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The role of lipid metabolism in cognitive functions among individuals with mental disorders: a cross-sectional study

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Abstract

Introduction: Mental illnesses are frequently associated with metabolic dysregulation and chronic inflammation, which may exacerbates cognitive decline beyond typical aging processes. While the link between lipid profiles and brain health is well-documented in the general population, this relationship remains complex and potentially non-linear in psychiatric patients due to the confounding effects of antipsychotic treatment and lifestyle factors.

Material and methods: The study was conducted among individuals with mental disorders in day support centers in Lublin and Łęczna. 91 participants with diagnoses F20, F25, F22, F31, F32, F40F48, F60F69 were included in final analyses. Biochemical data (TG, TC, LDL-C, HDL-C) were collected and cognitive functions were assessed using STMS, VFT and RAVLT.

Results: Dyslipidemia was identified in 79.1% of participants, with higher TG and TC concentrations observed in women than in men. Overall, elevated LDL-C levels were found in 55% of the participants, with no significant sex differences. While linear regression did not reveal significant associations, decision tree models (C&RT) showed that lower TG levels and aripiprazole treatment were the main predictors of better cognitive performance. However, these procognitive benefits were significantly moderated by body weight. In the SMI group, TG concentrations were higher than in the non-SMI group.

Conclusions: Our findings demonstrate that the association between lipid profiles and cognition in psychiatric patients is non-linear and highly dependent on metabolic and pharmacological moderators. While aripiprazole showed a potential procognitive effect, this benefit was significantly attenuated by obesity and dyslipidemia, highlighting the necessity of integrated metabolic monitoring and weight management to preserve cognitive health in this population.

Keywords: cognitive functions, lipids, dyslipidemia, SMI

Streszczenie

Wstęp: Zaburzenia psychiczne są często związane z dysregulacją metaboliczną i przewlekłym stanem zapalnym, które mogą nasilać spadek funkcji poznawczych wykraczający poza typowe procesy starzenia się. Chociaż związek między profilem lipidowym a zdrowiem mózgu jest dobrze udokumentowany w populacji ogólnej, zależność ta pozostaje złożona i potencjalnie nieliniowa u pacjentów psychiatrycznych ze względu na wpływ leczenia przeciwpsychotycznego oraz czynników stylu życia.

Materiał i metody: Badanie przeprowadzono wśród osób z zaburzeniami psychicznymi korzystających z dziennych ośrodków wsparcia w Lublinie i Łęcznej. Do analiz zakwalifikowano 91 osób z rozpoznaniami F20, F25, F22, F31, F32, F40F48 oraz F60F69. Zebrano dane biochemiczne (TG, TC, LDL-C, HDL-C), a funkcje poznawcze oceniono za pomocą testów STMS, VFT oraz RAVLT.

Dyskusja: Dyslipidemię stwierdzono u 79,1 % uczestników, przy czym wyższe stężenia TG i TC obserwowano u kobiet niż u mężczyzn. Łącznie u 55% badanych stwierdzono podwyższone LDL-C, bez istotnych różnic między płciami. Podczas gdy regresja liniowa nie wykazała istotnych zależności, modele drzew decyzyjnych (C&RT) ujawniły, że niższe stężenia TG oraz leczenie arypiprazolem były głównymi predyktorami lepszej sprawności poznawczej. Jednak te prokognitywne korzyści były istotnie modyfikowane przez masę ciała. W grupie osób z SMI stężenia TG były wyższe niż w grupie bez SMI.

Wnioski: Nasze wyniki wskazują, że związek pomiędzy profilem lipidowym a funkcjami poznawczymi u pacjentów psychiatrycznych ma charakter nieliniowy i w dużym stopniu zależy od moderatorów metabolicznych i farmakologicznych. Chociaż arypiprazol wykazywał potencjalne działanie prokognitywne, efekt ten był istotnie osłabiany przez otyłość i dyslipidemię, co podkreśla konieczność zintegrowanego monitorowania metabolicznego oraz kontroli masy ciała w celu zachowania zdrowia poznawczego w tej populacji.

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Słowa kluczowe: funkcje poznawcze, choroba psychiczna, lipidy, dyslipidemia

Introduction

Disorders of lipid homeostasis, also referred to as dyslipidemia, are manifested by elevated concentrations of lipids and lipoproteins in plasma. In clinical practice, two forms are most often diagnosed: hypercholesterolemia and atherogenic dyslipidemia. Hypercholesterolemia is diagnosed when LDL-C exceeds 115 mg/dL or total cholesterol (TC) exceeds 190 mg/dL. Atherogenic dyslipidemia—the lipid triad—comprises elevated triglycerides (TG > 150 mg/dL), low HDL-C (HDL-C < 40 mg/dL in men and < 45 mg/dL in women) and abnormal LDL-C [1].

