
Exploring the intricate interplay between metabolic abnormalities and multidimensional cognitive impairment in stable schizophrenia patients

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>

Xiao Wang, Jing Dang, Xin Yu, De Cao, Yanfang Wang, Qingwei Ji, Yu Wang, Xiaohu Zheng, Miao Chen, Jianping Feng, Song Song, Binhong Wang, Chuan Shi & Sha Liu

We are providing an unedited version of this manuscript to give early access to its findings. Before final publication, the manuscript will undergo further editing. Please note there may be errors present which affect the content, and all legal disclaimers apply.

If this paper is publishing under a Transparent Peer Review model then Peer Review reports will publish with the final article.

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

Xiao Wang^{1, 2#}, Jing Dang^{1, 2, 3#}, Xin Yu⁴, De Cao⁵, Yanfang Wang⁶, Qingwei Ji⁷, Yu Wang⁸, Xiaohu Zheng⁹, Miao Chen^{1, 2}, Jianping Feng^{1, 2, 10}, Song Song^{1, 2}, Binhong Wang^{10*}, Chuan Shi^{4*}, Sha Liu^{1, 2*}

1 Shanxi Key Laboratory of Artificial Intelligence Assisted Diagnosis and Treatment for Mental Disorder, First Hospital of Shanxi Medical University, Taiyuan, Shanxi 030001, China

2 Department of Psychiatry, First Hospital/First Clinical Medical College of Shanxi Medical University, Taiyuan, Shanxi 030001, China

3 Shanxi Medical University Academy of Medical Sciences, Jinzhong, Shanxi 030600, China

4 Peking University Institute of Mental Health (Sixth Hospital), Beijing 100191, China

5 The Sixth People's Hospital of Datong City, Datong, Shanxi 037008, China

6 Fifth People's Hospital of Linfen, Linfen, Shanxi 041000, China

7 Jincheng Psychiatric Hospital, Jincheng, Shanxi 048000, China

8 Changzhi Mental Health Center, Changzhi, Shanxi 046000, China

9 Yangquan Spiritual Kangning Hospital, Yangquan, Shanxi 045000, China

10 Taiyuan Psychiatric Hospital, Taiyuan, Shanxi 030045, China

Xiao Wang and Jing Dang are the co-first authors of the article.

* Correspondence:

Pro. Sha Liu; liusha1984114@163.com

Pro. Chuan Shi; shichuan@bjmu.edu.cn

Pro. Binhong Wang; wangbinhong2@126.com

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.

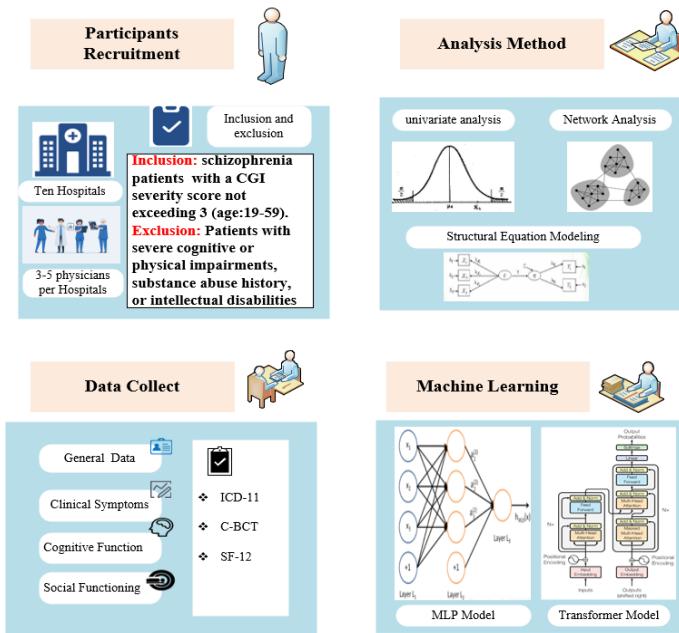


Fig. 1 Flow chart⁴⁴

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.

