Specific metabolic syndrome components predict cognition and social functioning in people with type 2 diabetes mellitus and severe mental disorders

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Abstract

Objective: Obesity and metabolic diseases such as metabolic syndrome (MetS) are more prevalent in people with type 2 diabetes mellitus (T2DM), major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia (SZ). MetS components might be associated with neurocognitive and functional impairments in these individuals. The predictive and discriminatory validity of MetS and its components regarding those outcomes were assessed from prospective and trans-diagnostic perspectives.

Methods: Metabolic syndrome components and neurocognitive and social functioning were assessed in 165 subjects, including 30 with SZ, 42 with BD, 35 with MDD, 30 with T2DM, and 28 healthy controls (HCs). A posteriori, individuals were classified into two groups. The MetS group consisted of those who met at least three of the following criteria: abdominal obesity (AO), elevated triglycerides...
Obesity and metabolic problems have reached pandemic proportions in recent decades, representing an increased socioeconomic burden that in turn is associated with increased morbimortality. For instance, people with type 2 diabetes mellitus (T2DM) and severe mental illness (SMI), such as major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia (SZ), have a higher prevalence of metabolic syndrome (MetS) than the general population. MetS is a cluster of certain medical conditions, such as abdominal obesity (AO), elevated triglycerides (TG), low- and high-density lipoprotein cholesterol (HDL), elevated fasting plasma glucose (FPG), and elevated blood pressure (BP). Unhealthy lifestyle behaviors, including smoking, poor eating habits and diet quality and reduced physical activity, are major drivers of the increase in MetS among individuals with SMI and T2DM. All these factors are strongly associated with poor quality of life, poor treatment adherence, and increased mortality in these populations. Moreover, treatment with psychopharmacological medications, especially certain mood stabilizers and antipsychotics, may cause weight gain and further increase the risk of metabolic disorders.

Results: Cognitive impairment was significantly greater in the MetS group (n = 82) than in the No-MetS group (n = 83), with small effect sizes (p < 0.05; η²p = 0.02 – 0.03). In both groups, the most robust associations between MetS components and neurocognitive and social functioning were observed with TG and FPG (p < 0.05). There was also evidence for a significant relationship between cognition and BP in the MetS group (p < 0.05). The combination of TG, FPG, elevated systolic BP and HDL best classified individuals with greater cognitive impairment (p < 0.001), and TG was the most accurate (p < 0.0001).

Conclusions: Specific MetS components are significantly associated with cognitive impairment across somatic and psychiatric disorders. Our findings provide further evidence on the summative effect of MetS components to predict cognition and social functioning and allow the identification of individuals with worse outcomes. Transdiagnostic, lifestyle-based therapeutic interventions targeted at that group hold the potential to improve health outcomes.

Keywords

cognition, metabolic syndrome, severe mental disorder, social functioning, type 2 diabetes mellitus

In recent years, the importance of a multimorbidity view that brings together the effects of mental and physical health has been increasingly recognized. Indeed, recent reviews highlight that abnormal metabolic pathways promote the onset of several SMI, such as SZ, and it is related to increased early morbimortality.
diagnosis allows the identification of individuals at a higher risk of developing chronic conditions. MetS components, such as FPG levels and especially the combination of elevated TG and reduced HDL, predict the risk of developing T2DM. Likewise, a recent study found that individuals with SMI who meet the criteria for MetS suffer from multiple comorbidities in comparison with healthy controls (HCs). Moreover, individuals with SMI and MetS have a more severe condition, a worse response to pharmacological treatments and a worse prognosis than individuals without MetS. On the other hand, recent studies have reported that MetS is significantly associated with cognitive impairment in individuals with SMI, which could in turn contribute to a decline in social functioning. Other studies have suggested that BP, HDL, and TG are important predictors of cognition in individuals with SMI, whereas AO is one of the predictors of cognitive impairment and quality of life. These relationships also apply to several nonpsychiatric conditions, including cardiometabolic illnesses. Indeed, individuals with T2DM who meet the criteria for MetS have worse cognitive performance and poorer quality of life than individuals without MetS. Likewise, metformin treatment has been associated with decreased cardiovascular risk and improved neurocognitive outcomes in patients with T2DM. In summary, increasing evidence supports the notion that MetS and its components are relevant risk factors or predictors of neurocognitive and social dysfunction across common noncommunicable diseases. Therefore, it is likely that the former represents a transdiagnostic component with implications for relevant outcomes.

