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Received: 17 April 2025

Revised: 8 December 2025

Accepted: 20 January 2026

Cite this article as: Wang, X., Dang, J., Yu, X. *et al.* Exploring the intricate interplay between metabolic abnormalities and multidimensional cognitive impairment in stable schizophrenia patients. *Transl Psychiatry* (2026). <https://doi.org/10.1038/s41398-026-03820-1>

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Exploring the Intricate Interplay Between Metabolic Abnormalities and Multidimensional Cognitive Impairment in Stable Schizophrenia Patients

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Trial registration: MR-11-23-007343.

Abstracts

Cognitive deficits across multiple domains are prevalent in patients with schizophrenia (PWS), and metabolic syndrome (MetS) may significantly contribute to this impairment. To clarify the complex relationships between individual MetS components and multidimensional cognitive dysfunction in PWS, we conducted a multicenter study involving 727 clinically stable patients recruited from ten psychiatric hospitals. Cognitive function was assessed using the Chinese Brief Cognitive Test (C-BCT). We employed network analysis and structural equation modeling (SEM) to explore these associations, with machine learning techniques applied for further validation. The results revealed statistically significant differences in several cognitive domains between patients with and without dyslipidemia (DL). Patients with hypertension (HT) also exhibited overall poorer cognitive performance. Network analysis indicated meaningful distinctions between patients presenting two or more MetS components (MetS-2+) and those without, showing a sparser network configuration in the MetS-2+ group. Across both groups, the Symbol Coding task demonstrated the highest strength centrality. SEM indicated that metabolic indicators, specifically DL and HT, mediated the relationship between clinical symptoms and cognitive function. Furthermore, a transformer-based machine learning model performed effectively in predicting cognitive dimensions, supporting the predictive utility of MetS components for multidimensional cognitive outcomes. In summary, specific MetS components, particularly DL and HT, show intricate associations with cognitive function in stable-phase PWS. Our findings suggest that management of HT in this population may represent a potential pathway for cognitive enhancement and improved social functioning.

Keywords:

Stable-phase schizophrenia, Metabolic syndrome, Cognition, Network analysis, Machine learning

1.Introduction

Schizophrenia is a complex and heterogeneous mental illness that imposes a heavy burden on individuals and society in general¹. The lifetime prevalence of schizophrenia is approximately 0.7%, with roughly 75% of these individuals exhibiting recurrent and persistent disabilities. Cognitive

impairment is one of the core features of schizophrenia²⁻⁴. Cognitive deficits in patients with schizophrenia (PWS) have been observed across multiple domains, including neurocognitive domains⁵⁻⁷ and social cognitive domains⁸⁻¹⁰. Cognitive impairment in PWS negatively affects social functioning more severely than positive or depressive symptoms, even during clinical remission¹¹. Thus, cognitive impairment has become a potential pharmacological target for enhancing the quality of life and functional outcomes in PWS¹¹⁻¹⁴.

Metabolic syndrome (MetS), which is very prevalent in PWS, is a group of cardiovascular risk factors associated with cognitive decline¹⁵, including obesity (OB), dyslipidemia (DL), hyperglycemia (HG), and hypertension (HT). MetS has been called a global epidemic by the World Health Organization (WHO) and is considered a major public health problem¹⁶. Meta-analyses indicate that the pooled prevalence of MetS in PWS ranges from approximately 30% to 40%, representing a risk 2 to 2.5 times greater than that observed in general population controls^{17, 18}.

The high risk of MetS in PWS is a major difficulty faced by clinical psychiatrists. This is partly because the cognitive impairment observed among PWS with MetS is more obvious than that in PWS without MetS^{19, 20}, counteracting or even exceeding the cognitive improvement caused by drugs²¹. PWS perform 1.5 to 2.0 standard deviations below healthy controls on various neurocognitive tasks, such as verbal fluency, working memory, and executive function. One meta-analysis found that, compared with PWS without MetS, cognitive impairment in PWS with MetS presented primarily as reductions in memory, attention, processing speed, and executive function²². A study of long-term use of olanzapine monotherapy for schizophrenia found that, compared with patients without MetS, patients with MetS exhibited worse memory and attention²³. A significant amount of studies have confirmed that schizophrenia patients with MetS suffer more severe

cognitive impairments^{19,22,24}. Whereas MetS is one of the few clinical syndromes that affects a large portion of the general population and may be reversed with established interventions, investigating the effect of MetS on cognitive impairment in PWS is of great significance for preventing cognitive decline and promoting social rehabilitation in this population.

However, most studies on MetS consider it as a whole, with no general consensus on the effects of specific components of MetS on various cognitive functions in schizophrenia patients. Recently, the impact of MetS components on cognitive function in PWS has received increased attention. Several studies have investigated the effects of various components of MetS on the cognitive domain of schizophrenia; however, the results have been contradictory²⁵⁻²⁷. While HG has been demonstrated as an independent risk factor^{23,28}, a study by Lancon found that patients with HT and OB have more cognitive deficits than controls²⁹. Other studies have found that cognitive deficits are only associated with HG, not with HT or abdominal OB^{30,31}. One study reported that high levels of triglycerides OB, and low levels of high-density lipoprotein (HDL) cholesterol were the only metabolic factors associated with memory impairment in PWS^{26,32}. Conversely, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study failed to find any association between MetS and cognitive domains³³. In fact, baseline data from another CATIE study also failed to show any relationship between MetS and cognitive impairment in PWS. Such substantial variability in results may be attributable to differences in study populations or variations in the criteria used for classification. Unfortunately, these disparate results may mask the impact of the individual components of MetS on cognition³⁴.

Current evidence leaves two critical questions unresolved: whether the impact of MetS on cognitive function in PWS originates from individual components or their synergistic effects, and

whether cognitive impairment is domain-specific or global. To address these gaps, this study assessed the prevalence of individual MetS components and the severity of cognitive impairment in PWS, and investigated the complex relationships between MetS and multidimensional cognitive dysfunction. Using network analysis, structural equation modeling (SEM), and machine learning approaches, we systematically examined these associations to generate evidence-based strategies for preventing cognitive decline and improving functional outcomes in this population.

2.Methods

2.1.1 Participants

The current study was conducted from March to August 2022, collecting stable-phase PWS from 10 hospitals in Shanxi Province for an observational cross-sectional study (The specific data collection process and the number of cases recruited by each clinical hospital are detailed in Supplementary Table S1.). Based on an α level of 0.05 and statistical power of 0.80, a priori power analysis using G*Power software estimated a minimum required sample size of approximately 550 participants. Therefore, the final enrollment of 727 participants (with 685 providing valid metabolic data) meets and exceeds this requirement, ensuring adequate power to detect clinically meaningful associations.