		DL	M (SD)	F	P	HG	M (SD)	F	P
ICD-11	P	no	1.19 (0.72)			no	1.16 (0.73)		
		yes	1.07 (0.81)	2.52	0.11	yes	1.26 (0.79)	0.94	0.33
	N	no	0.92 (0.68)			no	0.93 (0.70)		
		yes	0.99 (0.73)	0.98	0.32	yes	1.04 (0.55)	0.56	0.45
	D	no	0.54 (0.65)			no	0.51 (0.64)		
		yes	0.30 (0.50)	14.52	0.0002	yes	0.4 (0.57)	1.38	0.24
	M	no	0.45 (0.60)			no	0.42 (0.60)		
		yes	0.17 (0.42)	22.53	< .0001	yes	0.17 (0.38)	8.95	0.0029
	PS	no	0.54 (1.02)			no	0.54 (1.04)		
		yes	0.48 (1.24)	0.18	0.67	yes	0.42 (1.28)	1.69	0.19
	C	no	0.99 (0.83)			no	0.98 (0.82)		
		yes	1.10 (0.85)	2.44	0.12	yes	1.34 (0.83)	5.17	0.023
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)		
SC		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)		
		no	37.14 (14.44)			no	37.84 (14.66)		
CPT1		yes	41.25 (14.17)	7.00	0.01	yes	37.58 (11.89)	0	0.99
		no	38.62 (13.87)			no	39.20 (13.9)		
CPT2		yes	42.42 (13.43)	6.35	0.01	yes	39.79 (13.4)	0.03	0.86
		no	38.85 (12.23)			no	39.41 (12.47)		
CPT3		yes	42.26 (12.44)	7.13	0.01	yes	39.43 (10.46)	0.02	0.89
		no	38.10 (11.78)			no	38.93 (12.34)		
DST		yes	43.29 (13.71)	18.65	<.0001	yes	39.25 (11.32)	0.34	0.56
		no	46.80 (7.16)			no	47.15 (6.88)		
SF-12	PHT	yes	48.32 (6.63)	4.77	0.03	yes	46.16 (9.22)	0.08	0.78
		no	43.33 (9.22)			no	43.96 (9.12)		
MHT		yes	47.14 (8.24)	17.38	<.0001	yes	44.63 (9.68)	1.2	0.27
		no				no			

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 (13.65)	16.11	< .0001	no	38.79 (16.09)	0.32	0.57
		yes	34.88 (18.27)			yes	39.15 (14.74)		

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

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.

ARTICLE IN PRESS

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).

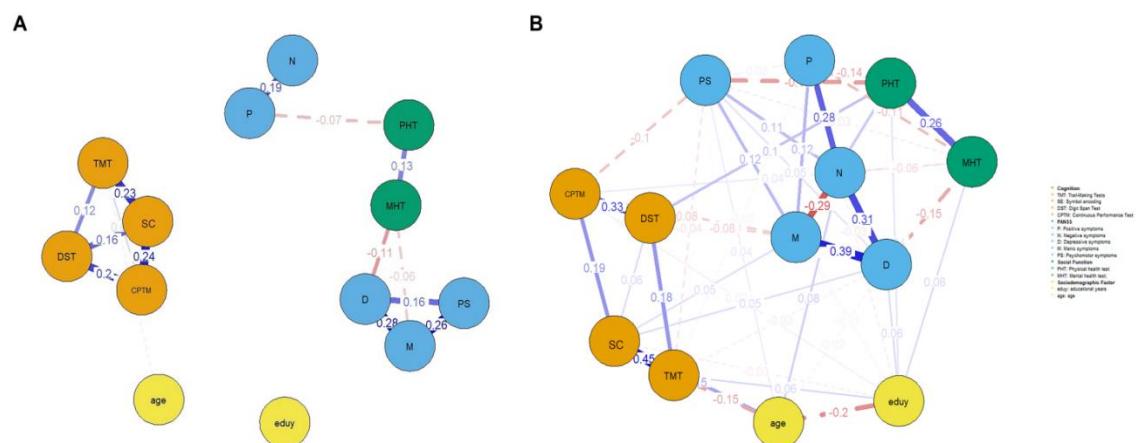


Fig. 2 Network analysis of groups with or without Mets-2+. A Group without Mets-2+. B Group with Mets-2+.