To our knowledge, no study has evaluated the contribution of MetS and its components to both neurocognitive and social functioning in people with SMI and T2DM. Moreover, the great heterogeneity of possible combinations of MetS components makes it difficult to estimate the risk of developing impaired cognitive or social functioning. No previous studies have been conducted to determine whether some combinations of MetS components predict cognitive performance and social functioning better than others in individuals with or without MetS diagnosis across T2DM and SMI. While MetS components might aid in the early detection of neurocognitive and functional impairment in at-risk populations, evidence supporting their potential application in clinical practice is scarce. To our knowledge, the discriminatory ability of MetS components for classifying individuals with greater cognitive impairment has not been tested. Therefore, research using samples of individuals with T2DM, MDD, BD, and SZ may help to determine the risk of neurocognitive and social dysfunction associated with MetS more effectively in these populations.

1.1 | Aims of the study

The aims of this study were threefold: (a) to explore whether baseline MetS components are significant predictors of cognitive performance and social functioning at the one-year follow-up, (b) to examine the discriminatory ability of specific MetS components for classifying individuals with greater cognitive impairment, and (c) to analyze the differences between specific MetS components, cognitive performance, and social functioning in people with or without MetS diagnosis across T2DM and SMI.

2 | MATERIALS AND METHODS

2.1 | Study design and ethical considerations

This article is part of a project aimed at identifying and validating peripheral biomarkers for neurocognitive deficits in MDD, BD, SZ, and T2DM. This prospective and comparative cohort project was conducted between April 2015 and January 2018, and it investigated the association and evolution of certain peripheral blood biomarkers and neurocognitive impairments in a unique longitudinal cohort of individuals with somatic and psychiatric disorders. Demographic and clinical data, neurocognitive and social functioning data, and biomarkers of peripheral blood were collected at baseline (T1) and after one year (T2). Individuals with SMI were recruited from mental health units (MHUs) in several towns in the province of Valencia, Spain (Foios, Catarroja, Paterna, and Sagunto); the psychiatry outpatient clinic and endocrinology department of the University Hospital Dr. Peset; and the Miguel Servet MHU in Valencia City. HCs were residents of the same areas as the individuals with SMI. Participants were demographically matched. All participants provided informed consent after the study procedures were explained. The ethical committees or an institutional review board at each participating center approved the study protocol, and the study was conducted in accordance with the ethical principles of the Declaration of Helsinki. For this article, only those variables related to this study aims were included in the analyses.

2.2 | Participants

SZ, BD, and MDD were diagnosed based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM 5). T2DM was diagnosed based on the Standards of Care criteria of the American Diabetes Association. Participants with MDD and BD had to meet
the remission criteria28 of an acute affective episode, and
individuals with SZ had to be clinically stable.29 Individuals
with T2DM had to be free of severe diabetic neuropathy
and kidney disease (serum creatinine <1.5 mg/dl) and, at
baseline and at 1-year follow-up, FPG levels were previ-
ously checked in this group to reduce possible biases due
to overlapping of the glycemic pathway between HC and
those with T2DM. For HC recruitment, the absence of
physical illness, pharmacological treatments, and family
history of SMI in first-degree relatives was required. An
ability to understand study procedures and willingness
to give written consent were required for participation.
General exclusion criteria for all groups included cur-
rent hospitalization, documented cognitive impairment
not secondary to psychiatric disorder (intellectual dis-
ability or major neurocognitive disorder, i.e., dementia),
disability or inability that prevented understanding of the
protocol, current substance abuse disorder (except for nic-
totine), pregnancy, intake of steroids, corticosteroids, an-
tioxidants, antibiotics, and immunologic therapies, fever
over 38°C, and history of vaccination within 4 weeks of
the evaluation. The same inclusion and exclusion criteria
were used at T1 and T2.