2.1.2 Inclusion Criteria:

- (1) Diagnosed with schizophrenia by at least two attending psychiatrists or one associate chief physician or above in psychiatry, in accordance with the diagnostic criteria for schizophrenia outlined in the International Classification of Diseases 11th Revision (ICD-11).
- (2) Stable-phase schizophrenia patients are defined as those who have been on stable treatment with antipsychotic medications for at least one month without changing medication or adjusting dosage

during this period, and with a Clinical Global Impression (CGI) severity score not exceeding 3.

(3) Aged over 18 years and under 60 years.

(4) Patients and/or their legal guardians provided informed consent.

2.1.3 Exclusion Criteria:

(1) Patients with organic brain disorders or severe physical illnesses who were unable to cooperate with the investigation.

(2) Individuals with a history of substance dependence or alcohol or drug abuse lasting more than 10 years.

(3) Patients with intellectual disabilities.

(4) Individuals exhibiting extreme excitement, rigidity, passive suicidality, or other non-cooperative behaviors or posing a risk.

(5) Use of any psychoactive substances in the three days preceding the assessment.

(6) Consumption of more than four standard drinks per day (180 ml of 40% alcohol, 600 ml of 12% wine, or 1440 ml of 5% beer) in the three days preceding the assessment.

(7) History of head trauma resulting in loss of consciousness for more than one hour.

(8) Receipt of MECT or ECT treatment within the past six months.

(9) Pregnant or breastfeeding women.

2.2 Data collection

(1) Sociodemographic and General Clinical Data

A self-designed sociodemographic and epidemiological registration form was used to collect information including age, gender, marital status, employment status, educational level, medication usage.

(2) Diagnostic Tools

The ICD-11 was employed for diagnosing schizophrenia³⁵. The ICD, which was developed by WHO, provides a standardized classification system for diseases globally. The 11th revision, released in 2018, is widely utilized in clinical and research settings.

(3) Clinical Symptoms

The ICD-11 Symptom Qualifier Scales for Schizophrenia and Other Primary Psychotic Disorders assessed six domains of symptoms, including positive, negative, depressive, manic, psychomotor, and cognitive symptoms, using a 4-point scale³⁶.

(4) Cognitive Function

The Chinese Brief Cognitive Test (C-BCT)³⁷, developed using the Delphi method, evaluates cognitive function in schizophrenia through trail-making tests (TMT)³⁸, symbol coding (SC), continuous performance test (CPT), and digit span test (DST), and categorizes dysfunction into normal, mild, moderate, and severe levels. The C-BCT offers a culturally adapted, brief (20 – 30 min) cognitive assessment tailored for Chinese populations, enhancing feasibility in clinical and large-scale settings. In contrast to the MCCB, it requires no specialized equipment, improving accessibility in primary care. However, its application is primarily validated in schizophrenia and MCI, whereas the MCCB covers a broader range of psychiatric disorders^{37, 39}. (Detailed C-BCT information is provided in Supplementary Information S1.)

(5) Social Functioning

The Short Form 12-Item Health Survey (SF-12), a simplified version of the SF-36 questionnaire, assesses physical and mental health status through 12 items within eight dimensions⁴⁰. It serves as a self-assessment scale.

2.3 Procedure

Participants were recruited from 10 hospitals in Shanxi Province, with 3-5 physicians participating from each site. Eligible patients identified in outpatient or inpatient settings were screened and enrolled after providing informed consent. Inclusion and exclusion criteria were applied, and reasons for non-participation were documented. Following enrollment, the attending physician or principal investigator collected general demographic and clinical information, physical examination findings, and current metabolic parameters (including serum lipids, blood glucose, and prolactin). Data on antipsychotic medications—including type, dosage, and concomitant use of other psychotropic drugs such as antidepressants—were also recorded. MetS was diagnosed according to the harmonized criteria established by the AHA/NHLBI, IDF, IAS, IASO, and WHF³⁹. The diagnosis of metabolic syndrome includes the following components. HT was defined as systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg, or self-reported use of antihypertensive medication by individuals with a known history of HT. Diabetes was defined as a fasting blood glucose (FBG) level ≥ 126 mg/dL or current use of glucose-lowering agents. An FBG level ≥ 100 mg/dL was classified as HG. Low HDL-C was defined as <40 mg/dL in men and <50 mg/dL in women. Elevated LDL-C was defined as ≥ 100 mg/dL. Hypertriglyceridemia was identified as a serum triglyceride level ≥ 150 mg/dL or self-reported use of medication for elevated triglycerides. Patients were assessed for psychiatric symptom severity and guided to complete cognitive (C-BCT) and social functioning (SF-12) evaluations, with all data entered electronically to ensure quality control. The total assessment time was approximately 35-40 minutes. The study was approved by the Ethics Committee of the First Hospital of Shanxi Medical University (Approval No. 2022-K033).

2.4 Statistical analysis

To control for potential confounding effects of age, sex, and medication, analysis of covariance (ANCOVA) was employed in this study. Blood glucose, blood pressure, blood lipids, and OB levels were included as dependent variables, with group assignment as the fixed factor, to evaluate adjusted intergroup differences in clinical symptoms and cognitive function. All analyses satisfied ANCOVA's prerequisite assumptions of linearity and homogeneity of regression slopes.

Network analysis was then used to explore the complex correlation between MetS components and multidimensional elements of cognitive dysfunction. The network was established based on partial correlations between variables, which made it possible to identify unique interactions between variables that could not be identified using multiple regression analysis⁴¹. In this study, 13 nodes were included: (1) five subscales of clinical symptoms; (2) four domains of cognitive functions as measured by the C-BCT; (3) two social functions as measured by the SF-12; (4) and two demographic characteristics (age and educational years). Participants were divided into two groups based on whether they had two or more components of MetS. Network models for the two groups were independently estimated using sparse graphical Gaussian models (GGM) combined with the graphical least absolute shrinkage and selection operator (LASSO) method. Model selection was based on extended Bayesian information criterion (EBIC). To assess the significance of each node, three centrality measures were employed: betweenness, closeness, and strength. Betweenness centrality is defined as the number of shortest paths between pairs of nodes that pass through the node of interest, indicating the node's role as a "bridge" in the network. Closeness identifies nodes that are, on average, closest to all other nodes, reflecting the node's ability to quickly interact with other nodes. Strength centrality measures the sum of absolute edge weights of all direct

connections a node has, indicating the node's connectivity within the network. Robustness analyses were carried out using the R-package "bootnet". Non-parametric bootstrapping with 1,000 replicates was conducted to estimate 95% confidence intervals (CI) for edge values. Differences in the estimated networks between the two groups were assessed using the R package "Network Comparison Test"(NCT).

