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Factors involved in working memory in patients with schizophrenia and bipolar disorder: The role of peripheral biomarkers

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ABSTRACT

Background and objectives: Cognitive impairment, especially working memory (WM) dysfunction, is a core feature of schizophrenia (SZ) and bipolar disorder (BD), influenced by various factors including lifestyle, psychopathology, pharmacological factors, inflammation, and metabolic dysfunction. This study aimed to investigate the role of metabolic, inflammatory, and intestinal permeability biomarkers in WM impairments in SZ and BD patients.

Methods: A cross-sectional, observational study included 146 outpatients (SZ=96, BD=50). We assessed sociodemographic, clinical, metabolic, and inflammatory markers. Cognitive performance was evaluated using the Screen for Cognitive Impairment in Psychiatry. Biomarkers included glycohemoglobin, C-reactive protein, and lipopolysaccharide-binding protein/soluble CD14. Multivariate analyses identified factors associated with WM dysfunction and, secondarily, with other cognitive deficits.

Results: WM impairment was present in 56.3 % of SZ and 52 % of BD patients, without inter-group differences. Independent predictors of WM dysfunction were antipsychotic polypharmacy (OR=2.415, $p = 0.011$), abdominal obesity (OR=2.884, $p = 0.016$), and elevated glycohemoglobin (OR=1.126, $p = 0.020$). While inflammatory and intestinal permeability markers correlated with metabolic parameters, they were not independent predictors of WM impairment.

Conclusion: WM deficits in SZ and BD are primarily associated with metabolic and pharmacological factors. Addressing modifiable metabolic factors, optimizing antipsychotic treatment, and exploring interventions such as metformin and lifestyle modifications may improve cognitive outcomes in these populations.

Introduction

Cognitive deficit is a key symptom of schizophrenia (SZ) and bipolar disorder (BD), often impairing real-life functioning more significantly than negative, positive, or affective symptoms.[1] Several studies have found both disorders are associated with cognitive impairment; however, the magnitude of deficits tends to be greater in SZ than in BD.[2] Recent cluster analyses suggest distinct transdiagnostic cognitive subgroups: one with intact cognition or "neuropsychologically normal" and another with "severe cognitive impairment".[3,4] Such classifications may help identify brain-specific phenotypes linked to shared genetic alterations or biomarkers.[5]

Working memory (WM) impairment is a core feature of both disorders, with no significant differences observed,[6] suggesting that it may be a sensitive and core indicator of cognitive dysfunction. WM involves temporarily storing and manipulating information for complex tasks such as reasoning and executive functions.[7] The specific focus on WM in this study is theoretically driven. As a core transdiagnostic deficit, WM

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impairments are well-documented across all disease stages, from onset to chronic phases[8,9] and serve as a robust trait marker largely independent of affective state.[10] Crucially, its essential role in executive functions and reasoning makes it a strong predictor of real-world social and functional outcomes in both disorders.[11] Furthermore, WM appears particularly sensitive to the influence of modifiable factors, positioning it as a key therapeutic target for cognitive remediation interventions aimed at improving patient functioning.[12,13] The Screen for Cognitive Impairment in Psychiatry (SCIP) test reliably assesses cognition, including WM, in psychotic and affective disorders,[14,15] and it is explicitly recommended by the International Society for Bipolar Disorders as a feasible tool for the routine screening of cognitive deficits in patients with BD.[16]

Emerging evidence indicates that metabolic, immunological, inflammatory, and neuroendocrine factors can influence neurocognitive processes.[17] Indeed, the immune system influences mental disorders through neuroinflammation and systemic inflammation, exacerbated by stress, metabolic changes, gut dysbiosis, and lifestyle factors as unhealthy diet or sedentary behavior.[18] These factors are involved in the development and functionality of psychiatric disorders such as SZ and BD with cognitive impairment.[19,20] Metabolic dysregulation appears critical to understanding cognitive impairment and immune-inflammatory alteration associated with brain damage. Among the various factors connecting metabolism, the immune system, and neuropsychiatric disorders; carbohydrate metabolic profiles—particularly insulin regulation—and metabolic syndrome, whether primary or secondary to pharmacological treatment, are key contributors. The interaction of glucose dysregulation with structural brain damage appears to be particularly compelling.[21] Similarly, the gut-brain axis affects cognitive impairment,[22] in unclear ways.

Cognitive and WM impairments likely have a multifactorial origin influenced by lifestyle, psychopathology, pharmacological factors, inflammation, and metabolic dysfunction. This study aims to explore the potential added value of incorporating biomarkers related to metabolism, systemic inflammation, and intestinal permeability as factors contributing to WM impairments in patients with SZ and BD patients.

Methods

Design

This is an observational, naturalistic, cross-sectional study of a project aimed at examining the role of inflammatory and gut permeability biomarkers in patients with SZ and BD.

We conducted the study according to the Declaration of Helsinki (2013). The Clinical Research Ethics Committee of Hospital Universitario Central de Asturias in Oviedo approved the study protocol (Ref. CEImPA 2021.345), and we obtained written informed consent from all participants before enrollment.

Participants

We recruited participants from two mental health outpatient clinics in Oviedo, Northern Spain, each with a catchment area population of about 80,000 inhabitants. Exclusion criteria included comorbidities such as gastrointestinal, hepatobiliary, hematopoietic, autoimmune, infectious diseases, cancer, or fever. We also excluded individuals with a recent treatment with antibiotics, immunosuppressants, anti-inflammatory agents, probiotic supplements, or vaccines. Psychiatric comorbidities except nicotine or cannabis dependence, eating disorders, specific dietary practices (e.g., veganism or vegetarianism), pregnancy, and breastfeeding were additional exclusion factors. For more information, readers can refer to the previously described protocol.[23]

An initial pool of 158 outpatients was screened in a single step using the protocol's predefined inclusion/exclusion criteria; no additional physical or psychiatric comorbidities beyond these criteria were applied. After excluding individuals without cognitive assessment, the final sample comprised 146 patients diagnosed by treating psychiatrists according to DSM-5 criteria: SZ ($n = 96$, 65.8 %) and BD ($n = 50$, 34.2 %).

Assessment

Data collection included sociodemographic, clinical, physical, and lifestyle parameters.