MetS diagnosis was assessed at both times following
the revised criteria of the National Cholesterol Educa-
tion Program (NCEP) Adult Treatment Panel III (ATP
III).4.30 This diagnosis requires the presence of at least
three of the following five criteria: AO, elevated TG, re-
duced HDL, elevated BP, and elevated FPG. NCEP ATP III
cut-off values to define these alterations are as follows: (i)
waist circumference (WC) >102 cm for men and >88 cm
for women will hereafter be used as a measure of AO, (ii)
TG ≥150 mg/dl or specific treatment for this lipid abnor-
mality, (iii) HDL levels <40 mg/dl for men and <50 mg/dl
for women or specific treatment for this lipid abnormality,
(iv) systolic BP (SBP) ≥130 mmHg and diastolic BP (DBP)
≥85 mmHg or treatment of previously diagnosed hyper-
tension, and (v) fasting FPG levels ≥100 mg/dl or previ-
ously diagnosed T2DM. Following this definition, the
participants with alterations in at least three criteria were
defined as having MetS, and the remaining participants
were classified as not having MetS.

The following MetS components were collected as fol-
lows: weight (kg), height (m), WC (cm), TG, HDL, SBP/
DBP (mmHg), and FPG. Body weight, height, and WC
were measured by calibrated scales. WC was measured in
the standing position at the end of normal expiration and
at the midway between the inferior costal margin and the
superior border of the iliac crest. BP was measured on the
right arm using an automatic sphygmomanometer with
participants in the sitting position after resting for 5 min-
utes. Average SBP and DBP values of at least two repeated
measurements were calculated. Under aseptic conditions,
fasting venous blood samples were collected between 8
and 9 am to measure TG, HDL and FPG levels. Individuals
with diseases followed the prescribed pharmacological
treatment throughout the study.

2.3  Assessments

The assessments were conducted by the same experi-
cenced psychologists and psychiatrists of the research group.
Sociodemographic data, including sex, age, years of edu-
cation, occupational status and laterality (defined as man-
ual, ocular and crural dominance), were collected.

Clinical evaluations were conducted using the follow-
ing scales: (i) Kaplan–Feinstein Scale (KFS),31 (ii) Charlson
Comorbidity Index (CCI),32 (iii) 17-item Hamilton Rating
Scale for Depression (HRSD),33 (iv) Young Mania Rating
Scale (YMRS),34 (v) Positive and Negative Syndrome Scale
(PANSS),35 and (vi) Clinical Global Impression (CGI)
scale.36 For smokers, current tobacco consumption, ex-
pressed as the number of cigarettes per day (CPD), and
breath carboxyhemoglobin (COHb) level, a validated mea-
sure of smoke exposure, were collected.37 The total num-
ber of prescribed psychopharmacological medications
and other medications were also registered.

Cognitive performance was evaluated using a com-
prehensive battery of neuropsychological tests and sub-
tests previously used by our group.36–41 Seven cognitive
domains were assessed: (i) verbal learning and memory: Com-
plutense Verbal Learning Test (TAVEC) total imme-
diate recall, short-term free recall and long-term free re-
call variables42; (ii) cognitive flexibility: Stroop Color and
Word test (SCWT) color/word subtest43 and Wisconsin
Card Sorting Test (WCST) categories completed and per-
severative errors44; (iii) verbal fluency: FAS and animal
naming test for phonemic and semantic fluency, respec-
tively45; (iv) working memory: Trail Making Test (TMT)
Part B45 and Wechsler Adult Intelligence Scale III edition
(WAIS-III) digit span backwards46; (v) short-term memory:
TAVEC immediate recall of the first learning trial and
immediate recall of the interference list42 and WAIS-III
digit span forward46; (vi) visual memory: Rey-Osterrieth
Complex Figure Test (ROCFT) figure two minutes after
the copy (fRey2) and 20 minutes after the copy (fRey20),47
and (vii) processing speed: finger tapping test (FTT) left uni-
manual, right unimanual, left bimanual, right bimanual
and average four scores,45,48 WAIS-III digit symbol coding
subtest,46 SCWT color and word subtests45 and TMT Part
A.48 A global cognitive score (GCS) was calculated by av-
eraging the seven cognitive domain scores.