As is well known, increased lipids are associated with excess body weight and are among the principal determinants of cardiovascular disease. These conditions are the leading cause of death among individuals with mental disorders. In psychiatric populations, increased serum lipid concentrations can reflect lifestyle, a tendency toward overweight and obesity, and long-term antipsychotic treatment [2].

Use of antipsychotics is associated with more than a two-fold higher risk of dyslipidemia compared with non-users [3]. The greatest increases in lipid concentrations are observed with olanzapine and clozapine [4].

The prevalence of dyslipidemia is estimated to be higher among people with mental disorders than among those without. Lifestyle factors, especially in psychotic disorders, such as poor diet related to lower socioeconomic status and tobacco smoking, play an important role [5].

Current research on the relationship between dyslipidemia and cognitive function in the general population indicates that the association is disputable and not fully understood; studies exist that both support and refute such a link [6].

With respect to other metabolic disturbances associated with overweight and obesity, numerous studies highlight adverse effects on domains such as memory, abstract reasoning, attention, and verbal fluency; the association tends to intensify with age.

The aim of this study was to analyze the relationship between lipid metabolism and cognitive functions, accounting for psychotropic medication class, age, education, and psychiatric diagnosis. We hypothesized that higher lipid values would be negatively associated with cognitive functions, and that the association would be moderated by medication type.

Materials and Methods

The study was conducted in day support centers for people with mental disorders in Lublin and Łęczna. The protocol received approval from the Bioethics Committee of the Medical University of Lublin (KE-0254/101/2013).

In stage one, 120 individuals with a psychiatric diagnosis [(F20), (F25), (F22), (F31), (F32), (F40–F48), (F60–F69)] who provided written informed consent were enrolled; 91 were included in the final analyses.

Inclusion criteria included: psychiatric diagnosis; current remission; age 20–66 years; no statin use; written informed consent.

Exclusion criteria included: reported co-occurrence of intellectual disability (*Intellectual Disabilities*, IDD), suspected comorbid dementing disorder, and exacerbation of symptoms of the primary condition, i.e., a mental disorder.

Cognitive functioning was assessed using the Short Test of Mental Status (STMS); the Verbal Fluency Test (VFT), which included both the Semantic (Categorical) Fluency Test and the Phonemic (Letter) Fluency Test; and the Rey Auditory Verbal Learning Test (RAVLT).

Statistical analyses were performed using Statistica software, version 13.3. The normality of variable distributions was assessed using the Shapiro–Wilk test. Homogeneity of variance was tested with Levene's test. In cases where some variables did not meet the assumption of normality, Box–Cox transformations were applied to approximate a normal distribution, or a base-10 logarithmic transformation (log10) or a power transformation (square root) was applied to the variables.

Hypothesis testing was conducted using Student's t-test. When the assumptions of parametric testing were not met, the Mann–Whitney U test was used. Additionally, one-way and two-way analyses of variance (ANOVA) were performed. Post hoc analyses were conducted using Tukey's HSD test. For comparisons involving more than two groups with unequal sample sizes, the Kruskal–Wallis test was applied, followed by post hoc analyses using Dunn's test. The strength of associations between variables was assessed using Spearman's rank correlation coefficient.

Multiple regression analysis (enter method) was conducted to assess the extent to which variables [X] and [Y] predict cognitive performance. To identify potential nonlinear relationships and interactions between lipid parameters and cognitive test outcomes, the Classification and Regression Trees

(C&RT) method was applied. The model was developed using a v-fold cross-validation procedure. Results were considered statistically significant at $p \leq 0.05$.

Results

A total of 91 participants were included in the study, 51 women and 40 men. Mean age was 46 years (SD ± 13.3); women 49 years and men 42 years.

The study group was not homogeneous with regard to somatic comorbidities co-occurring with mental disorders. Among the most prevalent conditions were arterial hypertension, ischemic heart disease, hypercholesterolemia, type 2 diabetes mellitus, a history of cancer (long-term medical history), and viral hepatitis not currently requiring pharmacological treatment. Type 2 diabetes mellitus was diagnosed in 13 participants (14%); all of these individuals were treated with metformin.

Biochemical blood analyses were performed using standardized equipment on fasting participants. The following parameters were assessed: triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C).

The present publication constitutes part of research reported in two previously published articles which address, among other issues, the relationship between overweight and obesity and cognitive functioning, taking into account indicators such as body weight, abdominal obesity, and waist-to-hip ratio (WHR) in the study population. The classification of psychotropic medications used in the present study was adopted from those publications [7, 8].

Anthropometric analysis indicated that in the studied group (N = 91), only 30% of participants (n = 27) had a normal body weight, while one participant (2%) was classified as underweight. Excess body weight was observed in the majority of participants: 35% (n = 32) were classified as overweight, and 33% (n = 31) were diagnosed with obesity (class I and II).