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 → HT → 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 ($\beta = 0.27, P < 0.05$).

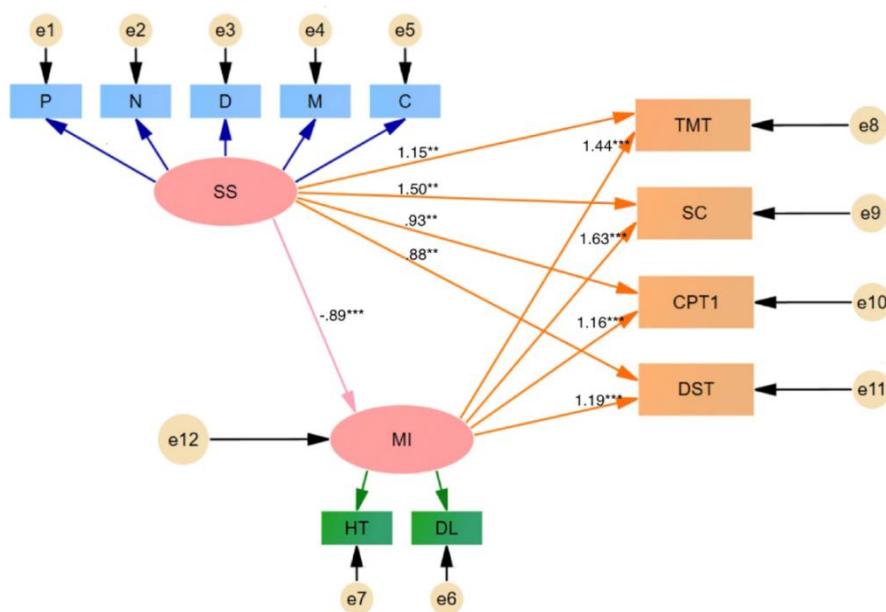


Fig. 3 The mediational effect model tested with SEM. NOTES: P: Positive symptoms; N: Negative symptoms; D: Depressive symptoms; M: Manic symptoms; C: Cognitive symptoms; TMT: Trail-making tests; SC: Symbol coding; CPT1: Continuous performance test 1; DST: Digit span test; HT: Hypertension; DL: Dyslipidemia;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

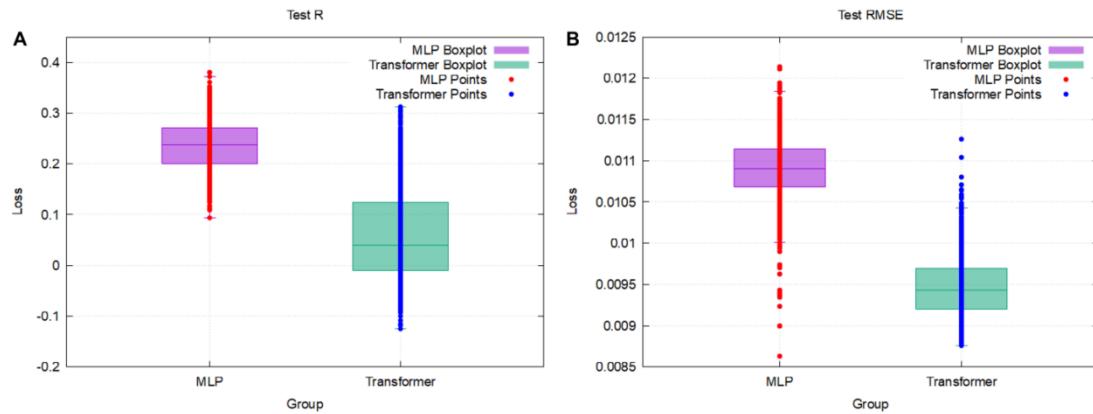


Fig. 4 Comparison of the test loss between the MLP and Transformer models. A the correlation coefficient (R). **B** the root mean square error (RMSE).