Social functioning was evaluated using (i) the
Functional Assessment Short Test (FAST),49 (ii) the Short
Form-36 Health Survey questionnaire (SF-36),50 and (iii)
the World Health Organization Quality of Life brief scale (WHO-QoL-Bref)\(^5\) \(^1\). A global social functioning score (GSFS) was calculated by averaging the total scores on the three scales.

### 2.4 Statistical analyses

Data were analyzed using Statistical Package for Social Sciences (SPSS) version 26.0 for Windows.\(^5\) Descriptive analyses were conducted using Student’s t-tests for independent samples for continuous variables and chi-square tests for categorical variables. Normality was assumed for all continuous variables because the sample was sufficiently representative of the target population, which was statistically verified. This fact guarantees that the variables are distributed in a normalized way. The differences between groups for MetS components, cognitive performance, and social functioning at T1 and T2 and their evolution overtime were assessed using a mixed one-way analysis of covariance (ANCOVA), with diagnosis (SMI and T2DM) and sex as covariables. It was adjusted for diagnosis and sex because these factors were differentially distributed between the two groups and were a confounding variable. The direct scores obtained for GCS and GSFS were transformed into Z-scores. For the calculation of the Z-scores, the mean and standard deviation of the individuals without MetS (No-MetS) at T1 were taken as reference values. Thus, a valid measure was obtained to contrast the objective condition of the study (exposure or not to MetS). To test the predictive capacity of MetS components at baseline to explain the variance in cognitive performance and social functioning at T2, a linear regression analysis was performed using a predictive model that included only MetS components that were significant for each MetS group. Other variables relevant to cognitive performance and social functioning were not included because the MetS components were optimal predictors per se. Likewise, to test the ability to discriminate individuals with greater cognitive impairment at T2 from MetS components at T1, a binary logistic regression was performed using a predictive model that included only MetS components that were significant for each group. Greater cognitive impairment was defined by scores greater than one standard deviation below the mean on the GCS. Subsequently, a receiver operating characteristic (ROC) curve was generated for the variables identified in the binary logistic regression as explanatory factors of cognitive performance. From this curve, optimal performance levels were delimited based on sensitivity and specificity values for each of the selected variables. For all analyses, \(p < 0.05\) was considered statistically significant. The procedure to create the predictive models was as follows: first, a predictive analysis was performed with MetS components one by one, then predictive models were generated that included and combined the statistically more powerful variables; finally, the optimal predictive combination was obtained. No more than five variables were included in each model, thus guaranteeing the correct performance of the analysis.

### 3 RESULTS

#### 3.1 Sample description

At T1, the sample consisted of 165 persons, including 30 with SZ, 42 with BD, 35 with MDD, 30 with T2DM, and 28 HCs. The total sample was classified into two groups: 83 in the No-MetS group (T2DM = 4, MDD = 27, BD = 22, SZ = 8 and HC = 22) and 82 in the MetS group (T2DM = 26, MDD = 8, BD = 20, SZ = 22 and HC = 6).

Forty participants were lost to follow-up at T2 (retention rate: 75.7\%). The sample consisted of 70 individuals in the No-MetS group (T2DM = 3, MDD = 18, BD = 18, SZ = 12 and HC = 19) and 55 individuals in the MetS group (T2DM = 22, MDD = 7, BD = 11, SZ = 15 and HC = 0).

A summary of the sociodemographic and clinical characteristics of the participants is presented in Table 1. Women represented half of the total sample (48%). The mean age of the whole sample was 49.9 (SD: 10.2) years. The MetS group was characterized by a significantly lower percentage of women than the No-MetS group. Age, mean number of years of education and laterality were similar in both groups. Moreover, the MetS group had significantly higher levels of multimorbidity and use of medications other than psychopharmacological agents.

