMI_BD_PRS_cognition_PsyCourse_Study_290725_revised_clean.docx	Main Document - MS Word	441.7 KB	Page 8
BMI_BD_PRS_cognition_PsyCourse_Study_290725_trackchanges.docx	Main Document - Tracked Changes	438.9 KB	Page 33
figures_BMI_cogn_PRS (1).pdf	Figure	192.5 KB	Page 58
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Data availability statement

The data that support the findings of this study are available from the PsyCourse Study upon reasonable request.

ABSTRACT

Introduction: Bipolar disorder (BD) is a severe mental disorder characterized by extreme mood swings, often accompanied by metabolic comorbidities, such as cardiovascular disease, which increase mortality and reduce quality of life. Both metabolic dysfunctions and BD are associated with cognitive dysfunction. Body mass index (BMI) is closely linked to metabolic health and cognitive performance. This study examined the link between BMI and cognitive function in individuals with BD and how genetic factors, namely polygenic risk scores (PRS) for BD and BMI, might influence this link. **Methods:** Genetic (PRS scores) and phenotypic data (sociodemographic factors, clinical symptoms and cognitive function) of 341 adult patients with BD diagnosis from the PsyCourse Study, a large, multi-site, and naturalistic longitudinal study were utilized for this study. First, we performed univariate and multivariate regression analyses to investigate associations between BMI and cognitive performance. Second, moderation analyses were conducted to examine the potential moderator effects of BD-PRS or BMI-PRS in the relationship between BMI and different cognitive outcomes. **Results:** BMI was associated with processing speed (TMT-A) and executive function (TMT-B), with individuals with higher BMI showing poorer performance. Moderation analyses revealed that the effect of BMI on cognition was moderated by BD-PRS only regarding the processing speed. BMI-PRS did not moderate the association between BMI and cognitive variables. **Conclusions:** Our findings indicate that the relationship between BMI and cognitive impairment in BD is partially moderated by BD genetic liability but not BMI genetic load.

Keywords: Polygenic risk scores (PRS), psychomotor speed, executive function, bipolar disorder, body mass index

SIGNIFICANT OUTCOMES

1. There exists a positive association between cognitive impairment and BMI in bipolar disorder.
2. Bipolar disorder genetic liability may moderate the relationship between BMI and processing speed.
3. Addressing obesity and promoting healthy lifestyles should be key to improving cognitive performance in bipolar disorder.

LIMITATIONS

1. The use of BMI as a single measure for assessing metabolic syndrome.
2. The potential effect of pharmacological treatment and somatic morbidities was not controlled for in the analyses.
3. The availability of peripheral blood biomarkers would have allowed a deeper insight into association with genetics, metabolic and cognitive aspects of bipolar disorder.

1. INTRODUCTION

Bipolar disorder (BD) is a severe mental health condition[1] with high rate of somatic comorbidities especially cardiovascular diseases [2], leading to increased mortality, reduced quality of life, and lower psychosocial and cognitive functioning.[2]Individuals with mood disorders are predisposed to metabolic dysfunction, while those with metabolic dysregulation, such as diabetes and obesity, experience more severe depressive symptoms. Overweight and obesity are well known to be prevalent in individuals with mood disorders, especially in BD [3]. Antipsychotic drugs, a common the treatment of BD, seem to be associated with an increased likelihood of weight gain or obesity [4]. Nevertheless, an increased prevalence of overweight has been described not only after short-time use of antipsychotics in first treated episode of psychosis [5], but also for drug-naïve BD patients [6].

Emerging evidence indicates that individuals with BD in euthymia show impairments in various cognitive domains which are highly relevant and determine psychosocial functioning outcomes [7,8]. Moreover, several studies found a negative effect of overweight and obesity on cognitive function in euthymic patients [9–11], likewise in individuals at risk for BD [12]. This implies that the prevalence of overweight and obesity negatively impacts cognitive performance of individuals with BD. The most robust differences between obese versus normal weight individuals with BD were observed in executive function and processing speed [13]. However, both metabolic dysfunction and mood disorders are independently associated with cognitive deficits [14]. In fact, in general population, increased body fat and metabolic dysfunction may independently contribute to impaired memory and executive functions as well as structural brain abnormalities in frontal and medial temporal lobe regions. These effects stem from inflammation, vascular changes, and oxidative stress linked to excess fat and insulin resistance [15]. Additionally, cognitive impairment may also influence behaviors and lifestyles that worsen these conditions. In this sense, the body mass index (BMI), a widely used score based on height and weight, serves as a key indicator of metabolic health. BMI is increasingly examined for its impact on various health outcomes, including cognitive performance.

One emerging area of research is the role of polygenic risk scores (PRS) in understanding the interplay between BMI and cognitive performance in BD. PRS represent the cumulative effect of multiple common genetic variants associated with a particular trait or condition. BD-PRS reflects the genetic risk to BD, while BMI-PRS indicates the genetic propensity for a higher BMI [16]. Although multifactorial in aetiology, previous evidence suggests a common genetic background between psychiatric and metabolic disorders [17]. Since the research showed that BMI-PRS has been associated with BD, the common biology between obesity and BD has been suggested [18]. Moreover, some studies have found shared genetic contributions to BMI and cognitive function, showing a small phenotypic correlation between the two traits but a moderate genetic correlation [19]. It has also been shown several individual genetic variants are associated with both traits. By studying the moderation effects of BD-PRS and BMI-PRS, the current study aimed to uncover how genetic factors influence the relationship between BMI and cognitive performance in individuals with BD. This approach allows for a more nuanced understanding of how individual genetic background can modulate the association of BMI on cognitive outcomes.

1.1 Aims of the study

The study aimed to evaluate the relationship between body mass index and cognitive function, investigating whether body mass index serves as a predictor of cognitive performance in a sample of euthymic patients with bipolar disorder. Additionally, it assessed the potential moderating effect of polygenic risk scores for bipolar disorder and body mass index on this relationship. Given the shared genetic background observed between psychiatric and metabolic disorders, we hypothesized that polygenic risk scores would moderate the relationship between body mass index and cognitive performance. Specifically, individuals with higher polygenic risk scores for body mass index or bipolar disorder were expected to exhibit poorer cognitive function as body mass index increased.

2. MATERIALS AND METHODS

2.1 Study design

This study used data from the PsyCourse Study, a longitudinal, naturalistic, multi-site study conducted in different sites in Germany and Austria (www.PsyCourse.de). More details about the study design can be found elsewhere [20]. All of the data used for analyses came from the baseline assessment with the exception of the verbal memory assessment collected at visit 2. Data were obtained from the PsyCourse dataset Version 5.0 (https://data.ub.uni-muenchen.de/251/) [21].

2.2 Participants

Adult patients (18-65 years) diagnosed with BD according to DSM-IV Structured Clinical Interview for DSM-IV [SCID] [22] were only included in the analyses if they were in euthymia at the time of assessment (scorer ≤ 23 on the Inventory of Depressive Symptomatology ($IDS\text{-}C_{30}$) rating scale [23,24] and ≤ 14 in the Young Mania Rating Scale (YMRS) [25].

All participants provided written informed consent. The Ethics Committees responsible at each participating centre approved the study, conducted in accordance with the Declaration of Helsinki.

2.3 Measures

2.3.1 Clinical, Functional and Neuropsychological assessment

Current affective symptomatology was assessed using the $IDS\text{-}C_{30}$ [23] to assess severity of depressive symptoms and the YMRS [25] for the (hypo)manic ones.

Cognitive performance was assessed using the following battery of neuropsychological tests: Trail Making Test (TMT) part A [26] and Digit Symbol Test (DST) [27] to assess processing speed; TMT part B [26] to assess executive function; Verbal Digit span (Backward) [27,28] to evaluate the working memory; Verbal learning and memory test (Deuthc: Verbaler Lern- und Merkfähigkeitstest [VLMT] [29], to assess learning and memory; Multiple-Choice Vocabulary Intelligence Test (Deutch: Mehrfachwahl Wortschatz-Intelligenz [MWT-B] [30] to assess crystallized intelligence. The Global Assessment of Functioning (GAF) measured the individual's psychosocial functioning [31].

2.3.2 Body mass index (BMI)

BMI of study participants was calculated as weight in kilograms divided by the squared height in meters.

2.3.2 Genotyping and PRS calculation

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 extensively described in other studies [32–34]. Genetic imputation was carried out via the Michigan Imputation Server using Minimac4 and the Haplotype Reference Consortium (HRC; Version r1.1) as the reference dataset. Genetic variants with R^2>0.3 and MAF>0.01 were kept post-imputation. The PRS-continuous shrinkage (CS) tool was used to infer posterior SNP effect sizes under continuous shrinkage priors, setting the global shrinkage parameter (ϕ) at six different values (i.e., ϕ = 1E-01, 1E-02, 1E-03, 1E-04, 1E-05, and 1E-06) [35] based on the GWAS summary stats for BD [36] and BMI [37]. In brief, to find the optimal phi value as regards predictive performance, a grid search was carried out based on the different ϕ thresholds, with larger phis (1E-01, 1E-02) representing very polygenic traits and smaller ϕ (1E-05, 1E-06) less polygenic traits. BD-PRS and BMI-PRS were calculated with PLINK 1.90 score function [38] using imputed genotypes. Ancestry multidimensional scaling components (MDS) analyses showed all the samples included overlapped with 1000 Genomes Project European reference populations.