Structural Equation Modeling (SEM) is a statistical tool for analyzing complex relationships among multiple variables, revealing both direct and indirect relationships between observed and latent variables. In research on MetS, SEM is particularly important as it can explore how various components of MetS, such as DL and HT, directly and indirectly affect cognitive and social functions⁴². AMOS 26.0 was used to construct, analyze, and verify the goodness of fit of the SEM. The Pearson correlation coefficient was used to test the correlation matrix among the research variables. Confirmatory factor analysis (CFA) and parameter estimation of SEM utilized the weighted least squares mean and variance adjusted (WLSMV) correction method. There were four goodness-of-fit indicators: maximum likelihood chi-square (χ^2), degrees of freedom (DF), comparative fit index (CFI), incremental fit index (IFI), and root mean square error of approximation (RMSEA). When the CFI or TLI values were greater than or equal to 0.90, and the RMSEA value was less than 0.05, we considered model fit to be ideal.

To further validate the relationship between components of MetS and cognitive function, this study employed classic deep learning algorithmic models (i.e., multilayer perceptron (MLP) and transformer) capable of capturing complex non-linear relationships that could be used to predict the cognitive dimensions using symptom assessments and metabolic indicators. The dataset was divided into training and testing sets at a 7:3 ratio. The loss function incorporated both MSE loss and L1

regularization loss as the total loss function, achieving high prediction accuracy, while simplifying the model. First, a classic MLP model was utilized for prediction. This study constructed a four-layer MLP neural network model, with an input of 36-dimensional vectors and an output of four-dimensional vectors. Both hidden layers consisted of 1024 neurons. The training consisted of 1000 epochs, with a batch size set to 24, and an Adam optimizer employed. After 1000 epochs of training, the loss value had essentially stabilized, denoting that model parameters had reached their optimum. Compared to the MLP model, the transformer model introduced a self-attention mechanism, which could more effectively extract global features⁴³. First, the data were expanded into a 512-dimensional space and then positional embeddings were added. Then, a four-layer, multi-head, self-attention mechanism was introduced for encoding, elevating the data into a higher-order space. Subsequently, a three-layer, multi-head, self-attention mechanism was employed in the decoder to reduce the data dimensionality to the final four-dimensional output space. The entire architecture was inspired by the classic seq2seq model, akin to text translation tasks in natural language processing. Two types of multi-head, self-attention mechanisms were utilized, with a dropout parameter of 0.1. Other training parameters remained consistent with the MLP model. A flow chart is shown in Fig. 1.

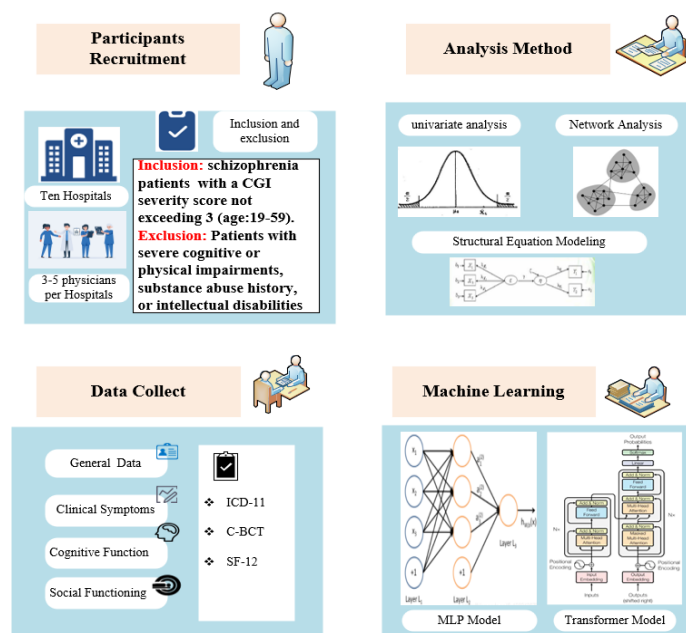


Fig. 1 Flow chart⁴⁴

3. Results

A total of 727 stable-phase PWS participated in this study, comprising 471 males and 256 females (Detailed data are presented in Table 1). Among the 727 participants, 724 completed the C-BCT assessment, and 685 had available metabolic-related data. In terms of concomitant medication use, 82.9% of patients were taking antipsychotic drugs at the time of enrollment, with a mean dosage of 10.12 mg/day (with risperidone as the standard, predominantly risperidone, olanzapine, and aripiprazole). The probability of receiving combined medication (antidepressants, mood stabilizers, or benzodiazepines) was 40.8%.

3.1 Cognitive differences

Stable-phase PWS were classified into two groups based on abnormalities in four different indicators (blood glucose, blood pressure, blood lipid, and OB). For DL, differences were statistically significant for depression symptoms ($F = 14.52, P = 0.0002$), and manic symptoms ($F = 22.53, P < 0.0001$). Additionally, significant differences were also observed in C-BCT, including

DST ($F = 18.65, P < 0.0001$), physical health test (PHT; $F = 4.77, P = 0.0334$), and mental health test (MHT; $F = 17.38, P < 0.0001$). For HG, there were statistically significant differences for manic ($F = 8.95, P = 0.0029$). For HT, depression symptoms ($F = 16.86, P < 0.0001$), manic symptoms ($F = 14.88, P = 0.0001$), psychomotor symptoms ($F = 30.01, P < 0.0001$), TMT ($F = 16.11, P < 0.0001$), SC ($F = 11.46, P = 0.0008$), CPT1 ($F = 8.54, P = 0.0036$), DST ($F = 16.88, P < 0.0001$), PHT ($F = 24.28, P < 0.0001$), and MHT ($F = 19.64, P < 0.0001$) were all found to be significantly different between groups. Regarding OB, statistically significant differences were found in depression symptoms ($F = 4.03, P = 0.045$), manic symptoms ($F = 10.57, P = 0.0012$), psychomotor symptoms ($F = 5.9, P = 0.0154$), cognitive symptoms ($F = 7.4, P = 0.0067$), and SC ($F = 3.35, P = 0.0678$).

Table 1. Sociodemographic characteristics of the normative sample.

Sociodemographic characteristics		Value (N=727)
Age (y)		42.9±11.5
Education		13±0.5
Gender	Male	471 (64.8%)
	Female	256 (35.2%)
Marriage	Unmarried	352 (48.4%)
	Married	145 (19.9%)
	Other	146 (20.1%)
Employment	Unemployed	470 (64.6%)
	Employed	60 (8.3%)
	Other	197 (27.1%)

Table 2. Cognitive differences between DL and HG based on abnormalities in four different indicators.