Particularly concerning results were obtained regarding abdominal obesity. According to the International Diabetes Federation (IDF) criteria, abdominal obesity was present in 70% of all participants (n = 70). Using the waist-to-hip ratio (WHR), abdominal obesity was identified in 67% of the participants (n = 61).

In the female subgroup (n = 51), the BMI distribution was similar to that observed in the entire sample (class I and II obesity: 35.3%; overweight: 35.3%). Notably, however, the prevalence of abdominal obesity in this subgroup was even higher. According to IDF criteria, abdominal obesity was present in 83% of women, while based on the WHR index, it was observed in as many as 94% of the female participants (Table 1).

Table 1. Distribution of BMI categories and prevalence of abdominal obesity in the study population.

Parameter	Total Group (N=91)	Women (n=51)
BMI Classification	**n (%)**	**n (%)**
Obesity Class II	5 (5%)	2 (3.9%)
Obesity Class I	26 (28%)	16 (31.4%)
Overweight	32 (35%)	18 (35.3%)
Normal	27 (30%)	14 (27.4%)
Underweight	1 (2%)	1 (1.9%)
Abdominal Obesity		
According to IDF	70 (77%)	40 (83%)
According to WHR	61 (67%)	45 (94%)

Psychotropic medications varied. The largest subgroup comprised individuals using atypical antipsychotics (A; 31 persons, 34%), followed by those taking typical plus atypical antipsychotics concurrently (T+A; 27 persons, 30%). Fourteen individuals (15%) used typical antipsychotics only (T), and the remaining group (P; 19 persons, 21%) included antidepressants, anxiolytics/hypnotics, and mood stabilizers/antiepileptics (Figure nr 1). The atypical antipsychotics (A) used by the participants included clozapine, olanzapine, quetiapine, risperidone, aripiprazole, and amisulpride. The typical antipsychotics (T) included perazine, chlorprothixene, haloperidol, perphenazine, levomepromazine, flupentixol, zuclopenthixol, and sulpiride.

The group of antidepressants included sertraline, vortioxetine, trazodone, paroxetine, mianserin, mirtazapine, duloxetine, venlafaxine, and escitalopram. The group of anxiolytic and hypnotic medications comprised diazepam, alprazolam, estazolam, lorazepam, clonazepam, zolpidem, zopiclone, and hydroxyzine.

The group of mood stabilizers and antiepileptic medications used by the participants included lithium carbonate, valproic acid, lamotrigine, carbamazepine, gabapentin, pregabalin, topiramate, and oxcarbazepine.

As mentioned above, 13 participants (15%) were taking metformin, while 7 participants (8%) were