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.

References:

1. McCutcheon RA, Reis Marques T, Howes OD. Schizophrenia-An Overview. *JAMA Psychiatry*. 2020;77(2):201-10.
2. Green MF, Horan WP, Lee J. Nonsocial and social cognition in schizophrenia: current evidence and future directions. *World Psychiatry*. 2019;18(2):146-61.
3. Bleuler E. [Dementia praecox or the group of schizophrenias]. *Vertebral*. 2010;21(93):394-400.
4. Dickinson D, Goldberg TE, Gold JM, Elvevåg B, Weinberger DR. Cognitive factor structure and invariance in people with schizophrenia, their unaffected siblings, and controls. *Schizophr Bull*. 2011;37(6):1157-67.
5. Nuechterlein KH, Green MF, Kern RS, Baade LE, Barch DM, Cohen JD, et al. The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. *Am J Psychiatry*. 2008;165(2):203-13.
6. Nuechterlein KH, Barch DM, Gold JM, Goldberg TE, Green MF, Heaton RK. Identification of separable cognitive factors in schizophrenia. *Schizophr Res*. 2004;72(1):29-39.
7. Green MF, Lee J, Wynn JK. Experimental approaches to social disconnection in the general community: can we learn from schizophrenia research? *World Psychiatry*. 2020;19(2):177-78.
8. Pinkham AE, Penn DL, Green MF, Harvey PD. Social Cognition Psychometric Evaluation: Results of the Initial Psychometric Study. *Schizophr Bull*. 2016;42(2):494-504.

9. Pinkham AE, Harvey PD, Penn DL. Social Cognition Psychometric Evaluation: Results of the Final Validation Study. *Schizophr Bull.* 2018;44(4):737-48.
10. Fett AK, Viechtbauer W, Dominguez MD, Penn DL, van Os J, Krabbendam L. The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: a meta-analysis. *Neurosci Biobehav Rev.* 2011;35(3):573-88.
11. Galderisi S, Rossi A, Rocca P, Bertolino A, Mucci A, Bucci P, et al. The influence of illness-related variables, personal resources and context-related factors on real-life functioning of people with schizophrenia. *World Psychiatry.* 2014;13(3):275-87.
12. Galderisi S, Rucci P, Mucci A, Rossi A, Rocca P, Bertolino A, et al. The interplay among psychopathology, personal resources, context-related factors and real-life functioning in schizophrenia: stability in relationships after 4 years and differences in network structure between recovered and non-recovered patients. *World Psychiatry.* 2020;19(1):81-91.
13. Galderisi S, Rucci P, Kirkpatrick B, Mucci A, Gibertoni D, Rocca P, et al. Interplay Among Psychopathologic Variables, Personal Resources, Context-Related Factors, and Real-life Functioning in Individuals With Schizophrenia: A Network Analysis. *JAMA Psychiatry.* 2018;75(4):396-404.
14. Bora E, Akdere BB, Alptekin K. The relationship between cognitive impairment in schizophrenia and metabolic syndrome: a systematic review and meta-analysis. *Psychol Med.* 2017;47(6):1030-40.
15. Goughari AS, Mazhari S, Pourrahimi AM, Sadeghi MM, Nakhaee N. Associations between components of metabolic syndrome and cognition in patients with schizophrenia. *J Psychiatr Pract.* 2015;21(3):190-7.
16. Faden J, Citrome L. Schizophrenia: One Name, Many Different Manifestations. *Med Clin North Am.* 2023;107(1):61-72.
17. Mitchell AJ, Vancampfort D, Sweers K, van Winkel R, Yu W, De Hert M. Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders--a systematic review and meta-analysis. *Schizophr Bull.* 2013;39(2):306-18.
18. Vancampfort D, Stubbs B, Mitchell AJ, De Hert M, Wampers M, Ward PB, et al. Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. *World Psychiatry.* 2015;14(3):339-47.
19. Chen F, Bertelsen AB, Holm IE, Nyengaard JR, Rosenberg R, Dorph-Petersen KA. Hippocampal volume and cell number in depression, schizophrenia, and suicide subjects. *Brain Res.* 2020;1727:1-15.
20. Bovolini A, Garcia J, Andrade MA, Duarte JA. Metabolic Syndrome Pathophysiology and Predisposing Factors. *Int J Sports Med.* 2021;42(3):199-214.
21. Correll CU, Detraux J, De Lepeleire J, De Hert M. Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder. *World Psychiatry.* 2015;14(2):119-36.
22. Fang X, Wang Y, Chen Y, Ren J, Zhang C. Association between IL-6 and metabolic syndrome in schizophrenia patients treated with second-generation antipsychotics. *Neuropsychiatr Dis Treat.* 2019;15:2161-70.
23. Barati E, Ghazizadeh H, Sadabadi F, Kazemi E, Ferns GA, Avan A, et al. Association of