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		DL	M (SD)	F	<i>P</i>	HG	M (SD)	F	<i>P</i>
ICD-11	P	no	1.19 (0.72)	2.52	0.11	no	1.16 (0.73)	0.94	0.33
		yes	1.07 (0.81)			yes	1.26 (0.79)		
	N	no	0.92 (0.68)	0.98	0.32	no	0.93 (0.70)	0.56	0.45
		yes	0.99 (0.73)			yes	1.04 (0.55)		
	D	no	0.54 (0.65)	14.52	0.0002	no	0.51 (0.64)	1.38	0.24
		yes	0.30 (0.50)			yes	0.4 (0.57)		
	M	no	0.45 (0.60)	22.53	< .0001	no	0.42 (0.60)	8.95	0.0029
		yes	0.17 (0.42)			yes	0.17 (0.38)		
	PS	no	0.54 (1.02)	0.18	0.67	no	0.54 (1.04)	1.69	0.19
		yes	0.48 (1.24)			yes	0.42 (1.28)		
	C	no	0.99 (0.83)	2.44	0.12	no	0.98 (0.82)	5.17	0.023
		yes	1.10 (0.85)			yes	1.34 (0.83)		
C-BCT	TMT	no	38.55 (15.63)	3.18	0.07	no	39.07 (15.4)	0.23	0.63

SF-12	SC	yes	41.25 (13.53)	2.30	0.13	yes	37.98 (14.5)	0.16	0.69
		no	39.34 (12.07)			no	39.64 (12.19)		
	CPT1	yes	40.97 (11.67)	7.00	0.01	yes	39.25 (9.56)	0	0.99
		no	37.14 (14.44)			no	37.84 (14.66)		
	CPT2	yes	41.25 (14.17)	6.35	0.01	yes	37.58 (11.89)	0.03	0.86
		no	38.62 (13.87)			no	39.20 (13.9)		
	CPT3	yes	42.42 (13.43)	7.13	0.01	yes	39.79 (13.4)	0.02	0.89
		no	38.85 (12.23)			no	39.41 (12.47)		
	DST	yes	42.26 (12.44)	18.65	<.0001	yes	39.43 (10.46)	0.34	0.56
		no	38.10 (11.78)			no	38.93 (12.34)		
	PHT	yes	43.29 (13.71)	4.77	0.03	yes	39.25 (11.32)	0.08	0.78
		no	46.80 (7.16)			no	47.15 (6.88)		
SF-12	MHT	yes	48.32 (6.63)	17.38	< .0001	yes	46.16 (9.22)	1.2	0.27
		no	43.33 (9.22)			no	43.96 (9.12)		
		yes	47.14 (8.24)			yes	44.63 (9.68)		

NOTES: **DL:** Dyslipidemia; **HG:** Hyperglycemia; **ICD-11:** International Classification of Diseases 11th Revision; **C-BCT:** Chinese Brief Cognitive Test; **SF-12:** Short-Form Health Survey 12;

P: Positive symptoms; **N:** Negative symptoms; **D:** Depressive symptoms; **M:** Manic symptoms; **PS:** Psychomotor symptoms; **C:** Cognitive symptoms; **TMT:** Trail-making tests; **SC:** Symbol

coding; **CPT1**: Continuous Performance Test 1; **CPT2**: Continuous Performance Test 2; **CPT3**: Continuous Performance Test 3; **DST**: Digit span test; **PHT**: Physical health test; **MHT**: Mental health test.

Table 3. Cognitive differences between HT and OB based on abnormalities in four different indicators.

		HT	M (SD)	F	<i>P</i>	OB	M (SD)	F	<i>P</i>
ICD-11	P	no	1.12 (0.72)	6.44	0.01	no	1.2 (0.74)	0.91	0.34
		yes	1.29 (0.76)			yes	1.15 (0.73)		
	N	no	0.92 (0.69)	0.07	0.79	no	0.93 (0.7)	0.03	0.87
		yes	0.97 (0.69)			yes	0.94 (0.69)		
	D	no	0.44 (0.60)	16.86	< .0001	no	0.57 (0.63)	4.03	0.045
		yes	0.65 (0.69)			yes	0.46 (0.64)		
	M	no	0.34 (0.54)	14.88	0.00	no	0.5 (0.61)	10.57	0.001
		yes	0.54 (0.67)			yes	0.33 (0.56)		
	PS	no	0.4 (0.89)	30.01	< .0001	no	0.66 (1.31)	5.9	0.02
		yes	0.83 (1.34)			yes	0.44 (0.85)		
	C	no	0.94 (0.84)	6.6	0.01	no	0.91 (0.84)	7.4	0.007
		yes	1.17 (0.77)			yes	1.07 (0.82)		
C-BCT	TMT	no	40.64 (13.65)	16.11	< .0001	no	38.79 (16.09)	0.32	0.57
		yes	34.88 (18.27)			yes	39.15 (14.74)		

SF-12	SC	no	40.4 (12.06)	11.46	0.00	no	40.88 (14.34)	3.35	0.07
		yes	37.63 (11.66)			yes	38.64 (9.77)		
	CPT1	no	38.85 (14.74)	8.54	0.00	no	37.03 (15.07)	1.08	0.30
		yes	35.25 (13.46)			yes	38.42 (13.98)		
	CPT2	no	39.62 (14.39)	1.04	0.31	no	38.25 (14.63)	1.43	0.23
		yes	38.32 (12.43)			yes	40.01 (13.21)		
	CPT3	no	39.49 (12.98)	0.19	0.66	no	38.5 (13.30)	2.44	0.12
		yes	39.22 (10.54)			yes	40.11 (11.49)		
	DST	no	40.2 (12.22)	16.88	< .0001	no	38.88 (13.10)	0.08	0.78
		yes	35.85 (11.82)			yes	39.00 (11.60)		
	PHT	no	47.93 (7.16)	24.28	< .0001	no	47.28 (7.55)	0.01	0.91
		yes	45.12 (6.56)			yes	46.94 (6.78)		
	MHT	no	45.05 (9.19)	19.64	< .0001	no	44.23 (8.64)	0.08	0.78
		yes	41.65 (8.67)			yes	43.86 (9.50)		

NOTES: **HT:** Hypertension; **OB:** Obesity; **ICD-11:** International Classification of Diseases 11th Revision; **C-BCT:** Chinese Brief Cognitive Test; **SF-12:** Short-Form Health Survey 12; **P:** Positive symptoms; **N:** Negative symptoms; **D:** Depressive symptoms; **M:** Manic symptoms; **PS:** Psychomotor symptoms; **C:** Cognitive symptoms; **TMT:** Trail-making tests; **SC:** Symbol coding; **CPT1:** Continuous Performance Test 1; **CPT2:** Continuous Performance Test 2; **CPT3:** Continuous Performance Test 3; **DST:** Digit span test; **PHT:** Physical health test; **MHT:** Mental health

test.