We collected demographic variables including age, sex, educational level, and employment status. We recorded vital signs and anthropometric measurements. We calculated body mass index (BMI) and determined the presence of metabolic syndrome using ATP-III criteria.[24]

Comprehensive clinical assessments were conducted by trained psychologists. These included duration of illness, history of suicide attempts, and details of psychopharmacological treatments, including chlorpromazine-equivalent doses of antipsychotics.[25] We assessed illness severity with the Clinical Global Impression (CGI-S)-Severity Scale and evaluated cognitive impairment with the Spanish adaptation of Screen for Cognitive Impairment in Psychiatry (SCIP-S).[14] The SCIP is a structured interview that assesses the following 5 cognitive domains: immediate verbal learning, working memory, verbal fluency, delayed verbal learning, and processing speed. For the analyses, we used the non-corrected raw scores from each of the instrument's five subtests. Cognitive impairment was defined as a dichotomous variable ('impaired' vs. 'unimpaired') for each cognitive domain separately. The classification was based on the optimal, empirically validated cut-off scores proposed by Rojo et al.[26] in the validation study of the SCIP-S. These cut-offs are designed to achieve high sensitivity, which is essential for a screening instrument. We focused on the WM domain to segment the sample, which we assessed using the Consonant Span Task (CST). Specifically, participants were classified as having impaired WM when their uncorrected raw score was below 20, as suggested by Rojo et al.

Lifestyle data included toxic substance use (alcohol, tobacco, cannabis), physical activity levels (measured using the International Physical Activity Questionnaire [IPAQ]), and adherence to the Mediterranean diet (assessed with the Mediterranean Diet Adherence Score [MEDAS]).[27]

Blood samples

For hematological and biochemical analyses, peripheral blood samples were conducted between 8:00 and 9:00 AM at the participating centers. Patients fasted overnight prior to the sampling. We used these samples to analyze metabolic parameters (as glycohemoglobin), vitamins, and inflammatory markers such as C-reactive protein (CRP) and blood-cell inflammatory ratios. We used the neutrophil, lymphocyte, monocyte, and platelet counts to calculate the neutrophil/lymphocyte (NLR), monocyte/lymphocyte (MLR), platelet/lymphocyte (PLR) ratios and the systemic immune-inflammation index (SII), calculated as (platelet × neutrophil)/lymphocyte count.

From the plasma samples, we analyzed bacterial translocation markers, including lipopolysaccharide-binding protein (LBP) and soluble CD14 (sCD14), as indirect markers of intestinal permeability. We obtained these levels following the protocols of commercial kits (Human sCD14 ELISA Kit, Hycult Biotech, Uden, Netherlands; Human Lipopolysaccharide Binding Protein ELISA Kit, Hycult Biotech, Uden, Netherlands).

Statistical analysis

We used descriptive analyses to characterize the sociodemographic, clinical, and biological features of the sample. To assess normality, we conducted Kolmogorov–Smirnov , and we also inspected histograms and Q–Q plots for continuous variables; distributional diagnostics are provided in Supplementary Material (Fig. S1). Initial exploratory analyses

utilized bivariate methods, including chi-square tests, Student's *t*-tests or Mann–Whitney U tests for independent samples, and Spearman correlations to examine potential associations between biomarkers. To identify independent predictors of WM dysfunction and other cognitive domains, a hierarchical logistic regression model was constructed. This approach was chosen to assess the incremental predictive value of different sets of variables in a theoretically-driven order. To prevent model overfitting, a variable pre-selection step was implemented: those variables that showed a significant association ($p < 0.05$) in the bivariate analyses were included as candidates. The sex variable was included *a priori* in the model due to its importance as a demographic covariate. Variance inflation factors (VIF) were computed for all predictors entered in multivariable models. VIFs ranged from 1.09 to 1.36 (tolerance 0.74–0.92), indicating no problematic multicollinearity (Supplementary Table S1).

The statistical analysis was performed using IBM SPSS Statistics, version 27.0. Statistical significance for Spearman correlations was set at $p < 0.002$, adjusted using a Bonferroni correction for multiple comparisons (5 × 5 comparisons). For all other tests, we applied a significance threshold of $p < 0.05$.

Results

Description of the sample

Sociodemographic and other clinical variables of the whole sample are in Table 1.

Participants mean age was 43.6 years (SD 12.4), with a range between 18 and 69, and 48.6 % ($n = 71$) were female. There was a greater proportion of women in the BD group (70 % vs 37.5 %, X^2=13.901, $p < 0.001$), and older mean age: 46.44 (SD 12.4) vs 42.07 (SD 12.19) years (t=−2.040, $p = 0.043$).

Most patients were treated with antipsychotic (96.9 % in the group of SZ and 82 % in the group of BD; $p = 0.002$), being clozapine in 9.4 % and 10 %, respectively ($p = 0.902$). Some 29.2 % of SZ patients and 50 % of BD patients ($p = 0.003$) used antidepressants, and 53.3 % and 54 % ($p = 0.933$) used benzodiazepines. As expected, a mood stabilizer was used only by 8.7 % of SZ patients and 91.3 % of BD patients ($p < 0.001$), with lithium being the most frequently prescribed, followed by valproate. CGI-S score was slightly higher in SZ group compared to the BD group (3.87 (1.16) vs 3.40 (1.18), $t = 2.330$, $p = 0.021$).

There were no significant differences between diagnostic groups in substance use or lifestyle factors such as diet and physical activity. Similarly, there were no differences in any blood biomarkers or the presence of metabolic syndrome ($p > 0.05$).

Also, significant associations between "key" plasma biomarkers of the whole sample are shown in a heatmap (Fig. 1).

Cognitive and working memory performance

We observed cognitive impairment (defined as dysfunction in more than two SCIP domains) in 66.7 % of SZ patients and 58 % of BD patients (X^2=1.068, $p = 0.301$). Specifically, deficits in working memory were detected in 56.3 % of SZ patients and 52 % of BD patients (X^2=0.240, $p = 0.624$). Table 1 displays the description of variables and differences between groups based on working memory status.

On the other hand, immediate verbal learning was impaired in 71.9 % of SZ patients and 56 % of BD patients (X^2=3.716, $p = 0.054$), verbal fluency in 46.9 % of SZ and 32 % of BD patients (X^2=2.991, $p = 0.084$), delayed verbal learning in 70 % of SZ and 58.8 % of BD patients (X^2=2.428, $p = 0.119$), and processing speed in 69.8 % of SZ and 68 % of BD patients (X^2=0.049, $p = 0.824$).

Factors involved in working memory dysfunction

Patients with WM dysfunction were significantly older, had lower

Table 1
Description of variables and differences based on working memory status.