#### 3.2 Between-group comparisons of MetS components, cognitive performance and social functioning at T1 and T2

MetS components at T1 and T2 for both groups are shown in Table 2. Overall, at T1, MetS components were significantly higher in the MetS group \((p < 0.01; \eta^2p = 0.03\) to 0.26). Similar findings were observed at T2 \((p < 0.0001; \eta^2p = 0.11\) to 0.32). At both assessments, moderate effect sizes were observed for all MetS components when compared between groups. As expected, individuals with MetS had significantly higher WC than those without MetS \((p < 0.0001; \eta^2p = 0.12)\). Furthermore, HDL was significantly lower in the MetS group \((p < 0.0001; \eta^2p = 0.15)\). The within-group presence of MetS components did not significantly differ over time.
TABLE 1 Sociodemographic and clinical characteristics of the sample at T1

| Variablesa | No-MetS (n = 83) | MetS (n = 82) | Statistical analyses t or χ² (p) |
|------------|-----------------|-------------|--------------------------------|
| Sociodemographic | | | |
| Sexb | 53 (64%) | 26 (32%) | 17.0*** |
| Age | 48.8 (9.2) | 51.1 (11.2) | NS |
| Years of education | 12.4 (4.8) | 12.5 (4.6) | NS |
| Dependent statusc | 18 (22%) | 23 (28%) | NS |
| Occupation statusd | 50 (60%) | 54 (66%) | NS |
| Lateralitye | 80 (96%) | 77 (94%) | NS |
| Clinical | | | |
| Tobaccof | 37 (44%) | 32 (39%) | NS |
| COHb | 0.9 (1.0) | 1.1 (1.3) | NS |
| KFS | 0.9 (1.5) | 1.6 (1.9) | 2.5** |
| CCI | 0.7 (1.2) | 1.3 (1.6) | 2.9** |
| HRSD | 6.5 (6.5) | 6.3 (5.9) | NS |
| YMRSg | 1.8 (2.7) | 2.8 (4.4) | NS |
| PANSS-P | 7.3 (1.4) | 8.7 (3.9) | 2.9** |
| PANSS-N | 8.7 (5.0) | 11.7 (8.4) | 2.7** |
| PANSS-G | 19.7 (8.0) | 23.4 (11.2) | 2.4** |
| CGI | 2.8 (1.4) | 3.0 (1.5) | NS |
| Psychiatric medicationsh | 2.0 (2.1) | 2.2 (2.1) | NS |
| General medicationsi | 3.0 (3.1) | 4.3 (2.7) | 2.6** |

Abbreviations: CCI, Charlson Comorbidity Index; CGI, Clinical Global Impression; COHb, carboxyhemoglobin; G, general; HRSD, Hamilton Rating Scale for Depression; KFS, Kaplan-Feinstein Scale; MetS, metabolic syndrome; N, negative; NS, not significant; P, positive; PANSS, Positive and Negative Syndrome Scale; T1, time 1; YMRS, Young Mania Rating Scale. NS = p > 0.05; *p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001; ****p ≤ 0.0001.

*Expressed as the mean (standard deviation) except when indicated.

bFemale n (%).

cDependent n (%).

dNot active n (%).

eRight-handers n (%).

fYes n (%).

gLower scores represent a better outcome.

hNumber

iChi-square test.

3.3 Predictive capacity of MetS components at T1 of neurocognitive performance and social functioning at T2

The results of the relative contributions of MetS components at T1 to explain the variation in GCS and GSFS scores at T2 are shown in Table 4. For individuals with MetS, TG alone was the most powerful predictor of GCS at T2 (12.6%), followed by the combination of SBP and DBP, which were the MetS components that explained 10.8% of GCS variance at T2. Moreover, the combination of TG and FPG significantly predicted GSFS at T2 and explained 19.1% of the variance.

For the No-MetS group, 12.5% of GCS variance at T2 could be explained by the combination of TG and FPG. Moreover, WC alone significantly predicted 14.3% of the variance in GSFS at T2, while the combination of TG, HDL, and FPG explained the largest percentage of variance (18.8%) of GSFS at T2.

3.4 Discriminatory ability of MetS components at T1 to classify individuals with greater cognitive impairment at T2

The results regarding the ability of MetS components at T1 to discriminate individuals with greater cognitive impairment at T2 are shown in Table 5. The combination of four components (TG, FPG, SBP, and HDL) was the model that best classified these individuals, with a correct classification rate of 87.1%. Next, the combination of TG, SBP, and FPG (86.3%), the combination of TG and SBP (81.5%), and TG alone (75%) were successively the best classifiers. ROC curve analysis was performed to assess the diagnostic usefulness of TG, which, as seen in the binary logistic regression, proved to be the most useful component in the classification of individuals with greater cognitive impairment (Figure 1). The analysis showed that the area under the ROC curve for the identification of individuals with greater cognitive impairment was 83.9% with TG (95% CI = 0.77–0.91). As seen in the figure, the TG level that best discriminates individuals with greater cognitive impairment will likely be between those points of the curve, with sensitivity between the 0.75 and 0.80 values.
### TABLE 2 Components related to metabolic syndrome at T1 and T2