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3.2 Network analysis

Participants were divided into two groups based on the presence or absence of two or more components of MetS (Mets-2+) and found differences between the two groups through network analysis. In the group without Mets-2+, depression, mania, and cognitive symptoms formed a triangular connection. Positive associations were also observed between positive and negative symptoms ($r = 0.19$), TMT and SC ($r = 0.23$), SC and CPT ($r = 0.24$), CPT and DST ($r = 0.20$). In the group with Mets-2+, a pentagonal connection was formed between positive, negative, depressive, manic, and cognitive symptoms. Among cognitive functions, SC showed the highest strength in both groups, indicating that it has many or strong connections with other nodes in the network. In patients without Mets-2+, CPT demonstrated a high level of closeness, meaning it had a short average distance from all other nodes, suggesting an influential role in the network. TMT showed the highest betweenness, indicating it lay on many of the shortest paths between every combination of two other nodes in the network. Comparisons of the two networks based on NCT results showed that the structure of the networks was variant between groups ($M = 0.31$, $P < 0.001$), and the global network strength test similarly revealed no significant differences in the weighted sum associations of trait facets ($S = 3.23$, $P = 0.618$; Fig. 2).

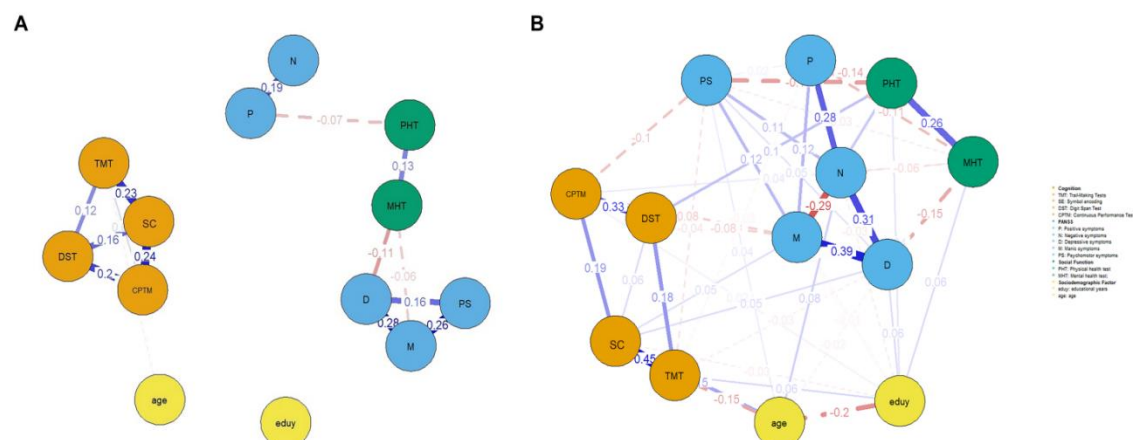


Fig. 2 Network analysis of groups with or without Mets-2+. **A** Group without Mets-2+. **B** Group with Mets-2+.

3.3 Role of MetS in Social Functioning

To gain a better understanding of the links among MetS, clinical symptoms, and cognitive function, we performed SEM. After adjustments and optimizations, the SEM reached a satisfactory level of fitness ($\chi^2 = 203.150$, CMIN/DF = 6.269, DF = 41, $P < 0.001$, CFI = 0.810, IFI = 0.816, RMSEA = 0.079). Schizophrenic symptoms (SS), encompassing positive, negative, depressive, manic, and cognitive symptoms, were identified as independent variables. Two components of MetS (HG and HT) were treated as mediating variables. Furthermore, four aspects of cognitive function were examined as dependent variables (Table 2 and Table 3). The findings revealed significant associations between MetS and SS (all with $P < 0.05$). Likewise, a significant correlation was observed between the two MetS dimensions and cognitive tests, including TMT, SC, CPT, and DST (all with $P < 0.05$). Additionally, SS exhibited a significant correlation with these cognitive tests (all with $P < 0.05$).

The standardized correlation coefficient indicated that SS exerted a significant negative influence on the two dimensions of MetS ($r = -0.89$). Furthermore, the impact strengths of the two dimensions of MetS on the TMT, SC, CPT1, and DST tests were 1.44, 1.63, 1.16, and 1.19, respectively. Additionally, the influence intensities of SS on the trail making test, symbol coding, continuous operation 1, and DST were 1.15, 1.50, 0.93, and 0.88, respectively (Fig. 3).

Direct effect, indirect effect, and total effect were tested on the latent variables of the hypothesized model. SS exerted a direct effect on TMT ($\beta = 1.15$, $P < 0.05$), SC ($\beta = 1.50$, $P < 0.05$), CPT1 ($\beta = 0.93$, $P < 0.05$), and DST ($\beta = 0.88$, $P < 0.05$) scores. For example, when SS increased by one standard deviation, TMT significantly increased by 1.15 standard deviations. Indirect effect

refers to the effect of one variable on another via a mediator (e.g., $SS \rightarrow HT \rightarrow TMT$). The indirect effect of SS on TMT via metabolic index was -1.07; the indirect effect of SS on TMT via metabolic index was -1.04; the indirect effect of SS on TMT via metabolic index was -1.46; and the indirect effect of SS on TMT via metabolic index was -1.29. The total effect is the sum of direct and indirect effects.

The mediational effect model analyzed by SEM is shown in Fig. 3. Among metabolic indicators, HT and DL mediated the influence between SS and cognition. SS had a negative association with HT ($\beta = -0.38, P < 0.05$), while SS had a positive association with DL ($\beta = 0.27, P < 0.05$).