	Global sample (N = 146) N (%) or mean (SD)	Working memory dysfunction (N = 80)	Working memory preserved (N = 66)	Statistics (p value)
Sex (male)	75 (51.4 %)	38 (47.5 %)	37 (56.1 %)	X^2=1.061 (0.303)
Age (years)	43.57 (12.41)	45.98 (12.36)	40.65 (11.91)	$t = 2.633$ (0.009)
Education level				X^2=5.128 (0.077)
Primary	20 (13.7 %)	14 (17.5 %)	6 (9.1 %)	(0.044) (University vs. others)
Secondary	89 (61 %)	51 (63.7 %)	38 (57.6 %)	
University	27 (25.3 %)	15 (18.8 %)	22 (33.3 %)	
Work status (PD)	66 (45.2 %)	40 (50 %)	26 (39.4 %)	X^2=1.642 (0.200)
Clinical variables:				
Diagnosis:				X^2=0.240 (0.624)
Schizophrenia	96 (65.8 %)	54 (67.5 %)	42 (63.6 %)	
Bipolar Disorder	50 (34.2 %)	26 (32.5 %)	24 (36.4 %)	
Years of illness	15.9 (11.3)	16.62 (11.47)	15.15 (11.08)	$U = 2384.0$ (0.447)
CGI-S score (1–7)	3.71 (1.18)	3.73 (1.11)	3.68 (1.26)	$t = 0.248$ (0.804)
Suicide attempts	21 (14.8 %)	13 (17.1 %)	8 (12.1 %)	X^2=0.496 (0.404)
Lifestyle habits:				
Tobacco use	50 (34.2 %)	26 (32.5 %)	24 (36.4 %)	X^2=0.240 (0.624)
Cigarettes/day	15.55 (8.89)	16.65 (9.45)	14.30 (7.48)	$U = 270.5$ (0.562)
Cannabis last month	19 (13 %)	12 (15 %)	7 (10.6 %)	X^2=0.617 (0.432)
OH (UBEs/week)	0.83 (2.27)	0.56 (2.09)	1.14 (2.44)	$U = 2203.0$ (0.020)
MEDAS (high adherence)	35 (24.4 %)	19 (24.5 %)	16 (24.6 %)	X^2=0.001 (0.972)
IPAQ score (moderate-high)	74 (51.7 %)	36 (46.2 %)	38 (58.5 %)	X^2=2.152 (0.142)
Physical health:				
BMI (kg/m2)	29.1 (6.9)	30.34 (6.39)	27.61 (7.26)	$t = 2.405$ (0.017)
Abdominal obesity	88 (60.7 %)	56 (70 %)	32 (49.2 %)	X^2=6.484 (0.011)
*cHDL <40/50 (men/ women)**	51 (34.7 %)	31 (38.3 %)	20 (30.3 %)	X^2=1.019 (0.313)
*Arterial Pressure ≥130/ 85 **	39 (26.9 %)	25 (31.3 %)	14 (21.5 %)	X^2=1.720 (0.190)
Metabolic syndrome	39 (26.7 %)	24 (30 %)	15 (22.7 %)	X^2=0.977 (0.323)

(*continued on next page*)

Table 1 (*continued*)

	Global sample (*N* = 146) N (%) or mean (SD)	Working memory dysfunction (*N* = 80)	Working memory preserved (*N* = 66)	Statistics (p value)
Tryglicerides (mg/dl)	141.6 (117.3)	157.9 (142.0)	121.6 (73.8)	*U* = 2295 (0.175)
*Glucose ≥100 mg/dl **	30 (20.5 %)	18 (22.5 %)	12 (18.2 %)	X^2=0.413 (0.520)
Glucose (mg/dl)	103.8 (34.1)	107.1 (42.4)	99.6 (18.4)	*U* = 2295 (0.175)
Glycohemoglobin (mmol/l)	36.14 (9.17)	38.06 (11.31)	33.66 (4.11)	*U* = 1534 (0.002)
Insulin (mUI/l)	16.62 (14.25)	17.11 (12.34)	16.00 (16.45)	*U* = 1888 (0.081)
Folic Acid	6.49 (4.29)	7.03 (4.73)	5.81 (3.61)	*U* = 1997.5 (0.216)
Vitamin B12	544.6 (217.8)	556.7 (233.5)	529.2 (197.1)	*U* = 2153.5 (0.579)
CRP (mg/dl)	0.59 (1.24)	0.64 (1.11)	0.53 (1.40)	*U* = 1978.5 (0.013)
NLR	1.89 (0.87)	1.87 (0.74)	1.91 (0.99)	*t*=−0.278 (0.781)
MLR	0.27 (0.09)	0.26 (0.11)	0.27 (0.07)	*t*=−0.307 (0.759)
PLR	115.6 (42.6)	117.1 (44.6)	113.6 (40.2)	*t* = 0.491 (0.624)
SII	462.3 (247.8)	464.5 (241.2)	459.5 (257.4)	*t* = 0.120 (0.904)
LBP (μg/dl)	14.89 (5.89)	15.54 (6.32)	14.15 (5.27)	*U* = 2184 (0.361)
sCD14 (μg/dl)	2.41 (0.70)	2.49 (0.67)	2.30 (0.74)	*U* = 1947.5 (0.098)
Psychopharmacological treatment:				
Antipsychotic (yes)	134 (91.8 %)	78 (97.5 %)	56 (84.8 %)	X^2=7.673 (0.006)
Number of antipsychotics [0 - 4]	1.27 (0.68)	1.43 (0.67)	1.09 (0.65)	*U* = 2008.0 (0.004)
CPZ-ED (mg/day)	571.5 (562.6)	647.6 (600.6)	479.3 (502.1)	*U* = 2086.5 (0.029)
Clozapine (yes)	14 (9.6 %)	8 (10 %)	6 (9.1 %)	X^2=0.034 (0.853)
Antidepressant (yes)	53 (36.3 %)	28 (35 %)	25 (37.9 %)	X^2=0.130 (0.719)
Benzodiazepine (yes)	76 (53.5 %)	41 (53.9 %)	35 (53 %)	X^2=0.012 (0.913)

*or treatment.