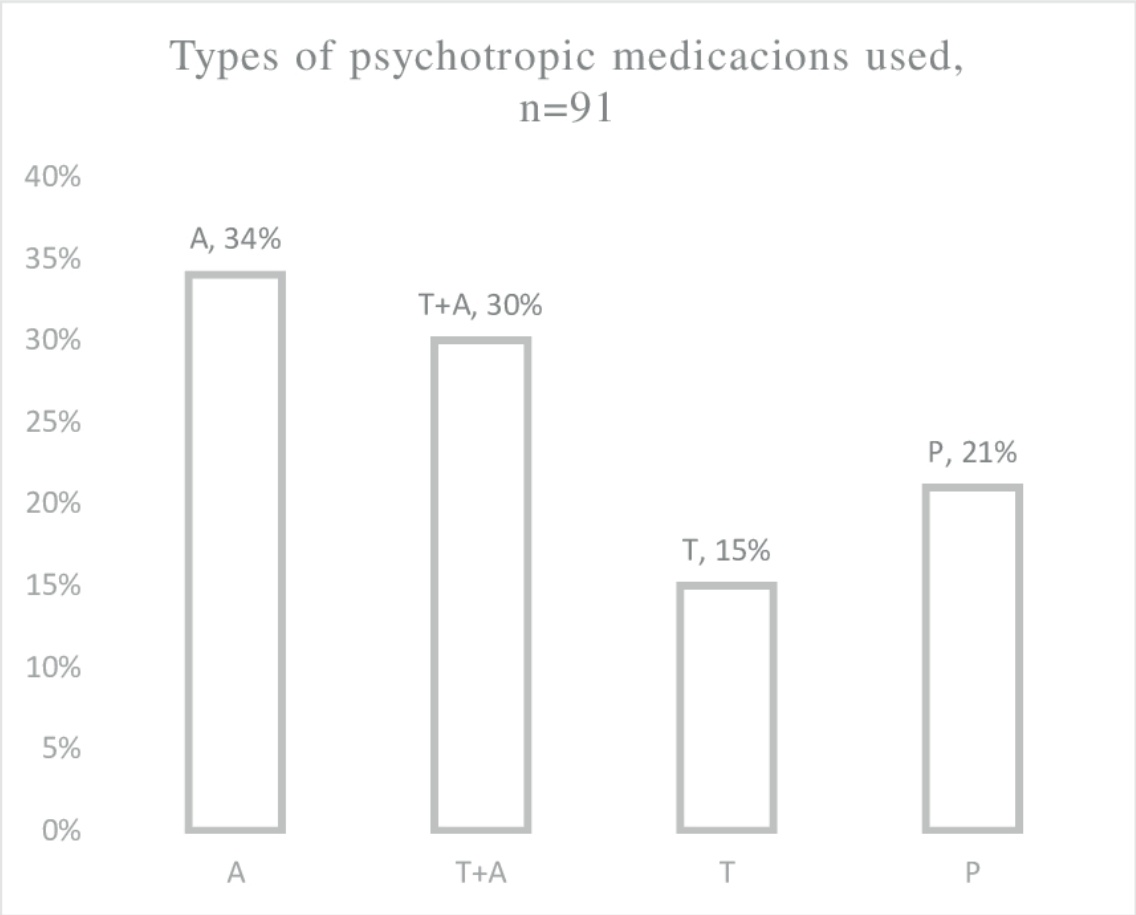

Figure 1. Types of medications used in the total study sample.
Footnote: T+A denotes concurrent use of typical and atypical antipsychotics (27 participants, 30%), A denotes atypical antipsychotics (31 participants, 34%), T denotes typical antipsychotics (14 participants, 15%), and P denotes other medications, including antidepressants, anxiolytics and hypnotics, and mood stabilizers/antiepileptic drugs (19 participants, 21%)(source: author's own elaboration)

receiving lipid-lowering medications from the fibrate and statin groups (atorvastatin, rosuvastatin, simvastatin, and fenofibrate).

The participants were partially comparable in terms of diet, as all individuals were enrolled in daytime, community-based support programs. From Monday to Friday, they consumed two meals per day at the support centers. A detailed breakdown of the study group according to basic sociodemographic characteristics is presented in Table 2.

Table 2. Basic sociodemographic characteristics of the study participants.

Place of residence							
Rular areas				Urban area			
N=22		24%		N=69		76%	
Employment status							
Yes				No			
N=16		18%		N=75		82%	
Source of income							
Salary		Permament allowence		Old-age pension		Disability pension	
N=16	17%	N=6	7%	N=12	13%	N=57	63%
Education level							
Primery		Vocational		Secondary		Post-secondary and higher	
N=13	14%	N=28	31%	N=29	32%	N=21	23%

Forty-five participants (49%) reported current tobacco smoking. Sixty-eight individuals (75%) subjectively reported being physically active, defined as engaging in at least 30 minutes of walking per day.

All participants had been hospitalized at least once due to a mental disorder. The number of psychiatric hospitalizations ranged from 1 to 25 (M = 4.73, SD = 6.00).

Lipid concentrations

Dyslipidemia was identified in 72 participants (79.1%): 45 women (88.2%) and 27 men (67.5%). Notably, mean age was higher in women (M = 49 years) than in men (M = 42 years; p = 0.008).

HDL-C was within reference ranges in 92.3% of participants (men < 40 mg/dL; women < 45 mg/dL). Low HDL-C was found in 5 women (9.8%) and 2 men (5%); the sex difference was not statistically significant (p = 0.36).

Elevated TC (> 190 mg/dL) was observed in 60.4% overall. TC > 190 mg/dL occurred in 37 women (73%) and 22 men (55%). Sex differences in TC were statistically significant (p = 0.03; women Me = 208 mg/dL; men Me = 187 mg/dL).

Elevated LDL-C (> 115 mg/dL) was present in 50 participants (55%): 33 women (65%) and 17 men (42.5%); the sex difference was not significant (p = 0.06).

Hypertriglyceridemia (TG > 150 mg/dL) was found in 37 individuals (40.7%). Elevated TG were somewhat more frequent in men (17 persons, 42.5%) than in women (20 persons, 39%), but the difference was not significant (p = 0.58). Atherogenic dyslipidemia was diagnosed in 4 individuals (4.4%).

Place of residence (rural vs. urban) had no significant impact on HDL-C, TG, TC, or LDL-C measured values among the participants (p > 0.05)

Psychiatric diagnosis and lipid concentrations

Participants were divided into two subgroups by diagnosis: severe mental illness (SMI; n = 63) and without SMI (n = 28). Median TG was 134.2 mg/dL in SMI versus 92 mg/dL in non-SMI; the difference was statistically significant (p = 0.004) (Table 3; Figure 2).