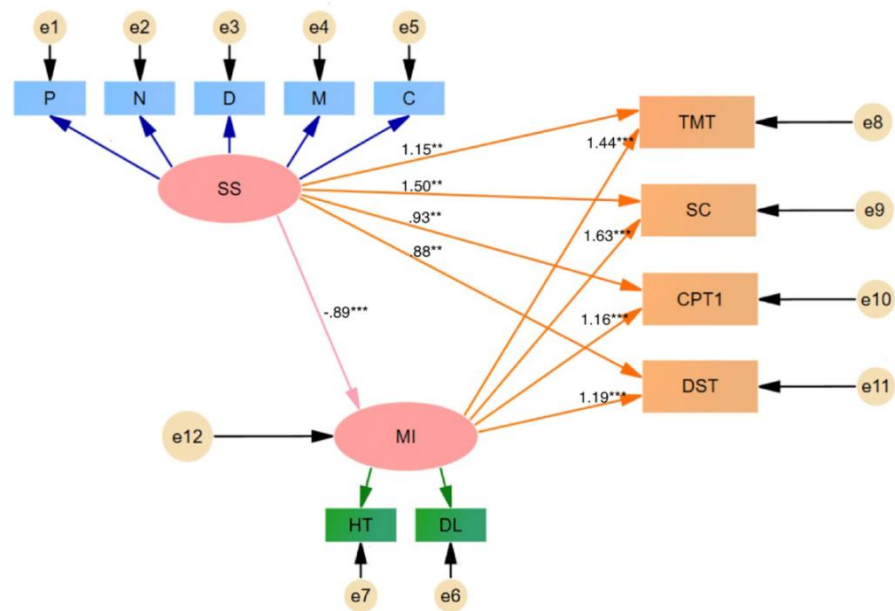


Fig. 3 The mediational effect model tested with SEM. NOTES: P: Positive symptoms; N: Negative symptoms; D: Depressive symptoms; M: Manic symptoms; C: Cognitive symptoms; TMT: Trail-making tests; SC: Symbol coding; CPT1: Continuous performance test 1; DST: Digit span test; HT: Hypertension; DL: Dyslipidemia; MI: Metabolic index; SS: Schizophrenia symptoms; e1 to e12 represent residuals.

3.4 Prediction Model

While all models converged well during training, the Transformer model attained a lower final

loss value compared to the MLP model (Fig. 4); however, to assess their real-world performance, they needed to undergo generalization testing on the test set. The chosen evaluation metrics are mean absolute error (MAE), root mean square error (RMSE), and Theil inequality coefficient (TIC). Based on these metrics, the models' performance on the test set is summarized in Table 4. As measures of predictive accuracy, MAE and RMSE both quantify the discrepancy between predicted and observed values. MAE represents the average absolute deviation, whereas RMSE, by squaring the residuals, places greater emphasis on larger errors. In model evaluation, lower values of either metric correspond to higher predictive accuracy. A TIC value close to 0 indicates that the model's predictions are close to the actual values, implying high prediction accuracy and low bias. Conversely, a TIC value close to 1 suggests significant discrepancies between the model's predictions and the actual values, indicating lower prediction accuracy and higher bias. The transformer model outperformed the MLP model in all four evaluation metrics. However, it is worth noting that the transformer model has significantly more parameters compared to the MLP model (approximately ten times as many). Since factors like parameter count were not relevant for the task in this study, the transformer model was better suited for completing the task, suggesting that metabolic abnormalities and clinical symptoms have a certain predictive ability for multidimensional cognitive function.

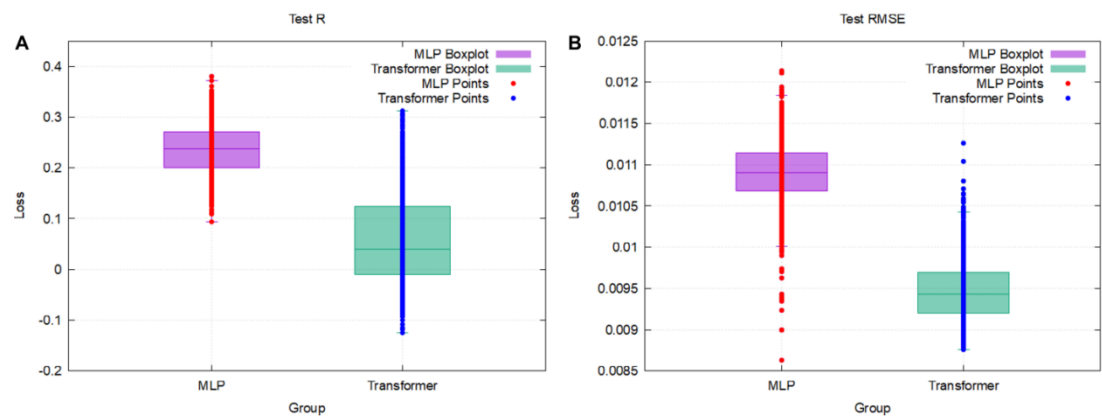


Fig. 4 Comparison of the test loss between the MLP and Transformer models. A the correlation coefficient (R). **B** the root mean square error (RMSE).

Table 4. MLP Model vs. Transformer Model Test Results.

	MLP Model	Transformer Model
MAE	0.00798	0.007237
RMSE	0.00959	0.00871
TIC	0.6706	0.6246
Number of model parameters	2141188	25507332

4. Discussion

This study explored the relationship between MetS components and cognition in stable PWS. We found significant correlation between MetS elements HT and DL and cognitive impairment, but not with other MetS factors. Based on these results, patients were divided into groups with and without HT and DL abnormalities for further analysis.

Network analysis was then used to further investigate the underlying complex relationships and compare differences between patients with Mets-2+ and without. Network metrics suggested meaningful differences between the two groups, indicating the network for patients with Mets-2+ was sparse relative to the network for those without. This means that the network for patients with Mets-2+ revealed smaller interconnectedness between cognitive factors and social functioning.

Possible reasons might include a greater impact of metabolic abnormalities on social functioning, overshadowing the influence of cognition on social functioning. This suggests that metabolic issues might significantly affect social functioning, potentially reducing the effectiveness of cognitive interventions when metabolic abnormalities are present⁴⁵. Information processing speed appears to be of particular importance for patients with Mets-2+, as SC and TMT had the highest level of strength and betweenness, while both information processing speed and attention show particular importance for patients without Mets-2+. Efficient processing of information is crucial for various aspects of daily functioning, including decision-making, problem-solving, and social interactions. PWS often experience impairments in information processing speed, which can significantly impact their ability to comprehend and respond to stimuli in a timely manner. This delay in processing can lead to difficulties in communication, decreased productivity, and impaired performance in tasks requiring quick cognitive processing; however, attention is vital for cognitive function, underpinning symptoms like disorganization thinking and poor social performance. It also affects daily activities and work/social interactions.

Therefore, interventions to improve information processing speed and attention, like cognitive rehab and medication, are essential for enhancing cognition and outcomes in this population. Considering these two MetS components (HT and DL) can have complex effects on multiple cognitive dimensions, a SEM was constructed to explore the relationships between these two factors and clinical symptoms, cognitive function, and social function.