- the IL6 Gene Polymorphism with Component Features of Metabolic Syndrome in Obese Subjects. *Biochem Genet.* 2019;57(5):695-708.
24. Takayanagi Y, Cascella NG, Sawa A, Eaton WW. Diabetes is associated with lower global cognitive function in schizophrenia. *Schizophr Res.* 2012;142(1-3):183-7.
 25. Lindenmayer JP, Khan A, Kaushik S, Thanju A, Praveen R, Hoffman L, et al. Relationship between metabolic syndrome and cognition in patients with schizophrenia. *Schizophr Res.* 2012;142(1-3):171-6.
 26. Friedman JI, Wallenstein S, Moshier E, Parrella M, White L, Bowler S, et al. The effects of hypertension and body mass index on cognition in schizophrenia. *Am J Psychiatry.* 2010;167(10):1232-9.
 27. Hochberger WC, Thomas ML, Joshi YB, Swerdlow NR, Braff DL, Gur RE, et al. Deviation from expected cognitive ability is a core cognitive feature of schizophrenia related to neurophysiologic, clinical and psychosocial functioning. *Schizophr Res.* 2020;215:300-07.
 28. Tahmi M, Palta P, Luchsinger JA. Metabolic Syndrome and Cognitive Function. *Curr Cardiol Rep.* 2021;23(12):180.
 29. Lancon C, Dassa D, Fernandez J, Richieri R, Padovani R, Boyer L. Are cardiovascular risk factors associated with verbal learning and memory impairment in patients with schizophrenia? A cross-sectional study. *Cardiovasc Psychiatry Neurol.* 2012;1-8.
 30. Perry BI, Salimkumar D, Green D, Meakin A, Gibson A, Mahajan D, et al. Associated illness severity in schizophrenia and diabetes mellitus: A systematic review. *Psychiatry Res.* 2017;256:102-10.
 31. Nandeesha H, Keshri N, Rajappa M, Menon V. Association of hyperglycaemia and hyperlipidaemia with cognitive dysfunction in schizophrenia spectrum disorder. *Arch Physiol Biochem.* 2023;129(2):497-504.
 32. Lancon C, Dassa D, Fernandez J, Richieri R, Padovani R, Boyer L. Are cardiovascular risk factors associated with verbal learning and memory impairment in patients with schizophrenia? A cross-sectional study. *Cardiovasc Psychiatry Neurol.* 2012;2012:204043.
 33. Huang BJ, Pu CC, Miao Q, Ma K, Cheng Z, Shi C, et al. Neurocognitive trajectories and their clinical implications in first-episode schizophrenia after one year of antipsychotic treatment. *Schizophr Res.* 2022;241:292-97.
 34. Bischoff E, Jakobs KM, Assendelft WJJ. Cardiovascular risk management in patients using antipsychotics: it is time to take action. *BMC Med.* 2020;18(1):339.
 35. Krawczyk P, Świecicki Ł. ICD-11 vs. ICD-10 - a review of updates and novelties introduced in the latest version of the WHO International Classification of Diseases. *Psychiatr Pol.* 2020;54(1):7-20.
 36. Keeley JW, Gaebel W. Symptom rating scales for schizophrenia and other primary psychotic disorders in ICD-11. *Epidemiol Psychiatr Sci.* 2018;27(3):219-24.
 37. Ye S, Xie M, Yu X, Wu R, Liu D, Hu S, et al. The Chinese Brief Cognitive Test: Normative Data Stratified by Gender, Age and Education. *Front Psychiatry.* 2022;13:933642.
 38. Llinàs-Reglà J, Vilalta-Franch J, López-Pousa S, Calvó-Perxas L, Torrents Rodas D, Garre-Olmo J. The Trail Making Test. *Assessment.* 2017;24(2):183-96.
 39. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International

- Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;120(16):1640-5.
40. Martínez-Pérez JE, Abellán-Perpiñán JM, Sánchez-Martínez FI, Ruiz-López JJ. A Spanish value set for the SF-6D based on the SF-12 v1. *Eur J Health Econ*. 2024.
 41. Parsons S, Songco A, Booth C, Fox E. Emotional information-processing correlates of positive mental health in adolescence: a network analysis approach. *Cogn Emot*. 2021;35(5):956-69.
 42. Levin BE, Llabre MM, Dong C, Elkind MS, Stern Y, Rundek T, et al. Modeling metabolic syndrome and its association with cognition: the Northern Manhattan study. *J Int Neuropsychol Soc*. 2014;20(10):951-60.
 43. Mars M. From Word Embeddings to Pre-Trained Language Models: A State-of-the-Art Walkthrough. *Applied Sciences-Basel*. 2022;12(17):1-19.
 44. Wang W, Sun X, Wong AC, So SH. Selective processing in attention and memory in schizophrenia: A meta-analysis of the negative priming effect. *J Psychiatr Res*. 2023;161:112-22.
 45. Kelly ME, Duff H, Kelly S, McHugh Power JE, Brennan S, Lawlor BA, et al. The impact of social activities, social networks, social support and social relationships on the cognitive functioning of healthy older adults: a systematic review. *Syst Rev*. 2017;6(1):259.
 46. Gifford KA, Badaracco M, Liu D, Tripodis Y, Gentile A, Lu Z, et al. Blood pressure and cognition among older adults: a meta-analysis. *Arch Clin Neuropsychol*. 2013;28(7):649-64.
 47. Tsai CK, Kao TW, Lee JT, Wu CJ, Hueng DY, Liang CS, et al. Increased risk of cognitive impairment in patients with components of metabolic syndrome. *Medicine (Baltimore)*. 2016;95(36):e4791.
 48. Cansino S, Torres-Trejo F, Estrada-Manilla C, Mercado-Canales A, Medina-Velázquez D, Esquivel-García R, et al. Effects of hypotension and hypertension on source memory and working memory. *Aging Ment Health*. 2022;26(9):1738-46.
 49. Cuoco F, Agostoni G, Lesmo S, Sapienza J, Buonocore M, Bechi M, et al. Get up! Functional mobility and metabolic syndrome in chronic schizophrenia: Effects on cognition and quality of life. *Schizophr Res Cogn*. 2022;28:100245.
 50. Zhu S, Bo J, Xia T, Gu X. Temporal patterns of cognitive decline after hypertension onset among middle-aged and older adults in China. *Sci Rep*. 2025;15(1):16300.
 51. Sveikata L, Zotin MCZ, Schoemaker D, Ma Y, Perosa V, Chokesuwanwattanaskul A, et al. Association of Long-Term Blood Pressure Variability with Cerebral Amyloid Angiopathy-related Brain Injury and Cognitive Decline. *medRxiv*. 2024:1-5.
 52. Cherubini A, Lowenthal DT, Paran E, Mecocci P, Williams LS, Senin U. Hypertension and cognitive function in the elderly. *Dis Mon*. 2010;56(3):106-47.
 53. Nagai M, Dote K, Kato M, Oda N, Saleh Velez FG, Dasari T. Day-to-Day Blood Pressure Variability and Cognitive Function in the Elderly With Acute Heart Failure. *Am J Hypertens*. 2025;38(7):439-49.
 54. Babroudi S, Tighiouart H, Schrauben SJ, Cohen JB, Fischer MJ, Rahman M, et al. Blood