Table 3. Psychiatric diagnosis (SMI vs. non-SMI) and lipid concentrations (sum of ranks; p-values).

Lipid	ME (SMI), N=63	ME (non-SMI), N=28	U*	p-value
LDL-C	113	134	726,00	0.181
TC	203	210	802,50	0.496
TG	134	95	552,00	0.004*

*Footnote: * p ≤ 0.05. Abbreviations as above./ U -The Mann–Whitney U test./Me=median*

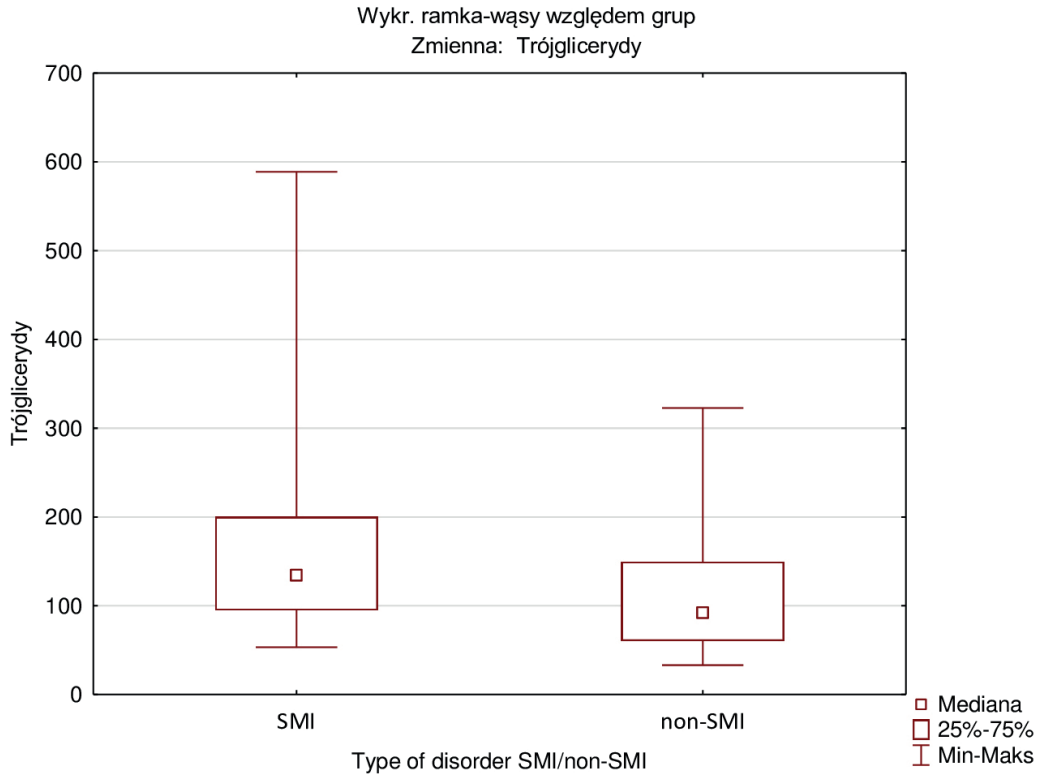

Figure 2. Differences in TG concentrations in the SMI vs. non-SMI groups.

Psychotropic medications and lipid concentrations

Psychotropic medication class did not differentiate lipid concentrations: HDL-C in women (p = 0.80) and men (p = 0.86), TG (p = 0.17), TC (p = 0.79), and LDL-C (p = 0.87) in the whole sample.

Type 2 diabetes mellitus and metformin use in relation to lipid concentrations and cognitive function

Type 2 diabetes mellitus, and consequently metformin use, differentiated the study group with respect to triglyceride (TG) levels (p = 0.004; Table 4). Participants with diabetes exhibited a significantly higher median TG level (Me = 197) compared to those without diabetes (Me = 119). No significant differences were observed in, total cholesterol (TC), or LDL cholesterol with respect to the presence or absence of type 2 diabetes mellitus/metformin use (p > 0.05).

Performance in the assessed cognitive function tests and subtests did not differ significantly according to the presence of type 2 diabetes mellitus or metformin use (p > 0.05).

Table 4. HDL, TG, TC, and LDL cholesterol concentrations according to type 2 diabetes mellitus and metformin use

Variable	ME (non-diabetes), N=78	ME (Diabetes), N=13	U*	p
TG	118	200	275,50	0,004*
TC	208	204	487,50	0,829
LDL-C	120	107	467,50	0,658

U -The Mann–Whitney U test; p – level of statistical significance; p ≤ 0.05./Me=median

Type 2 diabetes mellitus, metformin use, and cognitive functioning in relation to lipedema

Cognitive functioning did not differ significantly with respect to hypertriglyceridemia (p > 0.05), HDL cholesterol (p > 0.05), LDL cholesterol, or dyslipidemia (p > 0.05), when stratified by the presence of type 2 diabetes mellitus/metformin use versus their absence.