2.4 Statistical analyses

Descriptive statistics were used to define sample characteristics by calculating means and frequencies of variables.

The distribution of cognitive variables was evaluated performing the Kolmogorov-Smirnov statistics and by inspecting Q-Q plots and the distribution in the histograms. The cognitive variables not following a normal distribution (i.e. TMT-A, TMT-B, and Verbal Digit span Backward) were log-transformed to normalize their distribution and reducing the impact of the outliers. Scores on both TMTs were multiplied by -1 due to their inverse interpretation. Cognitive variables were considered the dependent variables. We used linear mixed models in all our analyses with recruitment centre as a random effect. First, we performed univariate regressions

to analyse associations between BMI and the different cognitive outcomes. Subsequently, when significant associations were detected between BMI and cognitive variables, we ran multivariate linear regression (backward stepwise method) for those cognitive variables, adjusting for age and sex since these variables may influence cognitive performance and BMI. To analyse the second aim, moderation (interaction) analyses were conducted to examine if BD-PRS (continuous and independent variable) has a moderator effect on the relationship between BMI and the different cognitive variables (dependent variables), that is, BD-PRS would modify the relationship between the independent and dependent variables. To assess the moderator effect, the interaction terms was added in each model (BMI × BD-PRS or BMI × BMI-PRS). Moderation analyses were run for all the cognitive variables regardless of being associated with BMI, as we wanted to evaluate if adding a moderating effect would modify this relationship. A significant interaction effect would indicate that the association between BMI and cognitive performance varies according to the level of the corresponding PRS, indicating a moderating effect. Every analysis included center as a random effect, age and sex as covariates, as well as the first two ancestry MDS to correct for potential effects of population genetic substructure. Similar moderation analyses were carried out to examine the potential moderator effect of BMI-PRS.

False discovery rate (FDR) was applied to adjust the results for multiple comparisons for the univariate and multivariate regression analyses. FDR was set at 5%, and adjusted *p-values* ≤.05 were considered significant. No multiple testing corrections were performed for the moderation analyses due to the exploratory nature of them. Alpha level set to $p \leq .05$. All analyses were conducted using IBM SPSS version 27.

3. RESULTS

The total sample consist of N=341 patients, with a mean (SD) age of 44.60 (12.3); 49.3% were female (n=168) and 50.7% male (n=173). See Table 1 for demographic and clinical variables.

3.1 Associations between BMI and cognitive outcomes

BMI was associated with TMT-A (p=.018) and TMT-B (p=.018) (see Table 2), specifically, individuals with higher BMI showed a poorer performance in these tests. Verbal Digit span

backward and DST were also associated with BMI, however, these findings did not survive adjustment for multiple comparisons.

We ran multivariate regressions analyses for those cognitive variables associated with BMI (see Table 3), adjusting for age and sex. Age and BMI were associated with TMT-B (p=.001 and p=.046 respectively). However, after the adjustment for multiple comparisons, the effect of age remained significant (adjusted-p=.002) and a trend was observed for BMI (adjusted-p=.061). For TMT-A, similar results were observed; age remained significant (adjusted-p=.002) and a trend for BMI was found (adjusted-p=.066).

3.2 Moderation effects of PRS between BMI and cognitive performance

After adjusting for age, sex, and ancestry principal components, BD-PRS interacted with BMI to predict lower performance in the TMT-A (for all the phi values, with all p-values<.035) and Verbal Digit span backward (p=.046 for phi_1E-01). Specifically, and for both cognitive variables, at higher BD-PRS levels, a more pronounced inverse association between BMI and cognitive performance was observed. In contrast, this association was not evident at lower BD-PRS levels. Moreover, the moderation effect of BD-PRS on the relationship between BMI and processing speed (TMT-A) was consistent across different phi values, indicating that the effect was not influenced by the assumption of polygenicity. No other moderation effects of BD-PRS were detected in the relationship between BMI and cognitive variables. See Table 4 and figure 1 for the significant interaction p-values and Table S1 for the non-significant results in supplementary material. Concerning BMI-PRS, no moderation effects were detected in the relationship between BMI and cognitive variables.

4. DISCUSSION

An association between increased BMI and cognitive impairment in BD has long been observed, however, the polygenic underpinnings of it have not yet been studied. As far as we know, this is the first study to investigate the effect of genetic liability of BD or BMI on the association between BMI and cognitive performance in BD. Our study revealed an association between BMI and one processing speed measure and executive functions. However, these associations resulted in a trend after controlling for age. Secondly, BD-PRS had a moderating effect between

BMI and processing speed, and to a lesser extent in working memory, suggesting that genetic predisposition to BD plays a significant role in how BMI affects processing speed. In contrast, BMI-PRS was not found as a moderator in the relationship between BMI and cognition suggesting that genetic risk factors specifically related to higher BMI do not appear to influence the extent to which BMI affects cognitive abilities beyond their possible influence on the main predictor, actual BMI.

Processing speed, attention and executive functions are essential for abilities like problem-solving, planning, and maintaining focus on complex tasks. As BMI increases, these impairments can make daily activities more challenging, ultimately impacting quality of life and productivity. These results are in line with prior research that has consistently found obesity associated with cognitive decline in psychiatric disorders, especially in people with BD. For instance, some studies [13] demonstrated significant deficits in processing speed and executive function among individuals with BD and higher BMI [9,13] . Regardless of psychiatric disorders, evidence also suggests that overweight and obese individuals have a lower performance on executive functioning abilities, specifically difficulties with decision-making, planning and problem-solving [39]. The cognitive decline associated with higher BMI may be partly explained by metabolic dysfunction, which is common in individuals with obesity. Conditions such as insulin resistance, systemic inflammation and dyslipidaemia disrupt brain function, particularly in areas responsible for attention and executive control [40]. In this line, the allostatic load (AL) model may also help us to explain this relationship [41]. Some studies found an increase in AL indexes in overweight individuals, and this index was negatively related to executive functions and changes in cortical thickness of regions monitoring behaviour [42,43]. Overweight and high-fat diets can lead to physiological stress and promote chronic low-inflammations states. Moreover, people with a higher BMI are thought to show an elevated impulsivity which makes delaying gratification more difficult [44–46]. This issue is associated with behaviours such as overeating, contributing to weight gain (Fagundo et al., 2012). Executive functions, which include skills related to self-regulation and monitoring, are crucial for controlling food intake and regulating body weight [48]. Some studies suggest that overeating could cause brain changes that disrupt cognitive processes

essential for managing food consumption [49]. For example, hippocampal dysfunction may reduce memory inhibition, making individuals more responsive to cues associated with food. On the other hand, poor cognitive-inhibitory predisposes people to be more influenced by these cues, heightening the risk of overeating and obesity.

Several cardiovascular risk factors are known to be associated with cognitive impairment, including higher BMI, elevated glucose and low levels of HDL cholesterol. Peripheral lipid has also been linked to cognitive performance, specifically with lower processing speed [50]. The association of BMI with specifically processing speed and executive function, and not memory, in our study suggests that there may be another pathophysiological mechanism behind this type of cognitive impairment. One possible explanation is that BMI is more related to arteriolosclerosis and venous collagenosis in the brain, which could contribute to attention/executive impairment [51]. Likewise, individuals with BD exhibit elevated rates of overweight and obesity, which in turn increase the risk of cardiovascular diseases, the primary cause of heightened mortality among individuals with BD. Obesity adversely affects BD by elevating the frequency of mood episodes, levels of disability, incidences of suicide attempts, comorbid conditions, cognitive decline, and abnormalities in white matter [52]. However, our findings suggest that we can't establish an independent relationship between BMI and cognition in BD, as both BMI and cognition are influenced by age. There is insufficient evidence to support a reliable and valid independent link between obesity and cognitive impairment in mid-life adults [53]. It is crucial to consider the impact of other potential confounding variables in the relationship between BMI and cognition. While age influences cognitive performance, somatic comorbidities also play a key role, as their severity and prevalence may increase over time, further impacting cognitive function. In fact, evidence show a high prevalence of physical morbidities in older adults with BD, especially cardiovascular and metabolic ones [54], with a possible association with poorer cognitive performance. However, this association does not seem independent and other risk factors as demographics, clinical characteristics and lifestyle factors may be involved [55].

Our findings highlight a potential avenue for clinical intervention targeting neurocognitive deficits in individuals with BD through BMI reduction, emphasizing the importance for clinicians to prioritize weight management as an essential part of treatment. Addressing obesity through lifestyle changes or medical interventions may not only enhance physical health but also alleviate cognitive impairments, thereby improving psychosocial functioning in both psychiatric and non-psychiatric populations. Indeed, a meta-analysis by Siervo and colleagues [56] demonstrated significant improvements in executive functioning and attention amongst non-psychiatric obese individuals who achieved substantial weight loss. Furthermore, a recent randomized controlled trial found that physical activity programs can positively influence neurocognitive and functional outcomes in individuals with psychiatric disorders and comorbid obesity [57].