Results indicated that HT not only directly influences cognition, but also serves as a mediator in the indirect relationship between psychiatric symptoms and various cognitive domains. As a mediating variable, HT might lead to a decline in information processing speed or memory¹⁵, and

these cognitive impairments may further affect an individual's daily life and social interaction abilities. This finding aligns with prior research linking blood pressure to cognitive dimensions⁴⁶⁻⁴⁹. A recent study indicates that cognitive function declines at an accelerated rate following a HT diagnosis, with the most severe impairment observed in information processing speed—particularly within the first few years after diagnosis⁵⁰. These findings highlight the crucial importance of early intervention during the post-diagnosis period and underscore the need for both clinicians and patients to prioritize proactive measures to preserve cognitive health. Elevated blood pressure may impair cognitive function both directly—through mechanisms such as neuroinflammation and brain atrophy^{51, 52} and indirectly by exacerbating comorbidities such as chronic kidney disease and heart failure^{53, 54}. Interestingly, PWS with DL had better attention and working memory than those without DL. Most research indicates that elevated levels of plasma low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), and triglycerides (TG), as well as decreases in high-density lipoprotein cholesterol (HDL-C), lead to a decrease in cognitive function. This could be due to increased β -amyloid plaques stimulating free radical production⁵⁵⁻⁵⁷. The findings are supported by studies, such as a 19-year study showing midlife HDL-C levels in the highest quartile are associated with over 50% less risk of myocardial infarction later in life, and higher midlife HDL-C reduces the risk of dementia⁵⁸.

Additionally, one study demonstrated that higher triglyceride levels correlate with better short-term memory, while another recent study linked increased LDL-C levels to improved general cognition and processing speed^{59, 60}. There were also studies showing conflicting associations between LDL-C, HDL-C, triglycerides, and cognition^{33, 34, 40, 55}. The inconsistencies may stem from variables such as age, gender, and cognitive assessment methods. Further research is warranted to

clarify the role of individual metabolic factors in cognition.

To further validate the impact of each MetS component on cognition, the current study ultimately employed transformer methodology to construct a non-linear prediction model. Compared to MLP models, the transformer models introduced self-attention mechanisms, which can more effectively extract global features. MetS components and clinical symptoms have a certain predictive ability for multidimensional cognitive functioning. Consequently, we observed that MetS as a whole didn't predict cognitive outcomes, supporting previous research⁶¹. To enhance cognitive performance or mitigate age-related decline, we must clarify how each MetS component affects cognition to guide interventions.

These findings must be interpreted in the context of the following limitations. First, due to the cross-sectional design of this study, it is impossible to establish causal relationships between components of metabolic syndrome and cognitive changes. Although significant associations were observed, the direction of these associations remains unclear — that is, whether metabolic dysregulation contributes to cognitive decline or whether cognitive impairment influences metabolic health. Additionally, despite the sample being recruited from ten clinical sites, the study population still represents a clinical sample, which may introduce selection bias and limit the generalizability of the findings to broader community-based populations⁶². Second, several crucial data points were unavailable, including the duration of HG or HT, as well as other moderating factors, such as smoking duration and so on that can potentially impact cognition. Finally, the cross-sectional nature of the current evaluation constrains our findings, as cross-sectional data cannot determine a causal link between MetS components and cognitive impairment.

Conclusions

Specific components of metabolic syndrome—particularly HT and DL—may have complex implications for multidimensional cognitive function in patients with stable schizophrenia. These results help reconcile previous inconsistencies in the literature concerning metabolic syndrome and cognitive performance, while also proposing a novel methodological framework for examining metabolic – cognitive interactions. Consequently, integrated treatment strategies that target both metabolic health and cognitive symptoms—rather than cognitive impairments alone—may more effectively promote functional recovery in schizophrenia patients with metabolic comorbidities. Further longitudinal studies are needed to evaluate the effectiveness of such combined interventions.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' contributions

XW and JD conducted the data analysis and interpretation, and drafted the initial manuscript. XY and CS conceived and designed the study. DC, YFW, QWJ, YW, XHZ, MC, JPF, SS and BHW were responsible for participant recruitment and data acquisition. SL and CS performed a critical review and revision of the manuscript for important intellectual content. All authors contributed to the scientific discussion, reviewed and edited the manuscript, and approved the final version for publication.

Funding

This study was supported by the National Natural Science Foundation of China (82271546 and 82201710); Fundamental Research Program of Shanxi Province (202203021211018 and 202103021223224); Shanxi Science and Technology Innovation Talent Team (202304051001049);

and Fund Program for the Scientific Activities of Selected Returned Overseas Professionals in Shanxi Province (20240041).

Ethics approval and consent to participate

All methods were performed in accordance with the relevant guidelines and regulations. The study was approved by the Ethics Committee of the First Hospital of Shanxi Medical University (Approval No. 2022-K033) and informed consent was obtained from all participants.

Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

Acknowledgments

The authors thank all the other members of the team for their contributions to this study.

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Table 1 Sociodemographic characteristics of the normative sample.

Table 2 Cognitive differences between DL and HG based on abnormalities in four different indicators.

Table 3 Cognitive differences between HT and OB based on abnormalities in four different indicators.

Table 4 MLP Model vs. Transformer Model Test Results.

Fig. 1 Flow chart.

Fig. 2 Network analysis of groups with or without Mets-2+. A Group without Mets-2+. B Group

with Mets-2+.

Fig. 3 The mediational effect model tested with SEM.

Fig. 4 Comparison of the test loss between the MLP and Transformer models. A the correlation coefficient (R). B the root mean square error (RMSE).

Table 1. Dsocio-demographic characteristics of the normative sample.

Dsocio-demographic characteristics		Value (N=727)
Age (y)		42.9±11.5
Education		13±0.5
Gender	Male	471 (64.8%)
	Female	256 (35.2%)
Marriage	Unmarried	352 (48.4%)
	Married	145 (19.9%)
	Other	146 (20.1%)
Employment	Unemployed	470 (64.6%)
	Employed	60 (8.3%)
	Other	197 (27.1%)

Table 2. Cognitive differences between DL and HG based on abnormalities in four different indicators.