When the study group was stratified according to the presence of type 2 diabetes mellitus/metformin use, differences were observed in the correlations between lipid parameters and the assessed cognitive functions. Statistically significant low positive correlations were found exclusively in the group of participants without diabetes between triglyceride levels and STMS Attention (r_s = 0.24, p = 0.03), STMS Learning (r_s = 0.23, p = 0.04), and STMS Calculation (r_s = 0.23, p = 0.03) (Table 5).

Table 5. Correlations between triglycerides (TG) and the assessed cognitive functions in the group of participants without type 2 diabetes mellitus.

Variable pair	Valid N	Spearman's R	t(N-2)	p
Global cognitive functions - STMS & Triglycerides	78	0.2212	1.9782	0.05
Allopsychic orientation STMS & Triglycerides	78	0.0835	0.7307	0.46
Attention STMS & Triglycerides	78	0.2453	2.2059	0.03*
Learning STMS & Triglycerides	78	0.2301	2.0616	0.04*
Calculating STMS & Triglycerides	78	0.2372	2.1293	0.03*
Abstract thinking STMS & Triglycerides	78	-0.0751	-0.6570	0.51
Information STMS & Triglycerides	78	0.2119	1.8906	0.06
Drawing STMS & Triglycerides	78	0.0204	0.1787	0.85
Recall STMS & Triglycerides	78	0.0332	0.2903	0.77
Letter fluency- P & Triglycerides	78	0.1558	1.3756	0.17
Semantic fluency - K & Triglycerides	78	0.0564	0.4929	0.62
Immidiate recall (Rey I) & Triglycerides	78	0.0312	0.2722	0.78
Immidiate recall (Rey II) & Triglycerides	78	0.0814	0.7122	0.47
Deleyed recall (Rey III) & Triglycerides	78	-0.0699	-0.6112	0.54

*Footnote: * p ≤ 0.05*

Lipid levels and cognitive function

Two-way ANOVAs of cholesterol concentrations versus cognitive functions measured by STMS, VFT, and RAVLT showed no statistically significant effects ($p > 0.05$) in women or men. Correlation analyses revealed no significant associations between TC, LDL-C, HDL-C, and TG and global cognitive measures (STMS total, VFT, RAVLT) in the overall sample or by sex ($p > 0.05$). Neither the presence of hypertriglyceridemia nor the dichotomization of TG as normal vs. elevated differentiated cognitive performance (STMS, VFT, RAVLT) overall or by sex ($p > 0.05$), and no significant differences were found for TG, LDL-C and the cognitive tests ($p > 0.05$) (Table 6).

Table 6. Associations between lipid concentrations and cognitive functions (N = 91).

Variable / Test	HDL-C (r, p)	TG (r, p)	TC (r, p)	LDL-C (r, p)
RAVLT III – Delayed recall	r = -0.03; p = 0.75	r = -0.05; p = 0.06	r = -0.06; p = 0.55	r = -0.05; p = 0.62
RAVLT II – Immediate recall	r = -0.01; p = 0.91	r = 0.05; p = 0.60	r = 0.16; p = 0.13	r = 0.17; p = 0.09
RAVLT I – Immediate recall	r = -0.08; p = 0.41	r = -0.002; p = 0.98	r = 0.09; p = 0.39	r = 0.17; p = 0.10
Semantic fluency – VFT	r = -0.0002; p = 0.99	r = 0.06; p = 0.55	r = 0.45; p = 0.17	r = 0.09; p = 0.37
Phonemic fluency – VFT	r = 0.07; p = 0.48	r = 0.02; p = 0.79	r = 0.006; p = 0.94	r = -0.01; p = 0.90
General cognition – STMS total	r = -0.02; p = 0.80	r = 0.10; p = 0.33	r = 0.12; p = 0.23	r = 0.13; p = 0.21

Footnote: r — Pearson correlation; p — significance level. Abbreviations as above.

No associations were observed between age and LDL-C ($p = 0.48$), TC ($p = 0.15$), or TG ($p = 0.29$); nor between age and HDL-C in women ($p = 0.43$) or men ($p = 0.14$).

However, correlations with individual STMS subtests showed significant associations with lipids (Table 7). In the full sample, weak positive correlations were found between TG and STMS Attention ($r_s = 0.25$, $p = 0.01$), LDL-C and STMS Figure (visuospatial/motor; $r_s = 0.21$, $p = 0.04$), and TC and STMS Attention ($r_s = 0.25$, $p = 0.01$). Among women, there was a weak positive correlation between TG and the STMS Counting subtest ($r = 0.28$, $p = 0.04$). Among men, HDL-C correlated positively with the STMS Delayed Recall subtest ($r_s = 0.32$, $p = 0.04$), and TG correlated with STMS Attention ($r_s = 0.42$, $p = 0.006$).