While the relationship between BD and BMI is well documented, the molecular mechanisms driving this connection remain unclear. BD contributes to chronic inflammation and oxidative stress, which are risk factors for cardiovascular disease [58]. Both lifestyle factors and side effects from medication contribute to metabolic comorbidities in people with BD. Nevertheless, elevated BMI is also observed in adolescents and in individuals who have not been treated with medication, suggesting the involvement of common pathophysiological mechanisms and genetic and/or epigenetic factors. In fact, some meta-analyses detected shared genetic determinants between BD and BMI [59].

In this regard, we analysed the potential influence of both BD-PRS and BMI-PRS on the relationship between BMI and cognition. Our results suggested that genetic predisposition to BD may play a significant role in how BMI affects processing speed. Individuals with a higher polygenic burden of BD might be more sensitive to cognitive challenges when they also have a higher BMI. The biological mechanisms underlying this could involve neuroinflammation, insulin resistance, or other metabolic disruptions that are common in both BD and obesity. Thus, individuals with a high BD-PRS might experience a stronger negative impact of BMI on processing speed tasks because both BD and obesity are linked to similar neurobiological pathways. The interaction of mood regulation pathways, metabolic dysfunction and brain regions involved in

processing speed may be more impaired in individuals with a genetic risk for BD [60]. Recognizing BD-PRS as a moderator between BMI and processing speed suggests that a high genetic susceptibility to BD intensifies the impact of BMI on some cognitive domains. This fact could lead to more personalized treatment strategies, where individuals with a high genetic risk for BD might benefit from closer monitoring of their BMI and cognitive function, as well as targeted interventions to address metabolic health and cognitive deficits. In this regard, integrative approaches addressing these areas alongside components like psychoeducation and mindfulness may be also an effective therapeutic option for this population [61].

Finally, BMI-PRS was not found as a moderator in the relationship between BMI and cognition suggesting that genetic risk factors related to higher BMI do not appear to influence the extent to which BMI affects cognitive abilities, beyond their effect on BMI. It indicated that the relationship between BMI and cognitive performance in BD may be driven more by environmental or lifestyle factors than genetic predisposition alone. For instance, factors like metabolic dysfunction, inflammation, reduced physical activity or overeating could play a more significant role in linking BMI with cognitive decline. This highlights the importance of considering both genetic and environmental influences separately when studying how body weight impacts cognitive health.

The present results must be considered in light of certain limitations. Firstly, the choice of BMI as a single measure for assessing metabolic syndrome, which is not without criticism as an obesity measure and should be considered as a proxy for body fat. However, BMI is commonly used as a single measure for assessing metabolic syndrome risk because it serves as a straightforward and non-invasive proxy for body fat [62]. Elevated BMI correlates with higher risks of metabolic disturbances like insulin resistance, hypertension, and dyslipidaemia, making it effective for large-scale population screening. Although BMI does not measure body fat distribution or metabolic health directly, it provides a useful first step in identifying individuals who may benefit from more detailed metabolic evaluations. Its simplicity and ease of calculation also make it practical for clinical and public health applications [63]. The availability of more biomarkers of peripheral blood would have allowed a deeper insight into the association with

genetics, metabolic and cognitive aspects of BD. Although information about some of these metabolic conditions was available in the PsyCourse (i.e. diabetes mellitus, hypertension and hypercholesterolemia/triglyceride levels), they were self-reported measurements based on an interview in which participants were asked if they were ever diagnosed with them. Lastly, we did not control for the influence of medication in the analyses, so we cannot rule out potential effects on both the BMI and cognitive performance [64]. Likewise, we did not account for other illness course variables that may influence cognition, such as the number of episodes and illness duration. Despite these limitations, a strength of the study is being a multi-site study with participants coming from different regions, which may increase the external validity of the results.

5. CONCLUSION

In conclusion, this study underscores that cognitive impairment in elevated BMI commonly observed in individuals with BD is likely more attributable to modifiable factors, including medication side effects, poor dietary habits, and a sedentary lifestyle. Moderating effects of BD-PRS could only by observed for processing speed and working memory. The BMI-PRS might have influenced BMI, but did not moderate the association between BMI and cognitive performance. These results provide important insights for clinical management. Weight management strategies should focus on mitigating medication side effects, promoting healthier lifestyle habits and increasing physical activity. This proactive approach holds promise, as these elements can be adjusted and incorporated into holistic treatment plans. By addressing obesity, there is potential to alleviate some cognitive deficits, thereby improving long-term outcomes. Future research should investigate whether weight loss interventions can have a direct positive impact on cognitive performance in BD. Longitudinal studies are crucial to determine whether reducing BMI can lead to lasting improvements in cognitive functions like processing speed and executive abilities and contribute to a more favourable overall prognosis.

Even so, future studies should aim to unravel the mechanisms underlying the genetic relationship between BD, BMI and cognition. Addressing metabolic health and cognitive impairment through lifestyle and medical interventions is essential for promoting a balanced

BMI and reducing the risk of metabolic diseases. Investigating the specific genetic pathways involved and their interaction with environmental factors could provide deeper insights. For instance, future studies could explore the mediating effect of cognitive PRS or other related PRS to provide a more comprehensive understanding of the role of PRS in the relationship between BMI and cognition. Understanding the mechanisms underlying this relationship is necessary for an early detection of individuals at risk of developing higher cognitive impairment.

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Conflict of interests

EV has received grants and served as consultant, advisor or CME speaker for the following entities: AB-Biotics, AbbVie, Adamed, Angelini, Biogen, Boehringer-Ingelheim, Celon Pharma, Compass, Dainippon Sumitomo Pharma, Ethypharm, Ferrer, Gedeon Richter, GH Research, Glaxo-Smith Kline, Janssen, Lundbeck, Medincell, Merck, Novartis, Orion Corporation, Organon, Otsuka, Roche, Rovi, Sage, Sanofi-Aventis, Sunovion, Takeda, and Viatris, outside the submitted work. IGA has received speaker or consultant honoraria from Aristo, Idorsia, Janssen, Merck, Schwabe, Recordati. BTB received honoraria from Angelini, AstraZeneca, Biogen, Boehringer

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Authors' contribution

Conception and study design: BS, LM, CT, SP, UH

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Drafting the manuscript and figures: BS, CT, RB

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Acquisition and/or processing and/or managing of data (phenotype data and/or biological data): JMB, UH, SP, KA, PF, MH, ANF, MOK, DRE, ECS, FS, IGA, VA, BTB, UD, DED, AJF, CF, GJ, CK, JR, EZR, MS, CS, JW, JZ, TGS

Critically revised the manuscript and agreed to the final version of the manuscript: All authors

Data availability statement

The data that support the findings of this study are available from the PsyCourse Study upon reasonable request.

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FIGURE LEGENDS

FIGURE 1.

Note. These figures demonstrate the interaction effect of BD-PRS: (*a)* between Body Mass Index (BMI) and the Trail Making Test part A (TMT-A), and *(b)* between BMI and the Digit Backward Span

Unravelling the link between body mass index and cognitive performance in individuals with bipolar disorder and exploration of PRS moderation effect: Findings from the PsyCourse Study.

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Data availability statement

The data that support the findings of this study are available from the PsyCourse Study upon reasonable request.

ABSTRACT

Introduction: Bipolar disorder (BD) is a severe mental disorder characterized by extreme mood swings, often accompanied by metabolic comorbidities, such as cardiovascular disease, which increase mortality and reduce quality of life. Both metabolic dysfunctions and BD are associated with cognitive dysfunction. Body mass index (BMI) is closely linked to metabolic health and cognitive performance. This study examined the link between BMI and cognitive function in individuals with BD and how genetic factors, namely polygenic risk scores (PRS) for BD and BMI, might influence this link. **Methods:** Genetic (PRS scores) and phenotypic data (sociodemographic factors, clinical symptoms and cognitive function) of 341 adult patients with BD diagnosis from the PsyCourse Study, a large, multi-site, and naturalistic longitudinal study were utilized for this study. First, we performed univariate and multivariate regression analyses to investigate associations between BMI and cognitive performance. Second, moderation analyses were conducted to examine the potential moderator effects of BD-PRS or BMI-PRS in the relationship between BMI and different cognitive outcomes. **Results:** BMI was associated with processing speed (TMT-A) and executive function (TMT-B), with individuals with higher BMI showing poorer performance. Moderation analyses revealed that the effect of BMI on cognition was moderated by BD-PRS only regarding the processing speed. BMI-PRS did not moderate the association between BMI and cognitive variables. **Conclusions:** Our findings indicate that the relationship between BMI and cognitive impairment in BD is partially moderated by BD genetic liability but not BMI genetic load.

Keywords: Polygenic risk scores (PRS), psychomotor speed, executive function, bipolar disorder, body mass index

SIGNIFICANT OUTCOMES

1. There exists a positive association between cognitive impairment and BMI in bipolar disorder.
2. Bipolar disorder genetic liability may moderate the relationship between BMI and processing speed.
3. Addressing obesity and promoting healthy lifestyles should be key to improving cognitive performance in bipolar disorder.

LIMITATIONS

1. The use of BMI as a single measure for assessing metabolic syndrome.
2. The potential effect of pharmacological treatment and somatic morbidities was not controlled for in the analyses.
3. The availability of peripheral blood biomarkers would have allowed a deeper insight into association with genetics, metabolic and cognitive aspects of bipolar disorder.