| Variables   | No-MetS         | MetS             | Statistical analyses |
|-------------|-----------------|------------------|----------------------|
|             | T1 (n = 83)     | T2 (n = 70)      | T1 (n = 82)          | T2 (n = 55) |
|             |                 |                  | T1 F (p)             | T2 F (p)   | T1-T2 F (p) |
| WC          | 92.9 (18.3)     | 94.9 (16.1)      | 107.3 (11.1)         | 110.0 (12.5) | 23.4**** .12 | 15.1**** .11 |
| TG          | 94.5 (39.6)     | 100.9 (47.6)     | 160.0 (60.4)         | 191.7 (88.1) | 58.2**** .26 | 57.7**** .32 |
| HDL         | 55.4 (12.2)     | 54.9 (12.8)      | 43.0 (9.9)           | 42.4 (10.3)  | 30.0**** .15 | 16.6**** .12 |
| SBP         | 119.3 (12.7)    | 118.4 (13.4)     | 135.3 (17.2)         | 136.4 (17.9) | 25.5**** .13 | 24.4**** .16 |
| DBP         | 73.9 (10.3)     | 73.0 (9.5)       | 79.2 (9.9)           | 81.8 (10.0)  | 5.0** .03    | 20.4**** .14 |
| FPG         | 94.5 (20.5)     | 96.2 (18.4)      | 121.7 (46.9)         | 128.9 (41.4) | 24.7**** .13 | 33.6**** .21 |

Abbreviations: ANCOVA, analysis of variance; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL, high-density lipoprotein; MetS, metabolic syndrome; NS, not significant; SBP, systolic blood pressure; T1, time 1; T2, time 2; TG, triglycerides; WC, waist circumference.

NS = p > 0.05; *p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001; ****p ≤ 0.0001. Effect size: $\eta^2_p$: small ≈ 0.02; moderate ≈ 0.15; large ≈ 0.35.

*Expressed as the mean (standard deviation).

### TABLE 3 Cognitive performance and social functioning at T1 and T2

| Variables   | No-MetS          | MetS             | Statistical analyses |
|-------------|------------------|------------------|----------------------|
|             | T1 (n = 83)      | T2 (n = 70)      | T1 (n = 82)          | T2 (n = 55) |
|             |                  |                  | T1 F (p)             | T2 F (p)   | T1-T2 F (p) |
| GCS         | 0.0 (1.0)        | 0.0 (0.9)        | −0.3 (0.9)           | −0.3 (0.9) | 3.9* .02    | 4.3* .03    | NS          |
| GSFS        | 0.0 (1.0)        | 0.0 (1.0)        | 0.1 (0.9)            | 0.0 (1.0)  | NS          | NS          | NS          |

Abbreviations: ANCOVA, analysis of covariance; GCS, global cognitive score; GSFS, global social functioning score; MetS, metabolic syndrome; NS, not significant; T1, time 1; T2, time 2.

NS = p > 0.05; *p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001; ****p ≤ 0.0001. Effect size: $\eta^2_p$: small ≈ 0.02; moderate ≈ 0.15; large ≈ 0.35.

*Z-scores expressed as the mean (standard deviation).