PD, permanent disability; CGI-S, clinical global impression severity; OH, alcohol; MEDAS, Mediterranean Diet Adherence Screener; IPAQ, International Physical Activity Questionnaire; BMI, body mass index; cHDL, cholesterol high density lipoprotein; CRP, C-Reactive Protein; NLR, neutrophil/lymphocyte; MLR, monocyte/lymphocyte; PLR, Platelet/lymphocyte ratios; SII, systemic inflammatory index; LBP, lipopolysaccharide-binding protein; sCD14, soluble CD14; CPZ-ED, chlorpromazine equivalent doses.

educational levels, and exhibited higher BMI and prevalence of abdominal obesity. Additionally, these patients were more frequently treated with antipsychotics, received higher chlorpromazine (CPZ) equivalent doses, and were more likely to undergo antipsychotic polytherapy (38.9 % vs. 22.7 %; X^2=10.620, p = 0.031). Interestingly, weekly alcohol consumption (standard drink units, UBE) was higher among patients with preserved working memory than among those with impaired working memory; however, because the vast majority of participants did not drink alcohol (n = 112, 76.7 %), this comparison is based on a small subgroup of drinkers and does not support firm conclusions. To preserve model stability and interpretability under marked

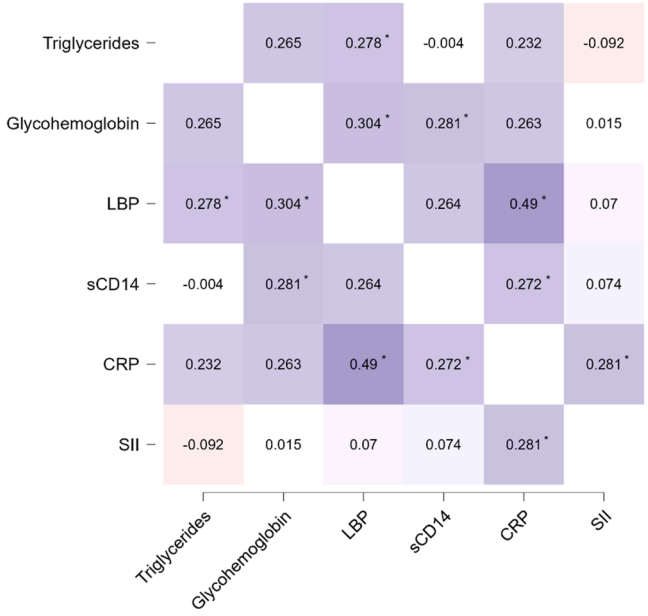

Fig. 1. Heatmap of associations between biomarkers
LBP, lipopolysaccharide-binding protein; sCD14, soluble CD14; CRP, C-Reactive Protein; SII, systemic inflammatory index; *$p < 0.002$.

zero inflation, UBE was not included as a predictor in the logistic regression.

Among the plasma biomarkers, glycohemoglobin and C-reactive protein levels were higher in patients with WM dysfunction ($p = 0.002$ and $p = 0.013$, respectively).

To identify the independent predictors of working memory (WM) dysfunction, we performed a hierarchical logistic regression. The selected variables were entered in three blocks: (1) age, sex, and education; (2) antipsychotic use, CPZ equivalent doses, number of antipsychotics, CGI-S, and diagnosis; (3) metabolic and inflammatory parameters. Variables were selected for inclusion if they showed a significant association in the bivariate analyses, with sex being included a priori based on its established clinical relevance. We also considered including sCD14 and LBP in the final block, given their near-significant associations in the bivariate analysis and/or correlation with other key markers. The full list of variables entered in each block is detailed in Table 2. The model identified three independent key factors associated

Table 2
Logistic regression for working memory dysfunction.

Predictors	B	S.E.	OR [95 % CI]	*P*
[1]***Constant***	−1.766	0.702		0.013
Age	0.048	0.016	1.049 [1.017–1.082]	0.002
Education (University)	−0.963	0.442	0.382 [0.161–0.907]	0.029
[2]***Constant***	−2.886	0.871		0.001
Age	0.054	0.017	1.056 [1.022–1.091]	0.001
Education (University)	−0.773	0.455	0.472 [0.189–1.126]	0.089
Number of antipsychotics	0.803	0.321	2.232 [1.190–4.187]	0.012
[3]***Constant***	−6.966	1.936		<0.001
Age	0.033	0.018	1.033 [0.998–1.070]	0.068
Education (University)	−0.390	0.492	0.677 [0.258–1.774]	0.427
Number of antipsychotics	0.882	0.347	2.415 [1.223–4.766]	0.011
Abdominal obesity	1.059	0.441	2.884 [1.215–6.847]	0.016
Glycohemoglobin	0.118	0.051	1.126 [1.019–1.244]	0.020

[1] Block 1: age, sex, and education (R Cox & Snell=0.114, R Nagelkerke=0.152).

[2] Block 2: antipsychotic use, CPZ equivalent doses, number of antipsychotics, Clinical Global Impression Scale, diagnosis (schizophrenia vs bipolar) (R = 0.163 & 0.219).

[3] Block 3: Body Mass Index, abdominal obesity, glycohemoglobin, C-reactive protein, LBP, sCD14 (R = 0.252 & 0.338).

with WM dysfunction: a greater number of antipsychotics (OR=2.415, $p = 0.011$), abdominal obesity (OR=2.884, $p = 0.016$) and glycohemoglobin level (OR=1.126, $p = 0.020$). Although education and age were initially relevant, their effects were not significant in the final model after accounting for other factors. The final model explains approximately 25.2 % to 33.8 % of the variability in WM dysfunction. Table 2 presents the regression analysis data.

It should be noted that the prevalence of abdominal obesity was not associated with the number of antipsychotic ($t = 0.180$, $p = 0.857$) or glycohemoglobin levels ($t = 1.371$, $p = 0.173$), nor did it depend on whether patients were receiving antipsychotic or not (X^2=1.984, $p = 0.159$).

As an exploratory analysis to assess the impact of these factors on other cognitive domains, several logistic regressions were performed. No model was obtained for verbal fluency. Regression models for immediate verbal learning, delayed verbal learning, and processing speed are presented in the Supplementary Material. The results showed that non-modifiable factors such as age and sex remained significant, while no associations were found with metabolic factors, except for abdominal obesity in processing speed. On the other hand, CRP emerged as an inflammatory predictor of immediate verbal memory.

Discussion

The present study aims to identify metabolic, inflammatory, and intestinal permeability biomarkers that reveal WM impairment in SZ and BD patients. Our findings underscore the multifactorial nature of WM deficits, highlighting the significant roles of pharmacological and metabolic factors, particularly abdominal obesity, and glucose metabolism dysregulation.