- Pressure, Incident Cognitive Impairment, and Severity of CKD: Findings From the Chronic Renal Insufficiency Cohort (CRIC) Study. *Am J Kidney Dis.* 2023;82(4):443-53.e1.
55. Agarwal M, Khan S. Plasma Lipids as Biomarkers for Alzheimer's Disease: A Systematic Review. *Cureus.* 2020;12(12):e12008.
56. Richardson TG, Sanderson E, Palmer TM, Ala-Korpela M, Ference BA, Davey Smith G, et al. Evaluating the relationship between circulating lipoprotein lipids and apolipoproteins with risk of coronary heart disease: a multivariable Mendelian randomisation analysis. *PLoS Med.* 2020;17(3):e1003062.
57. Rodriguez FS. Life-Course Pathways to Cognitive Aging: The Significance of Intellectual Stimulation in the Form of Education and Occupation for Public Policy and Prevention Plans. *Front Psychiatry.* 2021;12:719609.
58. Svensson T, Sawada N, Mimura M, Nozaki S, Shikimoto R, Tsugane S. The association between midlife serum high-density lipoprotein and mild cognitive impairment and dementia after 19 years of follow-up. *Transl Psychiatry.* 2019;9(1):26.
59. Goh VH, Hart WG. The association of metabolic syndrome and aging with cognition in Asian men. *Aging Male.* 2014;17(4):216-22.
60. Van den Kommer TN, Dik MG, Comijs HC, Jonker C, Deeg DJ. Role of lipoproteins and inflammation in cognitive decline: do they interact? *Neurobiol Aging.* 2012;33(1):196.e1-12.
61. Tournoy J, Lee DM, Pendleton N, O'Neill TW, O'Connor DB, Bartfai G, et al. Association of cognitive performance with the metabolic syndrome and with glycaemia in middle-aged and older European men: the European Male Ageing Study. *Diabetes Metab Res Rev.* 2010;26(8):668-76.
62. Nemoto T, Niimura H, Ryu Y, Sakuma K, Mizuno M. Long-term course of cognitive function in chronically hospitalized patients with schizophrenia transitioning to community-based living. *Schizophr Res.* 2014;155(1-3):90-5.

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. Socio-demographic characteristics of the normative sample.

Socio-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%)
Unemployed		470 (64.6%)
Employment	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)			no	1.16 (0.73)		
		yes	1.07 (0.81)	2.52	0.11	yes	1.26 (0.79)	0.94	0.33
	N	no	0.92 (0.68)			no	0.93 (0.70)		
		yes	0.99 (0.73)	0.98	0.32	yes	1.04 (0.55)	0.56	0.45
	D	no	0.54 (0.65)			no	0.51 (0.64)		
		yes	0.30 (0.50)	14.52	0.0002	yes	0.4 (0.57)	1.38	0.24
	M	no	0.45 (0.60)			no	0.42 (0.60)		
		yes	0.17 (0.42)	22.53	<.0001	yes	0.17 (0.38)	8.95	0.0029
	PS	no	0.54 (1.02)			no	0.54 (1.04)		
		yes	0.48 (1.24)	0.18	0.67	yes	0.42 (1.28)	1.69	0.19
C-BCT	C	no	0.99 (0.83)			no	0.98 (0.82)		
		yes	1.10 (0.85)	2.44	0.12	yes	1.34 (0.83)	5.17	0.023
	SC	no	38.55 (15.63)			no	39.07 (15.4)		
		yes	41.25 (13.53)	3.18	0.07			0.23	0.63
CPT1	TMT	no	39.34 (12.07)			no	39.64 (12.19)		
		yes	40.97 (11.67)	2.30	0.13	yes	39.25 (9.56)	0.16	0.69
	CPT1	no	37.14 (14.44)			no	37.84 (14.66)		
		yes	41.25 (14.17)	7.00	0.01	yes	37.58 (11.89)	0	0.99