1. INTRODUCTION

Bipolar disorder (BD) is a severe mental health condition[1] with high rate of somatic comorbidities especially cardiovascular diseases [2], leading to increased mortality, reduced quality of life, and lower psychosocial and cognitive functioning.[2]Individuals with mood disorders are predisposed to metabolic dysfunction, while those with metabolic dysregulation, such as diabetes and obesity, experience more severe depressive symptoms. Overweight and obesity are well known to be prevalent in individuals with mood disorders, especially in BD [3]. Antipsychotic drugs, a common the treatment of BD, seem to be associated with an increased likelihood of weight gain or obesity [4]. Nevertheless, an increased prevalence of overweight has been described not only after short-time use of antipsychotics in first treated episode of psychosis [5], but also for drug-naïve BD patients [6].

Emerging evidence indicates that individuals with BD in euthymia show impairments in various cognitive domains which are highly relevant and determine psychosocial functioning outcomes [7,8]. Moreover, several studies found a negative effect of overweight and obesity on cognitive function in euthymic patients [9–11], likewise in individuals at risk for BD [12]. This implies that the prevalence of overweight and obesity negatively impacts cognitive performance of individuals with BD. The most robust differences between obese versus normal weight individuals with BD were observed in executive function and processing speed [13]. However, both metabolic dysfunction and mood disorders are independently associated with cognitive deficits [14]. In fact, in general population, increased body fat and metabolic dysfunction may independently contribute to impaired memory and executive functions as well as structural brain abnormalities in frontal and medial temporal lobe regions. These effects stem from inflammation, vascular changes, and oxidative stress linked to excess fat and insulin resistance [15]. Additionally, cognitive impairment may also influence behaviors and lifestyles that worsen these conditions. In this sense, the body mass index (BMI), a widely used score based on height and weight, serves as a key indicator of metabolic health. BMI is increasingly examined for its impact on various health outcomes, including cognitive performance.

One emerging area of research is the role of polygenic risk scores (PRS) in understanding the interplay between BMI and cognitive performance in BD. PRS represent the cumulative effect of multiple common genetic variants associated with a particular trait or condition. BD-PRS reflects the genetic risk to BD, while BMI-PRS indicates the genetic propensity for a higher BMI [16]. Although multifactorial in aetiology, previous evidence suggests a common genetic background between psychiatric and metabolic disorders [17]. Since the research showed that BMI-PRS has been associated with BD, the common biology between obesity and BD has been suggested [18]. Moreover, some studies have found shared genetic contributions to BMI and cognitive function, showing a small phenotypic correlation between the two traits but a moderate genetic correlation [19]. It has also been shown several individual genetic variants are associated with both traits. By studying the moderation effects of BD-PRS and BMI-PRS, the current study aimed to uncover how genetic factors influence the relationship between BMI and cognitive performance in individuals with BD. This approach allows for a more nuanced understanding of how individual genetic background can modulate the association of BMI on cognitive outcomes.

1.1 Aims of the study

The study aimed to evaluate the relationship between body mass index ~~BMI~~ and cognitive function, investigating whether ~~BMI~~ body mass index serves as a predictor of cognitive performance in a sample of euthymic patients with ~~BD~~ bipolar disorder. Additionally, it assessed the potential moderating effect of polygenic risk scores for bipolar disorder and body mass index ~~BD-PRS and BMI-PRS~~ on this relationship. Given the shared genetic background observed between psychiatric and metabolic disorders, we hypothesized that polygenic risk scores would moderate the relationship between body mass index and cognitive performance. Specifically, individuals with higher polygenic risk scores for body mass index or bipolar disorder were expected to exhibit poorer cognitive function as body mass index increased.

2. MATERIALS AND METHODS

2.1 Study design

This study used data from the PsyCourse Study, a longitudinal, naturalistic, multi-site study conducted in different sites in Germany and Austria (www.PsyCourse.de). More details about the study design can be found elsewhere [20]. All of the data used for analyses came from the baseline assessment with the exception of the verbal memory assessment collected at visit 2. Data were obtained from the PsyCourse dataset Version 5.0 (https://data.ub.uni-muenchen.de/251/) [21].

2.2 Participants

Adult patients (18-65 years) diagnosed with BD according to DSM-IV Structured Clinical Interview for DSM-IV [SCID] [22] were only included in the analyses if they were in euthymia at the time of assessment (scorer ≤ 23 on the Inventory of Depressive Symptomatology ($IDS\text{-}C_{30}$) rating scale [23,24] and ≤ 14 in the Young Mania Rating Scale (YMRS) [25].

All participants provided written informed consent. The Ethics Committees responsible at each participating centre approved the study, conducted in accordance with the Declaration of Helsinki.

2.3 Measures

2.3.1 Clinical, Functional and Neuropsychological assessment

Current affective symptomatology was assessed using the $IDS\text{-}C_{30}$ [23] to assess severity of depressive symptoms and the YMRS [25] for the (hypo)manic ones.

Cognitive performance was assessed using the following battery of neuropsychological tests: Trail Making Test (TMT) part A [26] and Digit Symbol Test (DST) [27] to assess processing speed; TMT part B [26] to assess executive function; Verbal Digit span (Backward) [27,28] to evaluate the working memory; Verbal learning and memory test (Deuthc: Verbaler Lern- und Merkfähigkeitstest [VLMT] [29], to assess learning and memory; Multiple-Choice Vocabulary Intelligence Test (Deutch: Mehrfachwahl Wortschatz-Intelligenz [MWT-B] [30] to assess crystallized intelligence. The Global Assessment of Functioning (GAF) measured the individual's psychosocial functioning [31].

2.3.2 Body mass index (BMI)

BMI of study participants was calculated as weight in kilograms divided by the squared height in meters.

2.3.2 Genotyping and PRS calculation

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 extensively described in other studies [32–34]. Genetic imputation was carried out via the Michigan Imputation Server using Minimac4 and the Haplotype Reference Consortium (HRC; Version r1.1) as the reference dataset. Genetic variants with R^2>0.3 and MAF>0.01 were kept post-imputation. The PRS-continuous shrinkage (CS) tool was used to infer posterior SNP effect sizes under continuous shrinkage priors, setting the global shrinkage parameter (ϕ) at six different values (i.e., ϕ = 1E-01, 1E-02, 1E-03, 1E-04, 1E-05, and 1E-06) [35] based on the GWAS summary stats for BD [36] and BMI [37]. In brief, to find the optimal phi value as regards predictive performance, a grid search was carried out based on the different ϕ thresholds, with larger phis (1E-01, 1E-02) representing very polygenic traits and smaller ϕ (1E-05, 1E-06) less polygenic traits. BD-PRS and BMI-PRS were calculated with PLINK 1.90 score function [38] using imputed genotypes. Ancestry multidimensional scaling components (MDS) analyses showed all the samples included overlapped with 1000 Genomes Project European reference populations.

2.4 Statistical analyses

Descriptive statistics were used to define sample characteristics by calculating means and frequencies of variables.

The distribution of cognitive variables was evaluated performing the Kolmogorov-Smirnov statistics and by inspecting Q-Q plots and the distribution in the histograms. The cognitive variables not following a normal distribution (i.e. TMT-A, TMT-B, and Verbal Digit span Backward) were log-transformed to normalize their distribution and reducing the impact of the outliers. Scores on both TMTs were multiplied by -1 due to their inverse interpretation. Cognitive variables were considered the dependent variables. We used linear mixed models in all our analyses with recruitment centre as a random effect. First, we performed univariate regressions

to analyse associations between BMI and the different cognitive outcomes. Subsequently, when significant associations were detected between BMI and cognitive variables, we ran multivariate linear regression (backward stepwise method) for those cognitive variables, adjusting for age and sex since these variables may influence cognitive performance and BMI. To analyse the second aim, moderation (interaction) analyses were conducted to examine if BD-PRS (continuous and independent variable) has a moderator effect on the relationship between BMI and the different cognitive variables (dependent variables), that is, BD-PRS would ~~change the direction and/or strength of~~ modify the relationship between the independent and dependent variables. To assess the moderator effect, the interaction terms was added in each model (BMI × BD-PRS or BMI × BMI-PRS). Moderation analyses were run for all the cognitive variables regardless of being associated with BMI, as we wanted to evaluate if adding a moderating effect would modify this relationship. A significant interaction effect would indicate that the association between BMI and cognitive performance varies according to the level of the corresponding PRS, indicating a moderating effect. Every analysis included center as a random effect, age and sex as covariates, as well as the first two ancestry MDS to correct for potential effects of population genetic substructure. Similar moderation analyses were carried out to examine the potential moderator effect of BMI-PRS.

False discovery rate (FDR) was applied to adjust the results for multiple comparisons for the univariate and multivariate regression analyses. FDR was set at 5%, and adjusted *p-values* ≤.05 were considered significant. No multiple testing corrections were performed for the moderation analyses due to the exploratory nature of them. Alpha level set to $p \leq .05$. All analyses were conducted using IBM SPSS version 27.

3. RESULTS

The total sample consist of N=341 patients, with a mean (SD) age of 44.60 (12.3); 49.3% were female (n=168) and 50.7% male (n=173). See Table 1 for demographic and clinical variables.