Table 7. Statistically significant correlations between lipid concentrations and STMS subtests (Spearman's rho).

Stratification	Variable pair	N	Spearman's rho	p
All	TG & STMS Attention	91	rs = 0.25;	p = 0.01*
All	LDL-C & STMS Figure	91	rs = 0.21;	p = 0.04*
All	TC & STMS Attention	91	rs = 0.25;	p = 0.01*
Women	TG & STMS Counting	51	rs = 0.28;	p = 0.04*
Men	HDL-C & STMS Delayed Recall	40	rs = 0.32;	p = 0.04*
Men	TG & STMS Attention	40	rs = 0.42;	p = 0.006*

*Footnote: * $p \leq 0.05$. Abbreviations as above.*

Because individual STMS subtests are scored on short ordinal scales (typically 0–3), it was not feasible to compute covariance models between lipid concentrations and subtest scores while simultaneously adjusting for variables such as sex or diagnosis.

Education was not observed to be a significant factor with respect to participants' LDL-C, TC, TG, or HDL-C concentrations ($p > 0.05$).

BMI, lipid level and cognitive function

Multiple linear regression analysis was performed to examine the association between BMI, lipid profile parameters (TC, LDL-C, TG, HDL-C), and cognitive functions measured using the STMS, VFT, and RAVLT tests. However, no statistically significant model explaining these relationships was obtained ($p > 0.05$).

Statins, fibrates and cognitive functions

Statistical analysis did not reveal any differences

in cognitive performance measured with the STMS, VFT, and RAVLT tests between participants taking statins or fibrates and those not receiving these medications ($p > 0.01$).

Age, smoking, physical activity, sports, type of medication taken, lipid level and cognitive function. Results of the classification and regression tree (C&RT) analysis for all variables in relation to cognitive test outcomes.

An analysis using classification and regression trees was performed in order to identify the hierarchy of metabolic and pharmacological predictors influencing the cognitive functioning of the studied patients. This method enabled the identification of nonlinear relationships as well as key cut-off points for the independent variables.

Overall cognitive performance (STMS test)

The model developed for the variable representing overall cognitive functioning measured by the STMS yielded a coefficient of determination of $R^2 = 0.348$, indicating a moderate explanatory power of the independent variables (Table 8, Figure 3). The analysis showed that the strongest predictive value in this domain was associated with parameters of lipid metabolism and indicators of body fat distribution. The strongest predictor was triglyceride concentration (importance: 0.28), followed by the waist-to-hip ratio (WHR) (0.23) and fasting glucose concentration (0.19). BMI (0.12) and smoking status (0.12) contributed equally to the model structure, whereas waist circumference had the lowest contribution (0.06). These results suggest that overall cognitive functioning measured with the STMS in the studied patients was closely associated with disturbances in lipid metabolism (particularly triglyceride levels) and abdominal obesity.

Table 8. Predictor importance and overall model fit for cognitive performance (STMS) based on decision tree analysis.

Cognitive domain (Dependent variable)	Main predictor (Variable importance)	Model R^2
General cognitive function/STMS test scores	BMI: 0.12 Waist circumference: 0.06 WHR: 0.23 Fasting blood glucose: 0.19 TG: 0.28 Smoking/T-N: 0.12	R^2 tree: 0.348

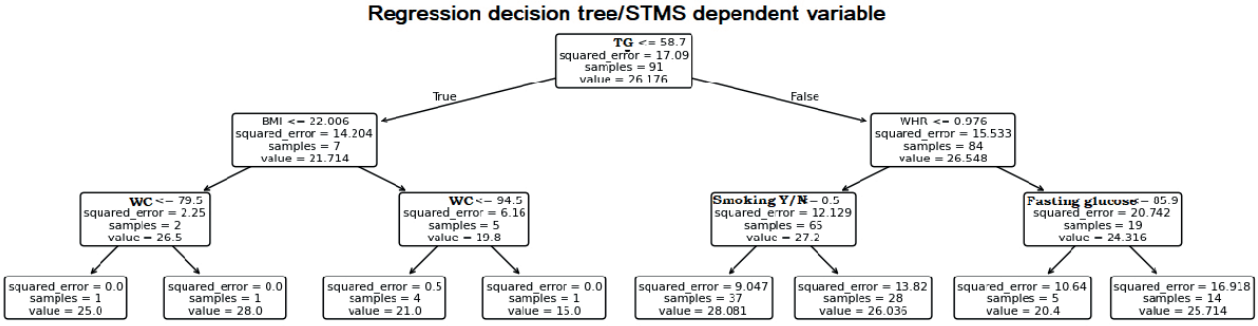

Figure 3. Regression decision tree for predicting STMS scores based on metabolic and lifestyle factors.