### TABLE 4 Predictive MetS components at T1 of cognitive performance and social functioning at T2.

| Dependent variables at T2 | Predictors at T1 | $\beta$ | 95% CI          | t       | Percent of variance explained (adjusted $R^2$) |
|---------------------------|------------------|---------|-----------------|---------|-----------------------------------------------|
| Group: No-MetS            |                  |         |                 |         |                                               |
| GCS                       | TG               | −0.29   | −0.01 to 0.00   | 2.39*   | 12.5                                          |
|                           | FPG              | −0.19   | −0.02 to 0.00   | 1.65*   |                                               |
| GSFS                      | WC               | −0.37   | −0.04 to 0.00   | 3.11*** | 14.3                                          |
|                           | TG               | −0.21   | −0.01 to 0.00   | 1.77*   | 18.8                                          |
|                           | HDL              | 0.28    | 0.00 to 0.04    | 2.33*   |                                               |
|                           | FPG              | −0.23   | −0.02 to 0.00   | 1.96*   |                                               |
| Group: MetS               |                  |         |                 |         |                                               |
| GCS                       | SBP              | 0.35    | 0.00 to 0.03    | 2.48**  | 10.8                                          |
|                           | DBP              | −0.32   | −0.05 to 0.00   | 2.28*   |                                               |
|                           | TG               | −0.35   | −0.009 to −0.002| 2.98**  | 12.6                                          |
| GSFS                      | TG               | −0.44   | −0.01 to 0.00   | 3.71*** | 19.1                                          |
|                           | FPG              | −0.19   | −0.008 to 0.001 | 1.60*   |                                               |

Abbreviations: DBP, diastolic blood pressure; FPG, fasting plasma glucose; GCS, global cognitive score; GSFS, global social functioning score; HDL, high-density lipoprotein; MetS, metabolic syndrome; NS, not significant; SBP, systolic blood pressure; T1, time 1; T2, time 2; TG, triglycerides; WC, waist circumference.

NS = p > 0.05; *p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001; ****p ≤ 0.0001.
The growing and dramatic impact of overweight/obesity and metabolic illnesses on physical and mental health is becoming increasingly well known. It is therefore crucial to determine the MetS components that play a key role in this relationship. To our knowledge, this is the first study to evaluate the predictive and discriminatory validity of MetS and its components regarding cognitive and social functioning across people with T2DM and SMI using a longitudinal design and a transdiagnostic perspective.

The results indicated that cognitive performance was significantly worse in individuals with MetS than in those without MetS, while social functioning was similar in both groups. In addition, TG and FPG were found to be key MetS components for predicting cognitive performance and social functioning across SMI and T2DM, regardless of MetS status. Moreover, BP was a significant predictor of cognitive function in individuals with MetS. Regarding discriminatory ability, TG seemed to be the most accurate MetS component for identifying individuals with greater cognitive impairment.15,16,19,20

These findings build upon growing evidence suggesting that individuals with SMI and T2DM, who also meet criteria for MetS, have worse cognitive performance than those without MetS. Moreover, evidence indicates that individuals with SMI and T2DM have an unhealthy lifestyle that, in addition to psychopharmacological medication intake, increases the risk of developing MetS.69 Thus, people with SMI and T2DM appear to be particularly vulnerable to cognitive and functional impairments linked to MetS. This could be explained by underlying pathophysiological pathways common to somatic and psychiatric diseases, such as immune-inflammatory processes, epigenetic regulatory mechanisms, or the microbiota-gut-brain system.15,17

These results have potential implications for the prevention and management of functional impairment in individuals with SMI and T2DM who meet criteria for MetS and individuals with MetS only. MetS is currently considered a major risk factor for the development of chronic diseases that involve high morbimortality, such as T2DM and SMI, and therefore, early detection and

| TABLE 5  | MetS components at T1 with ability to discriminate individuals with greater cognitive impairment at T2 |
|----------------|----------------------------------------------------------------------------------------------------------------------------------|
| Dependent variables | Predictors at T1 | β | Wald | Percent of variance explained | Global percentage correctly predicted |
| GCI | TG | 0.02 | 26.9**** | 0.31 to 0.42 | 75.0 |
|  | TG | 0.03 | 26.2**** | 0.44 to 0.58 | 81.5 |
|  | SBP | 0.08 | 16.5**** | 0.51 to 0.68 | 86.3 |
|  | TG | 0.03 | 24.2**** | 0.53 to 0.71 | 87.1 |
|  | SBP | 0.04 | 12.3**** |            |        |
|  | FPG | 0.07 | 11.9**** |            |        |
|  | TG | 0.03 | 19.9**** |            |        |
|  | FPG | 0.05 | 12.1**** |            |        |
|  | SBP | 0.07 | 9.7*** |            |        |
|  | HDL | −0.06 | 4.9* |            |        |

Abbreviations: FPG, fasting plasma glucose; GCI, greater cognitive impairment; HDL, high-density lipoprotein; MetS, metabolic syndrome; NS, not significant; SBP, systolic blood pressure; T1, time 1; T2, time 2; TG, triglycerides.