As expected, we found no significant differences in WM performance between SZ and BD patients, present in more than 50 % of cases. This finding further supports the transdiagnostic nature of WM deficits, as in previous studies.[6] WM, which is essential for language, executive functions, learning, and memory, is worse across all SZ and BD phases, impacting social and functional outcomes beyond diagnostic categories.[9]

Our model incorporated two final axes related to WM: antipsychotic polypharmacy and metabolic alterations, represented by abdominal obesity and glycohemoglobin (HbA1c).

Antipsychotics may impair cognitive functions, specifically, WM though direct pharmacodynamic effects and indirect influence on long-term metabolic and inflammatory factors.[28] Our study confirms that higher doses and, especially, polypharmacy (use of multiple antipsychotics) are associated with a greater impact on WM. Although clinical severity could explain this, our results do not show significant differences in CGI-S. Therefore, it may be more related to increased side effects, which translate into a deterioration of sustained attention, memory, and executive function.[29–31]

In a recent meta-analysis, Feber et al. found no significant differences in the effect on cognition among different antipsychotics, although there was a trend for first-generation antipsychotics and clozapine to have a more negative influence on cognition.[32] It is important to note that studies evaluating the impact of clozapine specifically on WM have shown mixed results, ranging from detrimental to neutral and beneficial effects, and doses-dependent.[33–36] Our results did not show differences in clozapine use in the WM impairment group.

Regarding the biomarkers, we observed a hierarchical relationship between the studied biomarkers and WM. Metabolic alterations emerged as the final vector influencing WM. A meta-analysis in individuals with SZ found that metabolic syndrome, particularly diabetes and hypertension, was linked to more severe global cognitive deficits.[37] However, the authors concluded that obesity (specifically increased BMI) was not significantly associated with these cognitive impairments. This contrasts with previous meta-analysis, which found a significant relationship between cognitive impairment and abdominal obesity consistent with our findings.[38] Abdominal obesity has also been associated with poorer memory function in the general population.[39] Arnoldussen et al. hypothesized that adipokines, produced by fat cells, can induce insulin resistance, disrupt the gut-brain axis, and increase systemic inflammation, which in turn may lead to neuroinflammation and contribute to the progression of dementia.[40]

On the other hand, many studies in the general population have linked diabetes and insulin resistance to cognitive impairments.[41,42] Even in healthy populations, researchers report cognitive impairments associated with hyperglycemia.[43] Some theories explained this association with a reduction in hippocampal volume.[44,45] Also, evidence suggests that poor glycemic control is linked specifically to WM impairment in patients with type 2 diabetes.[46] Furthermore, in psychotic disorders several studies have explored the relationship between glucose metabolism parameters and cognitive functioning.[47,48] Montalvo et al. found a greater association for glycohemoglobin (or HbA1c) than for other fasting-related glucose parameters.[21] Particularly, these authors found an inverse correlation between HbA1c levels and executive function and visual memory. Elevated postprandial glucose levels, a significant contributor to chronic hyperglycemia and increased glycohemoglobin, may promote excessive protein glycation, oxidative stress, and inflammation.[49]

A review by Chen et al. supports the potential of antidiabetic agents in improving cognitive function in schizophrenia, emphasizing the role of brain insulin resistance in cognitive deficits, and highlighting the therapeutic promise of targeting the insulin pathway.[50] Promising data indicate that metformin could significantly improve cognitive impairments in patients with SZ and BD, especially in processing speed, WM, verbal, and visual learning.[51] Additionally, combined treatment with liraglutide improved WM in preclinical studies.[52]

Regarding inflammatory or intestinal factors, only CRP emerged as a predictor of processing speed but not of WM in our study. Investigations of the association between increased intestinal permeability and cognitive impairment has yielded both positive and negative results.[53,54] Although our regression model of WM impairment did not retain intestinal permeability biomarkers, the observed correlations between them and metabolic and inflammatory biomarkers provide further evidence of the relationship between systemic inflammation, intestinal permeability, and metabolic dysfunction.[55,56] The positive association between glycohemoglobin and LBP or sCD14, along with studies linking inflammation to intestinal permeability, suggests that immune activation may increase intestinal permeability, which in turn contributes to metabolic dysfunction, particularly glucose dysregulation, as previously reported.[57] These findings also align with the hypothesis that both inflammatory and metabolic disturbances are key contributors to WM dysfunction,[58] underscoring the need for future research to explore their potential as therapeutic targets in psychiatric disorders.

Although education level played an important role in our model of WM, it lost significance once we introduced the other variables. But this is consistent with recent studies that confirm cognitive reserve is much more than just education level.[59–61]

We highlighted the importance of WM as a core and differential factor compared to other cognitive domains. While age does not emerge as a significant factor, modifiable factors such as antipsychotic polypharmacy and metabolic factors do show significance, unlike in other domains. This difference supports the idea that WM may be more sensitive to changes in modifiable conditions. Consequently, we emphasize the need to specifically assess this domain in both research and clinical evaluations, given its potential vulnerability to factors that can be altered or managed.

Limitations

We acknowledge some limitations. First, the cross-sectional nature of this observational study prevents us from establishing causal relationships. Second, while our methodology included a broad range of

biomarkers and clinical variables, we did not account for the potential impact of negative symptoms or depressive symptoms, both of which are known to affect cognitive function. Additionally, we did not assess the potential role of anticholinergic burden[30] and cognitive reserve,[60] which extends beyond educational level, both of which influence cognitive performance, and future researchers should consider them. Finally, cognitive performance was assessed using the SCIP, a brief screening instrument. As such, the psychometric stability of an individual subtest score is inherently lower than that of the total composite score. While our focused approach on working memory was theoretically driven, this reliance on a single measure from a screening tool warrants caution in the interpretation of our findings. Future research should aim to replicate these results using more comprehensive neuropsychological batteries. Nevertheless, this study has several strengths, including a well-characterized clinical sample and validated cognitive assessments. Additionally, objective biological measures, such as glycohemoglobin, C-reactive protein, and intestinal permeability biomarkers, provide a precise evaluation of the impact of systemic inflammation and metabolic dysfunction on cognition.

Conclusions

This study highlights the importance of metabolic endocrine factors, particularly glycemic control, in WM dysfunction in SZ and BD, emphasizing the interplay between metabolic and pharmacological factors. We provide further evidence that by addressing modifiable metabolic factors, such as with metformin or lifestyle improvements, and promoting a more rational use of antipsychotic polypharmacy, psychiatrists can improve cognitive health and mitigate its decline in everyday clinical practice.

Ethical considerations

We conducted the study according to the Declaration of Helsinki (2013). The study protocol received full approval from the Clinical Research Ethics Committee of Hospital Universitario Central de Asturias in Oviedo **(Ref. CEImPA 2021.345)**. Prior to their participation, all individuals provided written informed consent, ensuring they fully understood the study's purpose, procedures, potential risks, and their right to withdraw at any time.