3.1 Associations between BMI and cognitive outcomes

BMI was associated with TMT-A (p=.018) and TMT-B (p=.018) (see Table 2), specifically, individuals with higher BMI showed a poorer performance in these tests. Verbal Digit span backward and DST were also associated with BMI, however, these findings did not survive adjustment for multiple comparisons.

We ran multivariate regressions analyses for those cognitive variables associated with BMI (see Table 3), adjusting for age and sex. Age and BMI were associated with TMT-B (p=.001 and p=.046 respectively). However, after the adjustment for multiple comparisons, the effect of age remained significant (adjusted-p=.002) and a trend was observed for BMI (adjusted-p=.061). For TMT-A, similar results were observed; age remained significant (adjusted-p=.002) and a trend for BMI was found (adjusted-p=.066).

3.2 Moderation effects of PRS between BMI and cognitive performance

After adjusting for age, sex, and ancestry principal components, BD-PRS interacted with BMI to predict lower performance in the TMT-A (for all the phi values, with all p-values<.035) and Verbal Digit span backward (p=.046 for phi_1E-01). Specifically, and for both cognitive variables, at higher BD-PRS levels, a more pronounced inverse association between BMI and cognitive performance was observed. In contrast, this association was not evident at lower BD-PRS levels. Moreover, the moderation effect of BD-PRS on the relationship between BMI and processing speed (TMT-A) was consistent across different phi values, indicating that the effect was not influenced by the assumption of polygenicity. No other moderation effects of BD-PRS were detected in the relationship between BMI and cognitive variables. See Table 4 and figure 1 for the significant interaction p-values and Table S1 for the non-significant results in supplementary material. Concerning BMI-PRS, no moderation effects were detected in the relationship between BMI and cognitive variables.

4. DISCUSSION

An association between increased BMI and cognitive impairment in BD has long been observed, however, the polygenic underpinnings of it have not yet been studied. As far as we know, this is the first study to investigate the effect of genetic liability of BD or BMI on the association between BMI and cognitive performance in BD. Our study revealed an association between BMI

and one processing speed measure and executive functions. However, these associations resulted in a trend after controlling for age. Secondly, BD-PRS had a moderating effect between BMI and processing speed, and to a lesser extent in working memory, suggesting that genetic predisposition to BD plays a significant role in how BMI affects processing speed. In contrast, BMI-PRS was not found as a moderator in the relationship between BMI and cognition suggesting that genetic risk factors specifically related to higher BMI do not appear to influence the extent to which BMI affects cognitive abilities beyond their possible influence on the main predictor, actual BMI.

Processing speed, attention and executive functions are essential for abilities like problem-solving, planning, and maintaining focus on complex tasks. As BMI increases, these impairments can make daily activities more challenging, ultimately impacting quality of life and productivity. These results are in line with prior research that has consistently found obesity associated with cognitive decline in psychiatric disorders, especially in people with BD. For instance, some studies [13] demonstrated significant deficits in processing speed and executive function among individuals with BD and higher BMI [9,13] . Regardless of psychiatric disorders, evidence also suggests that overweight and obese individuals have a lower performance on executive functioning abilities, specifically difficulties with decision-making, planning and problem-solving [39]. The cognitive decline associated with higher BMI may be partly explained by metabolic dysfunction, which is common in individuals with obesity. Conditions such as insulin resistance, systemic inflammation and dyslipidaemia disrupt brain function, particularly in areas responsible for attention and executive control [40]. In this line, the allostatic load (AL) model may also help us to explain this relationship [41]. Some studies found an increase in AL indexes in overweight individuals, and this index was negatively related to executive functions and changes in cortical thickness of regions monitoring behaviour [42,43]. Overweight and high-fat diets can lead to physiological stress and promote chronic low-inflammations states. Moreover, people with a higher BMI are thought to show an elevated impulsivity which makes delaying gratification more difficult [44–46]. This issue is associated with behaviours such as overeating, contributing to weight gain (Fagundo et al., 2012). Executive functions, which include skills related to self-regulation

and monitoring, are crucial for controlling food intake and regulating body weight [48]. Some studies suggest that overeating could cause brain changes that disrupt cognitive processes essential for managing food consumption [49]. For example, hippocampal dysfunction may reduce memory inhibition, making individuals more responsive to cues associated with food. On the other hand, poor cognitive-inhibitory predisposes people to be more influenced by these cues, heightening the risk of overeating and obesity.

Several cardiovascular risk factors are known to be associated with cognitive impairment, including higher BMI, elevated glucose and low levels of HDL cholesterol. Peripheral lipid has also been linked to cognitive performance, specifically with lower processing speed [50]. The association of BMI with specifically processing speed and executive function, and not memory, in our study suggests that there may be another pathophysiological mechanism behind this type of cognitive impairment. One possible explanation is that BMI is more related to arteriolosclerosis and venous collagenosis in the brain, which could contribute to attention/executive impairment [51]. Likewise, individuals with BD exhibit elevated rates of overweight and obesity, which in turn increase the risk of cardiovascular diseases, the primary cause of heightened mortality among individuals with BD. Obesity adversely affects BD by elevating the frequency of mood episodes, levels of disability, incidences of suicide attempts, comorbid conditions, cognitive decline, and abnormalities in white matter [52]. However, our findings suggest that we can't establish an independent relationship between BMI and cognition in BD, as both BMI and cognition are influenced by age. There is insufficient evidence to support a reliable and valid independent link between obesity and cognitive impairment in mid-life adults [53]. It is crucial to consider the impact of other potential confounding variables in the relationship between BMI and cognition. While age influences cognitive performance, somatic comorbidities also play a key role, as their severity and prevalence may increase over time, further impacting cognitive function. In fact, evidence show a high prevalence of physical morbidities in older adults with BD, especially cardiovascular and metabolic ones [54], with a possible association with poorer cognitive performance. However, this association does not

seem independent and other risk factors as demographics, clinical characteristics and lifestyle factors may be involved [55].

Our findings highlight a potential avenue for clinical intervention targeting neurocognitive deficits in individuals with BD through BMI reduction, emphasizing the importance for clinicians to prioritize weight management as an essential part of treatment. Addressing obesity through lifestyle changes or medical interventions may not only enhance physical health but also alleviate cognitive impairments, thereby improving psychosocial functioning in both psychiatric and non-psychiatric populations. Indeed, a meta-analysis by Siervo and colleagues [56] demonstrated significant improvements in executive functioning and attention amongst non-psychiatric obese individuals who achieved substantial weight loss. Furthermore, a recent randomized controlled trial found that physical activity programs can positively influence neurocognitive and functional outcomes in individuals with psychiatric disorders and comorbid obesity [57].

While the relationship between BD and BMI is well documented, the molecular mechanisms driving this connection remain unclear. BD contributes to chronic inflammation and oxidative stress, which are risk factors for cardiovascular disease [58]. Both lifestyle factors and side effects from medication contribute to metabolic comorbidities in people with BD. Nevertheless, elevated BMI is also observed in adolescents and in individuals who have not been treated with medication, suggesting the involvement of common pathophysiological mechanisms and genetic and/or epigenetic factors. In fact, some meta-analyses detected shared genetic determinants between BD and BMI [59].

In this regard, we analysed the potential influence of both BD-PRS and BMI-PRS on the relationship between BMI and cognition. Our results suggested that genetic predisposition to BD may play a significant role in how BMI affects processing speed. Individuals with a higher polygenic burden of BD might be more sensitive to cognitive challenges when they also have a higher BMI. The biological mechanisms underlying this could involve neuroinflammation, insulin resistance, or other metabolic disruptions that are common in both BD and obesity. Thus, individuals with a high BD-PRS might experience a stronger negative impact of BMI on processing

speed tasks because both BD and obesity are linked to similar neurobiological pathways. The interaction of mood regulation pathways, metabolic dysfunction and brain regions involved in processing speed may be more impaired in individuals with a genetic risk for BD [60]. Recognizing BD-PRS as a moderator between BMI and processing speed suggests that a high genetic susceptibility to BD intensifies the impact of BMI on some cognitive domains. This fact could lead to more personalized treatment strategies, where individuals with a high genetic risk for BD might benefit from closer monitoring of their BMI and cognitive function, as well as targeted interventions to address metabolic health and cognitive deficits. In this regard, integrative approaches addressing these areas alongside components like psychoeducation and mindfulness may be also an effective therapeutic option for this population [61].

Finally, BMI-PRS was not found as a moderator in the relationship between BMI and cognition suggesting that genetic risk factors related to higher BMI do not appear to influence the extent to which BMI affects cognitive abilities, beyond their effect on BMI. It indicated that the relationship between BMI and cognitive performance in BD may be driven more by environmental or lifestyle factors than genetic predisposition alone. For instance, factors like metabolic dysfunction, inflammation, reduced physical activity or overeating could play a more significant role in linking BMI with cognitive decline. This highlights the importance of considering both genetic and environmental influences separately when studying how body weight impacts cognitive health.