		38.62					
	no	(13.87)			no	39.20 (13.9)	
CPT2		42.42	6.35	0.01			0.03 0.86
	yes	(13.43)			yes	39.79 (13.4)	
		38.85				39.41	
	no	(12.23)			no	(12.47)	
CPT3		42.26	7.13	0.01		39.43	0.02 0.89
	yes	(12.44)			yes	(10.46)	
		38.10				38.93	
	no	(11.78)			no	(12.34)	
DST		43.29	18.65	<.0001		39.25	0.34 0.56
	yes	(13.71)			yes	(11.32)	
		46.80				47.15 (6.88)	
	no	(7.16)					0.08 0.78
PHT		48.32	4.77	0.03			
	yes	(6.63)			yes	46.16 (9.22)	
SF-12		43.33				43.96 (9.12)	
	no	(9.22)					
MHT		47.14	17.38	<.0001			1.2 0.27
	yes	(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)			no	1.2 (0.74)		
		yes	1.29 (0.76)	6.44	0.01	yes	1.15 (0.73)	0.91	0.34
	N	no	0.92 (0.69)			no	0.93 (0.7)		
		yes	0.97 (0.69)	0.07	0.79	yes	0.94 (0.69)	0.03	0.87
	D	no	0.44 (0.60)			no	0.57 (0.63)		
		yes	0.65 (0.69)	16.86	< .0001	yes	0.46 (0.64)	4.03	0.045
	M	no	0.34 (0.54)			no	0.5 (0.61)		
		yes	0.54 (0.67)	14.88	0.00	yes	0.33 (0.56)	10.57	0.001
	PS	no	0.4 (0.89)			no	0.66 (1.31)		
		yes	0.83 (1.34)	30.01	< .0001	yes	0.44 (0.85)	5.9	0.02
C-BCT	C	no	0.94 (0.84)			no	0.91 (0.84)		
		yes	1.17 (0.77)	6.6	0.01	yes	1.07 (0.82)	7.4	0.007
	TMT	no	40.64 (13.65)			no	38.79 (16.09)		
		yes	34.88 (18.27)	16.11	< .0001	yes	39.15 (14.74)	0.32	0.57
		no	40.4 (12.06)			no	40.88 (14.34)		
		yes	37.63 (11.66)	11.46	0.00	yes	38.64 (9.77)	3.35	0.07
	CPT1	no	38.85 (14.74)			no	37.03 (15.07)		
		yes	35.25 (13.46)	8.54	0.00	yes	38.42 (13.98)	1.08	0.30
		no	39.62 (14.39)	1.04	0.31	no	38.25 (14.63)	1.43	0.23

		38.32		40.01		
	yes	(12.43)		yes	(13.21)	
	no	39.49 (12.98)	0.19	no	38.5 (13.30)	2.44
CPT3	yes	39.22 (10.54)	0.66	yes	(11.49)	0.12
	no	40.2 (12.22)		no	38.88 (13.10)	0.08
DST		35.85	16.88 < .0001		39.00	0.78
	yes	(11.82)		yes	(11.60)	
PHT	no	47.93 (7.16)	24.28 < .0001	no	47.28 (7.55)	0.01
SF-12	yes	45.12 (6.56)		yes	46.94 (6.78)	0.91
MHT	no	45.05 (9.19)	19.64 < .0001	no	44.23 (8.64)	0.08
	yes	41.65 (8.67)		yes	43.86 (9.50)	0.78

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

ARTICLE IN PRESS