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Declaration of competing interest

GP has been a consultant to and/or has received honoraria or grants from Adamed, Alter Medica, Angelini Pharma, Johnson & Johnson, Lundbeck, Otsuka and Viatris España. LGB has been a consultant to and/or has received lecture fees/grants from the Spanish Foundation of Psychiatry and Mental Health, Otsuka, Lundbeck, Johnson & Johnson, Casen Recordati, Angelini and Pfizer. PAS has been a consultant to and/or has received honoraria or grants from Adamed, Alter Medica, Angelini Pharma, CIBERSAM, Ethypharm Digital Therapy, European Commission, Government of the Principality of Asturias, Instituto de Salud Carlos III, Johnson & Johnson, Lundbeck, Otsuka, Pfizer, Plan Nacional Sobre Drogas, Rovi, Servier and Viatris España. MPGP has been a consultant to and/or has received honoraria/grants from Angelini, Otsuka-Lundbeck Alliance, Instituto de Salud Carlos III, Janssen-Cilag, Lundbeck, Otsuka, and Pfizer. The other has no competing interests. All other authors declare that they have no conflicts of interest related to the current work.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejpsy.2025.100334.

References

1. Cowman M, Holleran L, Lonergan E, O'Connor K, Birchwood M, Donohoe G. Cognitive predictors of social and occupational functioning in early psychosis: a systematic review and meta-analysis of cross-sectional and longitudinal data. *Schizophr Bull.* 2021;47(5):1243–1253. https://doi.org/10.1093/schbul/sbab033.
2. Lynham AJ, Cleaver SL, Jones IR, Walters JTR. A meta-analysis comparing cognitive function across the mood/psychosis diagnostic spectrum. *Psychol Med.* 2022;52(2):323–331. https://doi.org/10.1017/S0033291720002020.
3. Van Rheenen TE, Lewandowski KE, Tan EJ, et al. Characterizing cognitive heterogeneity on the schizophrenia-bipolar disorder spectrum. *Psychol Med.* 2017;47(10):1848–1864. https://doi.org/10.1017/S0033291717000307.
4. Amoretti S, Rabelo-da-Ponte FD, Rosa AR, et al. Cognitive clusters in first-episode psychosis. *Schizophr Res.* 2021;237:31–39. https://doi.org/10.1016/j.schres.2021.08.021.
5. Green MJ, Girshkin L, Kremerskothen K, Watkeys O, Quidé Y. A systematic review of studies reporting data-driven cognitive subtypes across the psychosis spectrum. *Neuropsychol Rev.* 2020;30(4):446–460. https://doi.org/10.1007/s11065-019-09422-7.
6. Gold JM, Barch DM, Feuerstahler LM, et al. Working memory impairment across psychotic disorders. *Schizophr Bull.* 2019;45(4):804–812. https://doi.org/10.1093/schbul/sby134.
7. Baddeley AD, Hitch GJ, Allen RJ. From short-term store to multicomponent working memory: the role of the modal model. *Mem Cognit.* 2019;47(4):575–588. https://doi.org/10.3758/s13421-018-0878-5.
8. Pothier W, Cellard C, Corbière M, et al. Determinants of occupational outcome in recent-onset psychosis: the role of cognition. *Schizophr Res Cogn.* 2019;18, 100158. https://doi.org/10.1016/j.scog.2019.100158.
9. De Pieri M, Berg X, Georgiadis F, et al. Negative Symptoms and their associations with other clinical variables and working memory across the schizophrenia spectrum and bipolar disorder. *Schizophr Bull Open.* 2024;5(1):sgae024. https://doi.org/10.1093/schizbullopen/sgae024.
10. Townsend J, Bookheimer SY, LC Foland-Ross, et al. fMRI abnormalities in dorsolateral prefrontal cortex during a working memory task in manic, euthymic and depressed bipolar subjects. *Psychiatry Res.* 2010;182(1):22–29. https://doi.org/10.1016/j.pscychresns.2009.11.010. Epub 2010 Mar 15. PMID: 20227857; PMCID: PMC2918407.
11. Depp CA, Mausbach BT, Harmell AL, et al. Meta-analysis of the association between cognitive abilities and everyday functioning in bipolar disorder. *Bipolar Disord.* 2012 May;14(3):217–226. https://doi.org/10.1111/j.1399-5618.2012.01011.x. PMID: 22548895; PMCID: PMC3396289.
12. Lee RS, Redoblado-Hodge MA, Naismith SL, et al. Cognitive remediation improves memory and psychosocial functioning in first-episode psychiatric out-patients. *Psychol Med.* 2013;43(6):1161–1173. https://doi.org/10.1017/S0033291712002127. JunEpub 2012 Dec 14. PMID: 23237010; PMCID: PMC3642720.
13. Bellani M, Biagianti B, Zovetti N, et al. The effects of cognitive remediation on cognitive abilities and real-world functioning among people with bipolar disorder: a systematic review: special Section on "Translational and Neuroscience Studies in Affective Disorders". Section Editor, Maria Nobile MD, PhD. This Section of JAD focuses on the relevance of translational and neuroscience studies in providing a better understanding of the neural basis of affective disorders. The main aim is to briefly summaries relevant research findings in clinical neuroscience with particular regards to specific innovative topics in mood and anxiety disorders. *J Affect Disord.* 2019;257:691–697. https://doi.org/10.1016/j.jad.2019.07.059. Epub 2019 Jul 19. PMID: 31377606; PMCID: PMC6711788.
14. Pino O, Guilera G, Rojo JE, et al. Spanish version of the Screen for Cognitive Impairment in Psychiatry (SCIP-S): psychometric properties of a brief scale for cognitive evaluation in schizophrenia. *Schizophr Res.* 2008;99(1–3):139–148. https://doi.org/10.1016/j.schres.2007.09.012.
15. Guilera G, Pino O, Gómez-Benito J, et al. Clinical usefulness of the screen for cognitive impairment in psychiatry (SCIP-S) scale in patients with type I bipolar disorder. *Health Qual Life Outcomes.* 2009;7:28. https://doi.org/10.1186/1477-7525-7-28.
16. Miskowiak KW, Burdick KE, Martinez-Aran A, et al. Assessing and addressing cognitive impairment in bipolar disorder: the International Society for Bipolar Disorders Targeting Cognition Task Force recommendations for clinicians. *Bipolar*