The present results must be considered in light of certain limitations. Firstly, the choice of BMI as a single measure for assessing metabolic syndrome, which is not without criticism as an obesity measure and should be considered as a proxy for body fat. However, BMI is commonly used as a single measure for assessing metabolic syndrome risk because it serves as a straightforward and non-invasive proxy for body fat [62]. Elevated BMI correlates with higher risks of metabolic disturbances like insulin resistance, hypertension, and dyslipidaemia, making it effective for large-scale population screening. Although BMI does not measure body fat distribution or metabolic health directly, it provides a useful first step in identifying individuals who may benefit from more detailed metabolic evaluations. Its simplicity and ease of calculation

also make it practical for clinical and public health applications [63]. The availability of more biomarkers of peripheral blood would have allowed a deeper insight into the association with genetics, metabolic and cognitive aspects of BD. Although information about some of these metabolic conditions was available in the PsyCourse (i.e. diabetes mellitus, hypertension and hypercholesterolemia/triglyceride levels), they were self-reported measurements based on an interview in which participants were asked if they were ever diagnosed with them. Lastly, we did not control for the influence of medication in the analyses, so we cannot rule out potential effects on both the BMI and cognitive performance [64]. Likewise, we did not account for other illness course variables that may influence cognition, such as the number of episodes and illness duration. Despite these limitations, a strength of the study is being a multi-site study with participants coming from different regions, which may increase the external validity of the results.

5. CONCLUSION

In conclusion, this study underscores that cognitive impairment in elevated BMI commonly observed in individuals with BD is likely more attributable to modifiable factors, including medication side effects, poor dietary habits, and a sedentary lifestyle. Moderating effects of BD-PRS could only by observed for processing speed and working memory. The BMI-PRS might have influenced BMI, but did not moderate the association between BMI and cognitive performance. These results provide important insights for clinical management. Weight management strategies should focus on mitigating medication side effects, promoting healthier lifestyle habits and increasing physical activity. This proactive approach holds promise, as these elements can be adjusted and incorporated into holistic treatment plans. By addressing obesity, there is potential to alleviate some cognitive deficits, thereby improving long-term outcomes. Future research should investigate whether weight loss interventions can have a direct positive impact on cognitive performance in BD. Longitudinal studies are crucial to determine whether reducing BMI can lead to lasting improvements in cognitive functions like processing speed and executive abilities and contribute to a more favourable overall prognosis.

Even so, future studies should aim to unravel the mechanisms underlying the genetic relationship between BD, BMI and cognition. Addressing metabolic health and cognitive impairment through lifestyle and medical interventions is essential for promoting a balanced BMI and reducing the risk of metabolic diseases. Investigating the specific genetic pathways involved and their interaction with environmental factors could provide deeper insights. For instance, future studies could explore the mediating effect of cognitive PRS or other related PRS to provide a more comprehensive understanding of the role of PRS in the relationship between BMI and cognition. Understanding the mechanisms underlying this relationship is necessary for an early detection of individuals at risk of developing higher cognitive impairment.

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Conflict of interests

EV has received grants and served as consultant, advisor or CME speaker for the following entities: AB-Biotics, AbbVie, Adamed, Angelini, Biogen, Boehringer-Ingelheim, Celon Pharma, Compass, Dainippon Sumitomo Pharma, Ethypharm, Ferrer, Gedeon Richter, GH Research, Glaxo-Smith Kline, Janssen, Lundbeck, Medincell, Merck, Novartis, Orion Corporation, Organon, Otsuka, Roche, Rovi, Sage, Sanofi-Aventis, Sunovion, Takeda, and Viatris, outside the submitted work. IGA has received speaker or consultant honoraria from Aristo, Idorsia, Janssen, Merck, Schwabe, Recordati. BTB received honoraria from Angelini, AstraZeneca, Biogen, Boehringer

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Authors' contribution

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Data analysis: BS, CT, SP, RB

Drafting the manuscript and figures: BS, CT, RB

Supervision, formal and accurate revision: MB, UH, CT, SP, EV, TGS

Acquisition and/or processing and/or managing of data (phenotype data and/or biological data): JMB, UH, SP, KA, PF, MH, ANF, MOK, DRE, ECS, FS, IGA, VA, BTB, UD, DED, AJF, CF, GJ, CK, JR, EZR, MS, CS, JW, JZ, TGS

Critically revised the manuscript and agreed to the final version of the manuscript: All authors

Data availability statement

The data that support the findings of this study are available from the PsyCourse Study upon reasonable request.

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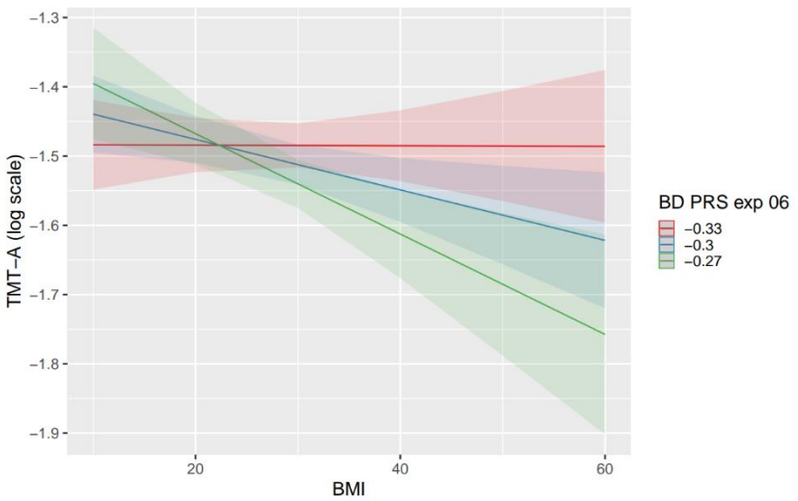
FIGURE LEGENDS

FIGURE 1.

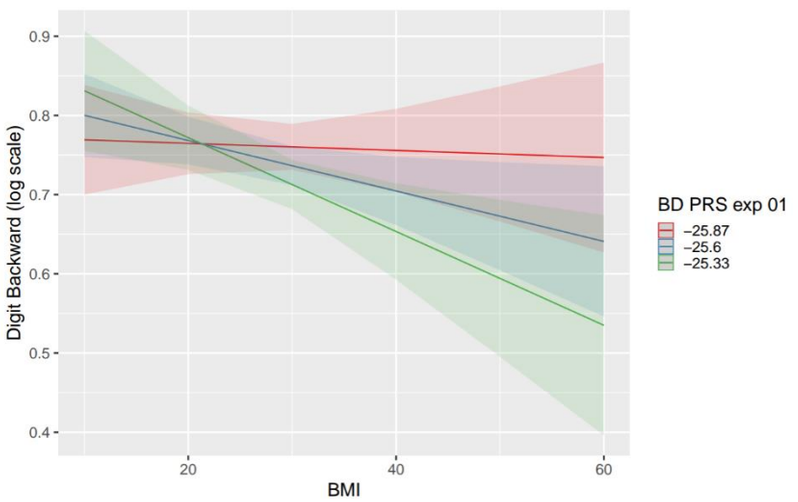
Note. These figures demonstrate the interaction effect of BD-PRS: (*a)* between Body Mass Index (BMI) and the Trail Making Test part A (TMT-A), and *(b)* between BMI and the Digit Backward Span

Figure 1. Moderation effect of BD-PRS between BMI and processing speed and working memory

a)



b)



Note. These figures demonstrate the interaction effect of BD-PRS: (*a)* between Body Mass Index (BMI) and the Trail Making Test part A (TMT-A), and *(b)* between BMI and the Digit Backward Span

Table 1. Sociodemographic, clinical, and cognitive variables of the BD sample

Sociodemographic variables	**Mean (*SD*) or n (%)**	**Median [IQR]**
Sex: female	168 (49.3)	
Age (in years)	44.60 (12.3)	47 [34-55]
MWT-B score	29.17 (4.4)	30 [27-32]
Living alone: Yes (%)	126 (37)	
Educational status: highest level	100 (30.3)	
Current paid employment: Yes (%)	162 (47.5)	
Clinical variables	**Mean (*SD*) or n (%)**	**Median [IQR]**
YMRS sum score	2.53 (3.6)	1 [0-4]
IDS-C_{30} sum score	9.62 (6.5)	9 [4-15]
GAF	64.08 (11.6)	65 [55-70]
Diagnosis type Bipolar I disorder	269 (78.9)	
Number of depressive episodes	7.79 (8.4)	5 [3-10]
Number of mania episodes	5.18 (8.0)	3 [2-6]
Duration of illness	12.58 (10.8)	10 [3-18]
Lifetime psychotic symptoms: Yes (%)	169 (54.5)	
Lifetime suicidal ideation: Yes (%)	257 (77.4)	
Suicide attempt: Yes (%)	92 (28.1)	
Family history of psychiatric illness: Yes (%)	259 (78.7)	
Number of antidepressants prescribed	0.55 (0.6)	0 [0-1]
Number of antipsychotics prescribed	0.96 (0.8)	1 [0-1]
Number of mood stabilizers prescribed	0.77 (0.6)	1 [0-1]
Number of tranquilizers prescribed	0.16 (0.4)	0 [0-0]
Physical measures	**Mean (*SD*) or n (%)**	**Median [IQR]**
Elevated cholesterol o triglyceride level: Yes (%)	48 (14.1)	
Hypertension: Yes (%)	68 (20.3)	
Diabetes: Yes (%)	21 (6.2)	

BMI	27.87 (5.9)	26.5 [23.6-31.3]
Neuropsychological assessment	**Mean *(SD)***	**Median [IQR]**
Processing speed (TMT-A time)	34.91 (15.2)	32.50 [25-41]
Executive Functioning (TMT-B time)	83.30 (39.1)	77 [56-100]
Processing Speed (DST) (number of correct symbols)*	63.37 (17.1)	62 [53-74]
Working Memory (Digit span backward)	6.08 (1.9)	6 [5-7]
Verbal Memory (verbal learning and memory test; sum of correctly recalled words)	48.04 (11.4)	48 [40-56.2]

Note: BMI: Body Mass Index; DST: Digit Symbol Test; GAF: Global Assessment of Functioning; IDS-C30: Inventory of Depressive Symptomatology; MWT-B: Multiple-Choice Vocabulary Intelligence Test; TMT: Trail Making Test; YMRS: Young Mania Rating Scale.