		DL	M (SD)	F	P	HG	M (SD)	F	P
ICD-11	P	no	1.19 (0.72)	2.52	0.11	no	1.16 (0.73)	0.94	0.33
		yes	1.07 (0.81)			yes	1.26 (0.79)		
	N	no	0.92 (0.68)	0.98	0.32	no	0.93 (0.70)	0.56	0.45
		yes	0.99 (0.73)			yes	1.04 (0.55)		
	D	no	0.54 (0.65)	14.52	0.0002	no	0.51 (0.64)	1.38	0.24
		yes	0.30 (0.50)			yes	0.4 (0.57)		
	M	no	0.45 (0.60)	22.53	< .0001	no	0.42 (0.60)	8.95	0.0029
		yes	0.17 (0.42)			yes	0.17 (0.38)		
	PS	no	0.54 (1.02)	0.18	0.67	no	0.54 (1.04)	1.69	0.19
		yes	0.48 (1.24)			yes	0.42 (1.28)		
	C	no	0.99 (0.83)	2.44	0.12	no	0.98 (0.82)	5.17	0.023
		yes	1.10 (0.85)			yes	1.34 (0.83)		
C-BCT	TMT	no	38.55 (15.63)	3.18	0.07	no	39.07 (15.4)	0.23	0.63
		yes	41.25 (13.53)			yes	37.98 (14.5)		
		no	39.34 (12.07)			no	39.64 (12.19)		
		yes	40.97 (11.67)			yes	39.25 (9.56)		
	SC	no	37.14 (14.44)	7.00	0.01	no	37.84 (14.66)	0	0.99
		yes	41.25 (14.17)			yes	37.58 (11.89)		
		no	38.55 (15.63)			no	39.07 (15.4)		
		yes	41.25 (13.53)			yes	37.98 (14.5)		
	CPT1	no	39.34 (12.07)	2.30	0.13	no	39.64 (12.19)	0.16	0.69
		yes	40.97 (11.67)			yes	39.25 (9.56)		

SF-12	CPT2	no	38.62 (13.87)	6.35	0.01	no	39.20 (13.9)	0.03	0.86
		yes	42.42 (13.43)			yes	39.79 (13.4)		
	CPT3	no	38.85 (12.23)	7.13	0.01	no	39.41 (12.47)	0.02	0.89
		yes	42.26 (12.44)			yes	39.43 (10.46)		
	DST	no	38.10 (11.78)	18.65	<.0001	no	38.93 (12.34)	0.34	0.56
		yes	43.29 (13.71)			yes	39.25 (11.32)		
SF-12	PHT	no	46.80 (7.16)	4.77	0.03	no	47.15 (6.88)	0.08	0.78
		yes	48.32 (6.63)			yes	46.16 (9.22)		
	MHT	no	43.33 (9.22)	17.38	<.0001	no	43.96 (9.12)	1.2	0.27
		yes	47.14 (8.24)			yes	44.63 (9.68)		

NOTES: **DL**: Dyslipidemia; **HG**: Hyperglycemia; **ICD-11**: International Classification of Diseases 11th Revision; **C-BCT**: Chinese Brief Cognitive Test; **SF-12**: Short-Form Health Survey 12; **P**: Positive symptoms; **N**: Negative symptoms; **D**: Depressive symptoms; **M**: Manic symptoms; **PS**: Psychomotor symptoms; **C**: Cognitive symptoms; **TMT**: Trail-making tests; **SC**: Symbol coding; **CPT1**: Continuous Performance Test 1; **CPT2**: Continuous Performance Test 2; **CPT3**: Continuous Performance Test 3; **DST**: Digit span test; **PHT**: Physical health test; **MHT**: Mental health test.

Table 3. Cognitive differences between HT and OB based on abnormalities in four different indicators.

		HT	M (SD)	F	P	OB	M (SD)	F	P
ICD-11	P	no	1.12 (0.72)	6.44	0.01	no	1.2 (0.74)	0.91	0.34
		yes	1.29 (0.76)			yes	1.15 (0.73)		
	N	no	0.92 (0.69)	0.07	0.79	no	0.93 (0.7)	0.03	0.87
		yes	0.97 (0.69)			yes	0.94 (0.69)		
	D	no	0.44 (0.60)	16.86	< .0001	no	0.57 (0.63)	4.03	0.045
		yes	0.65 (0.69)			yes	0.46 (0.64)		
	M	no	0.34 (0.54)	14.88	0.00	no	0.5 (0.61)	10.57	0.001
		yes	0.54 (0.67)			yes	0.33 (0.56)		
	PS	no	0.4 (0.89)	30.01	< .0001	no	0.66 (1.31)	5.9	0.02
		yes	0.83 (1.34)			yes	0.44 (0.85)		
	C	no	0.94 (0.84)	6.6	0.01	no	0.91 (0.84)	7.4	0.007
		yes	1.17 (0.77)			yes	1.07 (0.82)		
C-BCT	TMT	no	40.64	16.11	< .0001	no	38.79	0.32	0.57
			(13.65)				(16.09)		
		yes	34.88			yes	39.15		
			(18.27)				(14.74)		
	SC	no	40.4 (12.06)	11.46	0.00	no	40.88	3.35	0.07
							(14.34)		
		yes	37.63			yes	38.64 (9.77)		
			(11.66)						
	CPT1	no	38.85	8.54	0.00	no	37.03	1.08	0.30
			(14.74)				(15.07)		
		yes	35.25			yes	38.42		
			(13.46)				(13.98)		
	CPT2	no	39.62	1.04	0.31	no	38.25	1.43	0.23
			(14.39)				(14.63)		

	CPT3	yes	38.32 (12.43)	0.19	0.66	yes	40.01 (13.21)	2.44	0.12
		no	39.49 (12.98)			no	38.5 (13.30)		
		yes	39.22 (10.54)			yes	40.11 (11.49)		
		no	40.2 (12.22)			no	38.88 (13.10)		
		yes	35.85 (11.82)			yes	39.00 (11.60)		
SF-12	PHT	no	47.93 (7.16)	24.28	< .0001	no	47.28 (7.55)	0.01	0.91
		yes	45.12 (6.56)			yes	46.94 (6.78)		
	MHT	no	45.05 (9.19)	19.64	< .0001	no	44.23 (8.64)	0.08	0.78
		yes	41.65 (8.67)			yes	43.86 (9.50)		

NOTES: **HT:** Hypertension; **OB:** Obesity; **ICD-11:** International Classification of Diseases 11th Revision; **C-BCT:** Chinese Brief Cognitive Test; **SF-12:** Short-Form Health Survey 12; **P:** Positive symptoms; **N:** Negative symptoms; **D:** Depressive symptoms; **M:** Manic symptoms; **PS:** Psychomotor symptoms; **C:** Cognitive symptoms; **TMT:** Trail-making tests; **SC:** Symbol coding; **CPT1:** Continuous Performance Test 1; **CPT2:** Continuous Performance Test 2; **CPT3:** Continuous Performance Test 3; **DST:** Digit span test; **PHT:** Physical health test; **MHT:** Mental health test.

Table 4. MLP Model vs. Transformer Model Test Results.

	MLP Model	Transformer Model
MAE	0.00798	0.007237
RMSE	0.00959	0.00871
TIC	0.6706	0.6246

Number of model parameters	2141188	25507332
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