Disord. 2018;20(3):184–194. https://doi.org/10.1111/bdi.12595. MayEpub 2018 Jan 18. PMID: 29345040.
17. Saxena V, Marin-Valencia I. Mental health across the metabolic spectrum. *Biol Psychiatry Glob Open Sci.* 2024;5(2), 100443. https://doi.org/10.1016/j.bpsgos.2024.100443.
18. Bauer ME, Teixeira AL. Inflammation in psychiatric disorders: what comes first? *Ann N Y Acad Sci*. 2019;1437(1):57–67. https://doi.org/10.1111/nyas.13712.
19. Gonzalez-Blanco L, Garcia-Portilla MP, Dal Santo F, et al. Predicting real-world functioning in outpatients with schizophrenia: role of inflammation and psychopathology. *Psychiatry Res*. 2019;280, 112509. https://doi.org/10.1016/j.psychres.2019.112509.
20. Ortega MA, Fraile-Martinez O, García-Montero C, et al. Understanding immune system dysfunction and its context in mood disorders: psychoneuroimmunoendocrinology and clinical interventions. *Mil Med Res*. 2024;11(1):80. https://doi.org/10.1186/s40779-024-00577-w.
21. Montalvo I, González-Rodríguez A, Cabezas Á, et al. Glycated haemoglobin is associated with poorer cognitive performance in patients with recent-onset psychosis. *Front Psychiatry*. 2020;11:455. https://doi.org/10.3389/fpsyt.2020.00455.
22. Frileux S, Boltri M, Doré J, Leboyer M, Roux P. Cognition and gut microbiota in schizophrenia spectrum and mood disorders: a systematic review. *Neurosci Biobehav Rev*. 2024;162, 105722. https://doi.org/10.1016/j.neubiorev.2024.105722.
23. Paniagua G, Couce-Sánchez M, González-Blanco L, et al. Comparative analysis of gut microbiome-derived short-chain fatty acids in patients with severe mental disorder: insights from schizophrenia and bipolar disorder. *Prog Neuropsychopharmacol Biol Psychiatry. Published online March*. 2025;25. https://doi.org/10.1016/j.pnpbp.2025.111345.
24. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Circulation.* 2005;112(17):2735–2752. https://doi.org/10.1161/CIRCULATIONAHA.105.169404.
25. Gardner DM, Murphy AL, O'Donnell H, Centorrino F, Baldessarini RJ. International consensus study of antipsychotic dosing. *Am J Psychiatry*. 2010;167(6):686–693. https://doi.org/10.1176/appi.ajp.2009.09060802.
26. Rojo E, Pino O, Guilera G, Gómez-Benito J, Purdon SE, Crespo-Facorro B, Cuesta MJ, Franco M, Martínez-Arán A, Segarra N, Tabarés-Seisdedos R, Vieta E, Bernardo M, Mesa F, Rejas J. Spanish working group in cognitive function. neurocognitive diagnosis and cut-off scores of the screen for cognitive impairment in psychiatry (SCIP-S). *Schizophr Res*. 2010;116(2–3):243–251. https://doi.org/10.1016/j.schres.2009.08.005. FebEpub 2009 Sep 9. PMID: 19744832.
27. Schröder H, Fitó M, Estruch R, et al. A short screener is valid for assessing Mediterranean diet adherence among older Spanish men and women. *J Nutr*. 2011;141(6):1140–1145. https://doi.org/10.3945/jn.110.135566.
28. MacKenzie NE, Kowalchuk C, Agarwal SM, et al. Antipsychotics, metabolic adverse effects, and cognitive function in schizophrenia. *Front Psychiatry*. 2018;9:622. https://doi.org/10.3389/fpsyt.2018.00622.
29. Singh A, Kumar V, Pathak H, et al. Effect of antipsychotic dose reduction on cognitive function in schizophrenia. *Psychiatry Res*. 2022;308, 114383. https://doi.org/10.1016/j.psychres.2021.114383.
30. Martínez-Cao C, García-Fernández A, González-Blanco L, et al. What factors should we modify to promote high functioning and prevent functional decline in people with schizophrenia? *Front Psychiatry*. 2023;14, 1181758. https://doi.org/10.3389/fpsyt.2023.1181758.
31. Lähteenvuo M, Tiihonen J. Antipsychotic polypharmacy for the management of schizophrenia: evidence and recommendations. *Drugs*. 2021;81(11):1273–1284. https://doi.org/10.1007/s40265-021-01556-4.
32. Feber L, Peter NL, Chiocchia V, et al. Antipsychotic drugs and cognitive function: a systematic review and network meta-analysis. *JAMA Psychiatry*. 2025;82(1):47–56. https://doi.org/10.1001/jamapsychiatry.2024.2890.
33. Dal Santo F, Jarratt-Barnham I, González-Blanco L, García-Portilla MP, Bobes J, Fernández-Egea E. Longitudinal effects of clozapine concentration and clozapine to N-desmethylclozapine ratio on cognition: a mediation model. *Eur Neuropsychopharmacol*. 2020;33:158–163. https://doi.org/10.1016/j.euroneuro.2020.01.016.
34. Haddad C, Salameh P, Sacre H, Clément JP. Calvet B. Effects of antipsychotic and anticholinergic medications on cognition in chronic patients with schizophrenia. *BMC Psychiatry*. 2023;23(1):61. https://doi.org/10.1186/s12888-023-04552-y.
35. Rajji TK, Mulsant BH, Davies S, et al. Prediction of working memory performance in schizophrenia by plasma ratio of clozapine to N-desmethylclozapine. *Am J Psychiatry*. 2015;172(6):579–585. https://doi.org/10.1176/appi.ajp.2015.14050673.
36. Cheuk NKW, Tse W, Tsui HKH, et al. A systematic review and meta-analysis of the effect of clozapine on cognitive functions in patients with treatment-resistant schizophrenia. *Schizophr Res*. 2024;268:205–222. https://doi.org/10.1016/j.schres.2023.09.027.
37. Hagi K, Nosaka T, Dickinson D, et al. Association between cardiovascular risk factors and cognitive impairment in people with schizophrenia: a systematic review and meta-analysis. *JAMA Psychiatry*. 2021;78(5):510–518. https://doi.org/10.1001/jamapsychiatry.2021.0015.
38. Bora E, Akdede BB, Alptekin K. The relationship between cognitive impairment in schizophrenia and metabolic syndrome: a systematic review and meta-analysis [published correction appears in. *Psychol Med.* 2018;48(7):1224. https://doi.org/10.1017/S0033291717003932. MayPsychol Med. 2017;47(6):1030-1040.