* Only participants that fully completed the test were included.

Table 2. Associations between BMI and cognitive variables

	β	s.e.	*Adjusted p-value*
TMT-A	-.004	.002	**.018**
TMT-B	-.005	.002	**.018**
Digit span backward	-.003	.001	.059
DST	-.327	.164	.059
VLMT	-.218	.154	.158
Note: DST: Digit Symbol Test; TMT: Trail Making Test; VLMT: Verbaler Lern- und Merkfähigkeitstest			

Table 3. Multivariate regression analyses

Outcome		β	s.e.	*Adjusted p value*
TMT-A	BMI	-.003	.001	.066
	age	-.006	.001	**.002**
TMT-B	BMI	-.003	.002	.061
	age	-.007	.001	**.002**
Note: BMI: Body Mass Index; TMT: Trail Making Test				

Table 4. Moderation effects of BD-PRS on associations between BMI and cognitive performance

	BD-PRS								
	β	***SE***	***p***	***β***	***SE***	***p***	***β***	***SE***	***p***
Outcomes /Cognition	**BMI**			**BD-PRS phi_1E-01**			**Interaction**		
TMT-A	-.343	.130	**.009**	.330	.144	**.023**	-.013	.005	**.009**
Digits Span Backward	-.263	.130	**.044**	.216	.143	.132	-.010	.005	**.046**
Outcomes /Cognition	**BMI**			**BD-PRS phi_1E-02**			**Interaction**		
TMT-A	-.202	.081	**.014**	.428	.205	**.037**	-.018	.007	**.015**
Outcomes /Cognition	**BMI**			**BD-PRS phi_1E-03**			**Interaction**		
TMT-A	-.115	.053	**.031**	.552	.325	.090	-.024	.011	**.035**
Outcomes /Cognition	**BMI**			**BD-PRS phi_1E-04**			**Interaction**		
TMT-A	-.082	.036	**.023**	.919	.546	.093	-.042	.019	**.028**
Outcomes /Cognition	**BMI**			**BD-PRS phi_1E-05**			**Interaction**		
TMT-A	-.058	.021	**.008**	1.585	.805	**.050**	-.073	.028	**.010**
Outcomes /Cognition	**BMI**			**BD-PRS phi_1E-06**			**Interaction**		
TMT-A	-.040	.013	**.003**	2.676	1.210	**.028**	-.120	.043	**.005**
BMI-PRS									
Note: BD: Bipolar disorder; BMI: Body Mass Index; PRS: Polygenic Risk Score; TMT-A: Trail Making Test, part A;									
Analyses were corrected by age, sex and MDS. Recruitment center was introduced as random effect									

Table S1. Moderation effects of BD-PRS and BMI-PRS on associations between BMI and cognitive performance

	BD-PRS								
	β	***SE***	***p***	***β***	***SE***	***p***	***β***	***SE***	***p***
Outcomes /Cognition	**BMI**			**BD-PRS phi_1E-01**			**Interaction**		
TMT-B	-.224	.148	.132	.183	.164	.265	-.009	.006	.137
DST	-16.047	13.289	.228	13.446	14.671	.360	-.621	.518	.232
VLTM correct word	-12.841	14.570	.379	14.339	15.719	.363	-.499	.568	.381
Outcomes /Cognition	**BMI**			**BD-PRS phi_1E-02**			**Interaction**		
TMT-B	-.107	.093	.250	.180	.233	.441	-.009	.008	.265
DST	-11.126	8.285	.180	21.500	20.865	.304	-.970	.730	.185
Digits Span Backward	-.153	.081	.060	.258	.203	.205	-.013	.007	.064
VLTM correct word	-9.610	9.696	.323	24.519	23.643	.301	-.844	.856	.326
Outcomes /Cognition	**BMI**			**BD-PRS phi_1E-03**			**Interaction**		
TMT-B	-.042	.060	.489	.096	.369	.795	-.008	.013	.522
DST	-6.552	5.412	.227	28.364	32.970	.390	-1.370	1.153	.235
Digits Span Backward	-.099	.053	.062	.379	.321	.238	-.020	.011	.070
VLTM correct word	-6.546	6.875	.342	38.258	39.977	.340	-1.388	1.469	.346
Outcomes /Cognition	**BMI**			**BD-PRS phi_1E-04**			**Interaction**		
TMT-B	-.032	.041	.435	.142	.620	.820	-.015	.021	.482
DST	-5.501	3.656	.133	56.157	55.510	.313	-2.833	1.925	.142

Digits Span Backward	-.059	.036	.102	.522	.543	.337	-.029	.019	.119
VLTM correct word	-2.428	4.881	.619	37.872	69.924	.589	-1.257	2.581	.627
Outcomes /Cognition	**BMI**			**BD-PRS phi_1E-05**			**Interaction**		
TMT-B	-.020	.025	.420	.268	.919	.771	-.022	.032	.495
DST	-3.115	2.202	.158	74.299	82.384	.368	-3.947	2.893	.174
Digits Span Backward	-.031	.022	.146	.735	.809	.364	-.038	.028	.183
VLTM correct word	-.807	2.976	.787	35.381	104.355	.735	-.997	3.951	.801
Outcomes /Cognition	**BMI**			**BD-PRS phi_1E-06**			**Interaction**		
TMT-B	-.024	.015	.121	1.375	1.398	.326	-.067	.049	.177
DST	-2.006	1.391	.150	109.546	126.141	.386	-6.073	4.470	.175
Digits Span Backward	-.014	.013	.287	.859	1.220	.482	-.037	.043	.386
VLTM correct word	.421	1.454	.772	-38.704	129.200	.765	1.542	4.693	.743
BMI-PRS									
Outcomes /Cognition	**BMI**			**BMI-PRS phi_1E-01**			**Interaction**		
TMT-A	.004	.008	.567	-.133	133	.317	.004	.005	.394
TMT-B	-.010	.009	.250	.131	.150	.383	-.004	.005	.428
DST	.712	.802	.375	-12.895	13.691	.347	.519	.485	.285
Digits Span Backward	-.005	.008	.494	.035	.133	.791	-.002	.005	.708
VLTM correct word	.358	.887	.687	-5.683	14.971	.705	.279	.541	.607

Outcomes /Cognition	**BMI**			**BMI-PRS phi_1E-02**			**Interaction**		
TMT-A	.005	.007	.474	-.202	.175	.250	.007	.006	.293
TMT-B	-.006	.008	.412	.096	.198	.627	-.003	.007	.682
DST	.718	.707	.311	-19.973	18.028	.269	.785	.640	.221
Digits Span Backward	-.004	.007	.516	.030	.176	.867	-.002	.006	.758
VLTM correct word	.164	.798	.837	-3.826	20.078	.849	.238	.725	.743
Outcomes /Cognition	**BMI**			**BMI-PRS phi_1E-03**			**Interaction**		
TMT-A	.004	.007	.582	-.244	.239	.306	.008	.009	.379
TMT-B	-.005	.008	.480	.085	.269	.752	-.003	.010	.760
DST	.827	.687	.230	-32.179	24.409	.188	1.237	.871	.157
Digits Span Backward	-.005	.007	.420	.076	.238	.750	-.004	.008	.648
VLTM correct word	.241	.777	.757	-7.949	27.247	.771	.437	.992	.660
Outcomes /Cognition	**BMI**			**BMI-PRS phi_1E-04**			**Interaction**		
TMT-A	.003	.006	.566	-.339	.302	.263	.011	.011	.326
TMT-B	-.005	.006	.454	.093	.341	.785	-.003	.012	.783
DST	.707	.573	.219	-43.225	30.852	.162	1.649	1.101	.135
Digits Span Backward	-.006	.006	.291	.168	.302	.578	-.007	.011	.540
VLTM correct word	.113	.671	.866	-5.157	35.333	.884	.418	1.288	.746
Outcomes /Cognition	**BMI**			**BMI-PRS phi_1E-05**			**Interaction**		
TMT-A	.004	.006	.541	-.396	.372	.288	.013	.013	.323
TMT-B	-.006	.007	.435	.141	.420	.737	-.006	.015	.707

DST	.704	.658	.286	-45.338	38.244	.237	1.750	1.357	.198
Digits Span Backward	-.008	.006	.209	.296	.371	.426	-.011	.013	.382
VLTM correct word	-.219	.749	.770	13.632	42.204	.747	-.291	1.537	.850
Outcomes /Cognition	**BMI**			**BMI-PRS phi_1E-06**			**Interaction**		
TMT-A	.000	.004	.945	-.273	.405	.501	.008	.014	.589
TMT-B	-.005	.004	.295	.137	.456	.764	-.007	.016	.679
DST	.252	.399	.527	-39.398	41.887	.348	1.482	1.492	.321
Digits Span Backward	-.006	.004	.106	.377	.403	.350	-.015	.014	.307
VLTM correct word	.011	.487	.982	-2.935	47.353	.951	.312	1.741	.858
Note: DST: Digit Symbol Test; TMT-A: Trail Making Test, part A; TMT-B: Trail Making Test, part B; VLMT: Verbaler Lern- und Merkfähigkeitstest									
Analyses were corrected by age, sex and MDS. Recruitment center was introduced as random effect									

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Barcelona, July 30th, 2025

Dr. Ida Hageman
Editors-in-Chief
Acta Psychiatrica Scandinavica
Dear Dr. Ida Hageman,

We would like to express our gratitude for the valuable feedback provided by the reviewers on our article entitled *"Unravelling the link between body mass index and cognitive performance in individuals with bipolar disorder and exploration of PRS moderation effect: Findings from the PsyCourse Study",* submitted to Acta Psychiatrica Scandinavica.