NS = p > 0.05; *p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001; ****p ≤ 0.0001.
intervention for those at high risk of developing MetS is crucial. Based on the results of this study, it is proposed that some MetS components are especially useful to discriminate between individuals with disease and healthy individuals, thereby representing key elements for agile and accurate prevention. Thus, early detection of changes in those MetS components offers an opportunity to promote healthy lifestyle behaviors in individuals with SMI and T2DM, which in turn may reduce the risk of developing cardiometabolic complications. In this respect, we emphasize the importance of including MetS components as promising illness diagnostic markers for individuals with SMI and T2DM. Furthermore, our findings converge with the current therapeutic strategy of increasing physical activity and improving the quality of the dietary patterns to address MetS. On the other hand, the recently issued Royal Australian and New Zealand College of Psychiatrists (RANZCP) clinical guidelines for depression place lifestyle-based interventions as the first step in the primary healthcare approach. In keeping with current views that lifestyle is a multidimensional construct, our results further emphasize the need to implement therapeutic interventions that are sensitive to lifestyle changes, thus encouraging regular physical exercise, restorative sleep patterns, improved diet quality, and increased social interaction, among others. Of note, all these behaviors are modifiable. The efficacy of lifestyle-based interventions is widely acknowledged for the prevention and treatment of several noncommunicable diseases and represents the grounds of lifestyle medicine. The recent development of lifestyle psychiatry is gaining momentum. Lifestyle modifications reportedly have a positive impact on symptom severity and neurocognitive function for individuals with SMI, which goes beyond their known efficacy to treat metabolic comorbidities. Moreover, the negative impact of several MetS components on cognition might be prevented with nutritional and dietary interventions specifically designed to improve cognition in individuals with SMI and T2DM. However, further studies are needed to determine whether lifestyle modifications have sustained, long-term effects in the SMI population. This evidence should be urgently translated into clinical practice, given the poor literacy for nutritional and lifestyle medicine among healthcare professionals and trainees.

This paper cannot be concluded without pointing out some of its limitations and strengths. Thus, the limitations of the study include its relatively small sample size, which reduces the generalization of the results to populations of individuals with clinical characteristics similar to those studied. Moreover, after a year of follow-up, high experimental mortality was observed. This may have led to a potential bias in the retention of individuals who completed the assessments and were thus in a presumably better clinical condition. Despite these limitations, this study is characterized by a novel transdiagnostic approach and a comprehensive assessment of cognitive and functional outcomes in individuals with or without MetS across populations with somatic and psychiatric disorders. Furthermore, being a multicenter study increases the external validity of the results.

Our current findings emphasize the need to promote lifestyle-based interventions for people with SMI and T2DM. The use of mobile health (m-health) technologies offers a promising opportunity to gather real-time data on lifestyle changes and self-care, which may be particularly useful for the prevention, tracking, and management of metabolic complications during the course of chronic illnesses. Further research is required to address the mental health effects derived from metabolic complications and changes in lifestyle. In this regard, studies that include more longer-term observations of concomitant lifestyle behaviors could serve to detect changes in metabolic conditions that allow the prevention of neurocognitive impairment among those with somatic and mental disorders. Therefore, considering lifestyle from a holistic perspective, rather than assessing individual behaviors in isolation, becomes essential to understanding the interactions between lifestyle and mental health. Additionally, rigorous further research on the identification of other clinical markers related to changes in lifestyle could not only improve our understanding of mental and physical health but also help to achieve excellence in clinical practice and improve precision psychiatry, which is likely to change the current compartmentalized mental health approach.

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CONFLICT OF INTERESTS

None.

AUTHORS’ CONTRIBUTION

JVS-O, VB-M, PC-G, and RT-S: conception and design of the study; acquisition and analysis of data; drafting the manuscript and figures. GS-V, CS-M, VMV, IE-L, AH-M, JV-L, and BC-F: drafting the manuscript and figures. JV-F and RM-B: Formal analysis. All authors have read and agreed to the published version of the manuscript.
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DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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