39. Masi S, Georgiopoulos G, Khan T, et al. Patterns of adiposity, vascular phenotypes and cognitive function in the 1946 British Birth Cohort. *BMC Med*. 2018;16(1):75. https://doi.org/10.1186/s12916-018-1059-x. Published 2018 May 28.
40. Arnoldussen IA, Kiliaan AJ, Gustafson DR. Obesity and dementia: adipokines interact with the brain. *Eur Neuropsychopharmacol*. 2014;24(12):1982–1999. https://doi.org/10.1016/j.euroneuro.2014.03.002.
41. Sebastian MJ, Khan SK, Pappachan JM, Jeeyavudeen MS. Diabetes and cognitive function: an evidence-based current perspective. *World J Diabetes*. 2023;14(2):92–109. https://doi.org/10.4239/wjd.v14.i2.92.
42. Okura T, Heisler M, Langa KM. Association between cognitive function and social support with glycemic control in adults with diabetes mellitus. *J Am Geriatr Soc*. 2009;57(10):1816–1824. https://doi.org/10.1111/j.1532-5415.2009.02431.x.
43. Repple J, Karliczek G, Meinert S, et al. Variation of HbA1c affects cognition and white matter microstructure in healthy, young adults. *Mol Psychiatry*. 2021;26(4):1399–1408. https://doi.org/10.1038/s41380-019-0504-3.
44. Gold SM, Dziobek I, Sweat V, et al. Hippocampal damage and memory impairments as possible early brain complications of type 2 diabetes. *Diabetologia*. 2007;50(4):711–719. https://doi.org/10.1007/s00125-007-0602-7.
45. Garfield V, Farmaki AE, Eastwood SV, et al. HbA1c and brain health across the entire glycaemic spectrum. *Diabetes Obes Metab*. 2021;23(5):1140–1149. https://doi.org/10.1111/dom.14321.
46. Embury CM, Lord GH, Drincic AT, Desouza CV, Wilson TW. Glycemic control level alters working memory neural dynamics in adults with type 2 diabetes. *Cereb Cortex*. 2023;33(13):8333–8341. https://doi.org/10.1093/cercor/bhad119.
47. Salvi V, Tripodi B, Cerveri G, et al. Insulin-resistance as a modifiable pathway to cognitive dysfunction in schizophrenia: a systematic review. *Schizophr Res*. 2024;274:78–89. https://doi.org/10.1016/j.schres.2024.09.008.
48. Zhang X, Yang M, Du X, et al. Glucose disturbances, cognitive deficits and white matter abnormalities in first-episode drug-naive schizophrenia. *Mol Psychiatry*. 2020;25(12):3220–3230. https://doi.org/10.1038/s41380-019-0478-1.
49. González P, Lozano P, Ros G, Solano F. Hyperglycemia and oxidative stress: an integral, updated and critical overview of their metabolic interconnections. *Int J Mol Sci*. 2023;24(11):9352. https://doi.org/10.3390/ijms24119352.
50. Chen Q, Cao T, Li N, et al. Repurposing of anti-diabetic agents as a new opportunity to alleviate cognitive impairment in neurodegenerative and neuropsychiatric disorders. *Front Pharmacol*. 2021;12, 667874. https://doi.org/10.3389/fphar.2021.667874.
51. Shao T, Huang J, Zhao Y, et al. Metformin improves cognitive impairment in patients with schizophrenia: associated with enhanced functional connectivity of dorsolateral prefrontal cortex. *Transl Psychiatry*. 2023;13(1):315. https://doi.org/10.1038/s41398-023-02616-x.
52. Babic I, Gorak A, Engel M, et al. Liraglutide prevents metabolic side-effects and improves recognition and working memory during antipsychotic treatment in rats. *J Psychopharmacol*. 2018;32(5):578–590. https://doi.org/10.1177/0269881118756061.
53. Ishida I, Ogura J, Aizawa E, et al. Gut permeability and its clinical relevance in schizophrenia. *Neuropsychopharmacol Rep*. 2022;42(1):70–76. https://doi.org/10.1002/npr2.12227.
54. González-Blanco L, Dal Santo F, García-Portilla MP, et al. Intestinal permeability biomarkers in patients with schizophrenia: additional support for the impact of lifestyle habits. *Eur Psychiatry*. 2024;67(1):e84. https://doi.org/10.1192/j.eurpsy.2024.1765.
55. Dal Santo F, González-Blanco L, García-Portilla MP, et al. From gut to brain: a network model of intestinal permeability, inflammation, and psychotic symptoms in schizophrenia. *Eur Neuropsychopharmacol*. 2024;79:32–37. https://doi.org/10.1016/j.euroneuro.2023.10.004.
56. Maqoud F, Calabrese FM, Celano G, et al. Role of increasing body mass index in gut barrier dysfunction, systemic inflammation, and metabolic dysregulation in obesity. *Nutrients*. 2024;17(1):72. https://doi.org/10.3390/nu17010072.
57. Li C, Li X, Han H, et al. Effect of probiotics on metabolic profiles in type 2 diabetes mellitus: a meta-analysis of randomized, controlled trials. *Medicine*. 2016;95(26):e4088. https://doi.org/10.1097/MD.0000000000004088.
58. Gruber JR, Ruf A, Süß ED, et al. Impact of blood glucose on cognitive function in insulin resistance: novel insights from ambulatory assessment. *Nutr Diabetes*. 2024;14(1):74. https://doi.org/10.1038/s41387-024-00331-0.
59. García-Portilla P. Cognitive reserve: "Whoever Had, Retained" …, and Much More. *Span J Psychiatry Ment Health*. 2024;17(3):127–128. https://doi.org/10.1016/j.sjpmh.2024.08.002.
60. Magdaleno Herrero R, Murillo-García N, Á Yorca-Ruiz, et al. Biomarkers as proxies for cognitive reserve: the role of high density lipoprotein cholesterol in first episode of psychosis. *Span J Psychiatry Ment Health*. 2024;17(3):146–153. https://doi.org/10.1016/j.rpsm.2023.03.002.
61. Amoretti S, Anmella G, Bernardo M, et al. Impact of cognitive reserve in clinical, neurocognitive and lifestyle factors in chronic schizophrenia and early stages of schizophrenia. *Span J Psychiatry Ment Health*. 2024;17(3):168–174. https://doi.org/10.1016/j.sjpmh.2024.01.003.