We believe that the changes made have significantly improved our article, and we hope they address the concerns raised by the reviewers. We kindly request that you and the reviewers reassess our manuscript considering these changes. Our answers to all the requests are written below in bold type. The changes in the manuscript have been highlighted in yellow. Please find below our detailed responses to each of the reviewers' comments.

Yours sincerely,

Carla Torrent

Dear reviewers,

We appreciate all your comments on our manuscript, and we value your time and expertise in carefully reviewing it. We believe that all the comments have been very useful in improving the quality of the article. Answers to all your queries are provided below in bold type. We have highlighted all the changes made in the manuscript in yellow.

Reviewer 1:

The article is original and has translational potential. Pending clarification of some minor issues, the manuscript could be a candidate for publication.

Thank you for your time in reviewing our manuscript and your positive comments.

Reviewer 2:

The authors investigate the potential moderating effect of BD-PRS on the relationship between BMI and cognitive performances. The Authors found that higher BMI predicts lower scores at TMT-A and TMT-B. BD-PRS interacted with TMT-A and digit span.

The Study is interesting and provides new insight on the relationship between BMI and cognitive function. There are some issues I have to raise:

Thanks for taking the time to review our manuscript and provide us with positive feedback and valuable suggestions to improve the quality of our report.

Q1. At the end of the introduction the Authors should clearly state what they expect to find and why.

A1. Following the reviewer's suggestion, we have added our hypothesis at the end of the introduction section (see page 7), as follows: *"Given the shared genetic background observed between psychiatric and metabolic disorders, we hypothesized that PRS would moderate the relationship between BMI and cognitive performance. Specifically, individuals with higher polygenic risk scores for BMI or BD were expected to exhibit poorer cognitive function as BMI increased"*.

Q2. The Authors corrected the multivariate regressions only for age and sex. However, there are other variables that can influence cognition in bipolar, such as duration of disease, type of bipolar disorder, number of episodes, and medications. In order to strengthen the results found, the Authors should include these variables into the model. Otherwise, this is an important limitation of the study.

A2. Thanks for this insightful observation. We agree with the reviewer that multiple variables related to the illness course of bipolar disorder may influence cognitive performance. However, we did not include these variables in our multivariate models because the primary purpose of the study was to assess the potential influence of PRS on the relationship between BMI and cognition in bipolar disorders. Our intention was not to test different augmented models with clinical and demographic variables previously identified in the literature as contributors to cognitive

impairment in this population. As a first step before assessing the moderating effect of PRS, we assessed the relationship between BMI and cognitive variables only adjusting the models by those variables (age and sex) that may influence both variables.

To clarify this issue in the manuscript we revised a sentence in Methods section (see page 10): *"Subsequently, when significant associations were detected between BMI and cognitive variables, we ran multivariate linear regression (backward stepwise method) for those cognitive variables, adjusting for age and sex since these variables may influence cognitive performance and BMI".*

Secondly, we have also expanded a sentence in the study limitations section to highlight this issue (see page 17): "*Lastly, we did not control for the influence of medication in the analyses, so we cannot rule out potential effects on both the BMI and cognitive performance [64]. Likewise, we did not account for other illness course variables that may influence cognition, such as the number of episodes and illness duration."*

Q3. The description of the moderation analysis is too vague in the methods and in the discussion. Specifically, in Table 4, the Authors described all the phy values- However, in the methodology phy values are not fully explained. Even though the methodology is not wrong, a clearer explanation of the moderation performed might ease the understandability of the results.

A3. We would like to thank the reviewer for this comment that will definitely enhance the clarity and interpretability of our results. Firstly, to better describe the moderation analysis, we have included the following additional sentences in the methods section (see page. 10): "*To assess the moderator effect, the interaction term was added in each model (BMI × BD-PRS or BMI × BMI-PRS). ... "A significant interaction effect would indicate that the association between BMI and cognitive performance varies according to the level of the corresponding PRS, indicating a moderating effect".*

Secondly, we have clarified the interpretation of the different phy values used in the PRS-CS models. Phi refers to the global shrinkage parameter assumed in the models when posterior SNP effect sizes are inferred. Larger phis (1E-01, 1E-02) are more appropriate for very polygenic traits while smaller phis (1E-05, 1E-06) would be a better option for less polygenic traits. In this study, we did a small-scale grid search to find the optimal phi value as regards predictive performance. We have now included this information in the Methods section (page 9): *"The PRS-continuous shrinkage (CS) tool was used to infer posterior SNP effect sizes under continuous shrinkage priors, setting the global shrinkage parameter (φ) at six different values (i.e., φ = 1E-01, 1E-02, 1E-03, 1E-04, 1E-05, and 1E-06) [35] based on the GWAS summary stats for BD [36] and BMI [37]. In brief, to find the optimal phi value as regards predictive performance, a grid search was carried out based on the different φ thresholds, with larger phis (1E-01, 1E-02) representing very polygenic traits and smaller φ (1E-05, 1E-06) less polygenic traits."*

Lastly, for the TMT-A outcome, the moderation results were highly consistent across the different phi values tested. This suggests that the moderation effect of the BD-PRS on the relationship

between BMI and processing speed is robust across different levels of aggregation of genetic variants and not dependent on the assumed level of polygenicity. We have added a sentence in the 3.2 results section (see page 11) to help understand these results: *"Moreover, the moderation effect of BD-PRS on the relationship between BMI and processing speed (TMT-A) was consistent across different phi values, indicating that the effect was not influenced by the assumption of polygenicity".*

Q4. Accordingly, in the results, the Authors should clearly state what is the direction of the moderating effect of BD-PRS. Is this factor adding strength or weakens the association? A clearer definition of such moderating effect would help.

A4. We appreciate the reviewer's suggestions and agree that clarifying the direction of the moderating effect enhances the interpretability of our findings. In order to enhance clarity and avoid confusion to the readers We have edited a sentence in the statistical analyses subsection (page 10): *"...that is, BD-PRS would ~~change the direction and/or strength of~~ modify the relationship between the independent and dependent variables".*

We have also updated the results section to explicitly state the direction of the BD-PRS moderating effect. In addition, we made a little change in the discussion to clarify this effect.

Results (page 11): *"Specifically, and for both cognitive variables, at higher BD-PRS levels, a more pronounced inverse association between BMI and cognitive performance was observed. In contrast, this association was not evident at lower BD-PRS levels".*

Discussion (page 15): "Recognizing BD-PRS as a moderator between BMI and processing speed suggests that a high genetic susceptibility to BD intensifies the impact of BMI on some cognitive domains."

Q5. In the methods, it is not clear why the Authors performed the moderation analyses for all the cognitive variables (since they found that the association exists only for some cognitive tests). Possibly, they wanted to evaluate if adding a moderating effect would strengthen the relationship beteween BMI and certain cognitive performances. If this is the case, they should clearly state this purpose in the methods.

Thanks again for this comment; we agree that it is necessary to clarify this issue. As the reviewer correctly points out, that's the reason why we performed moderation analyses for all the cognitive variables despite not finding an association for all of them. This reflects a distinct research question.

Moreover, it is important to note, in moderation analyses a significant relationship between the independent variable and the outcome (dependent variable) is not a prerequisite to examine moderation. Our purpose was to assess whether the effect of BMI on cognitive variables changes depending on the level of a third variable, the moderator (e.g. BD-PRS or BMI-PRS). While BMI might not have a direct effect on cognitive performance overall, such effects could emerge or vary

significantly at different levels of genetic risk. The rationale for exploring whether the interaction between BMI and BD-PRS or BMI-PRS influence the cognitive outcomes is the existent evidence suggesting a common genetic background between psychiatric and metabolic disorders and shared genetic contributions to BMI and cognitive function. Therefore, to make this objective clearer, we have included additional sentences in the methods section to clearly state this purpose as follows (see page 10):

"Moderation analyses were run for all the cognitive variables regardless of being associated with BMI, as we wanted to evaluate if adding a moderating effect would modify this relationship. A significant interaction effect would indicate that the association between BMI and cognitive performance varies according to the level of the corresponding PRS, indicating a moderating effect".