The structure of the generated tree allowed the identification of specific clinical pathways associated with the level of cognitive functioning:

- Lipid metabolism and body fat distribution: The first split of the cohort was based on triglyceride concentration, with a critical cut-off point of 58.7 mg/dl. Among patients with higher levels of this parameter (≥ 58.7 mg/dl), abdominal obesity emerged as a key determinant of cognitive performance. In this group, individuals with a high WHR (≥ 0.976) showed a further relationship with fasting glycaemia (glucose cut-off point: 85.9 mg/dl).
- Role of nicotine use: The model revealed an interaction between metabolic burden and lifestyle factors. In the branch representing individuals at high metabolic risk (elevated TG and WHR), smoking constituted an additional negative predictor, reducing the mean predicted STMS score from 28.08 (non-smokers) to 26.04 (smokers).
- Among patients with low triglyceride levels (≤ 58.7 mg/dl), the model indicated the importance of BMI (threshold: 22.01) and waist circumference. The lowest levels of cognitive performance in this subgroup were observed among patients whose waist circumference exceeded 94.5 cm, suggesting that even in the presence of a normal lipid profile, the accumulation of adipose tissue in the abdominal area remained negatively associated with neuropsychological functioning.
- None of the lipid-lowering medications (LLMs) or other drugs used by the participants were included in the decision tree regression model with respect to STMS test scores. The number of psychiatric hospitalizations was also not identified as a significant predictor.

Delayed Recall RAVLT

The model for the domain of episodic memory achieved the highest predictive power (R^2 = 0.716) (Table 9). The key factor differentiating patients' performance was pharmacotherapy with aripiprazole (importance: 0.74), which constituted the primary splitting criterion in the tree structure. Body weight (0.20) also played a significant role, indicating the influence of metabolic burden on the efficiency of memory processes. Other variables, such as quetiapine use (0.04) and age (0.01), showed only marginal importance. These findings suggest that episodic memory deficits in the studied group were mainly determined by the profile of antipsychotic treatment and anthropometric parameters rather than by patients' age.

Table 9. Predictor importance and overall model fit Delayed Recall RAVLT based on decision tree analysis.

Cognitive domain (Dependent variable)	Main predictor (Variable importance)	Model R^2
Delayed Recall RAVLT	Quetaplex: 0.04 Arypiprazol: 0.74 Age: 0.01 Body weight: 0.20	R^2 tree: 0.716

A detailed analysis of the decision tree showed that among patients with lower body weight (≤ 72.25 kg), performance in the RAVLT test was determined by the use of aripiprazole (Abilify). The presence of this medication in the treatment regimen was associated with significantly higher memory scores (mean 9.0 among individuals weighing more than 68.5 kg, with the highest observed value of 49.0 in a single node). Among patients with higher body weight (≥ 72.25 kg), age emerged as the key predictor (threshold: 35.5 years). In older individuals, an additional factor associated with lower performance was higher LDL cholesterol concentration (≥ 199.5 mg/dl). In younger individuals with higher body weight, the use of quetiapine (Ketrel/Quetaplex) had a negative impact on memory, reducing the mean score to 2.06.

Phonemic verbal fluency

In the domain of phonemic fluency (letter P test), the regression model achieved a coefficient of determination of R^2 = 0.363 (Table 10). The analysis showed that the strongest predictive factors in this domain were engagement in sports activity (importance: 0.31) and age (0.30), which constituted the primary splitting criteria in the tree structure. Clinical and metabolic variables also had a significant impact on the results, including the number of hospitalizations (0.15) and fasting glucose concentration (0.13). Less importance was attributed to waist circumference (0.09) and smoking status (0.02).

Table 10. Predictor importance and overall model fit for phonemic verbal fluency based on decision tree analysis.

Cognitive domain (Dependent variable)	Main predictor (Variable importance)	Model R^2
Phonemic verbal fluency (letter P test)	Age: 0.30 Waist circumference: 0.09 Fasting glucose: 0.13 Number of hospitalizations: 0.15 Smoking/Y-N: 0.02 Sports/Y-N: 0.31	R^2 tree: 0.363

The structural analysis of the tree allowed the identification of specific decision pathways. Among individuals who did not engage in sports, age emerged as the key predictor (threshold: 39.5 years). In this subgroup, older patients with a higher number of hospitalizations achieved the lowest scores (M = 7.89) in phonemic fluency, whereas among younger individuals a high waist circumference constituted a negative factor. In contrast, among physically active individuals the highest cognitive performance was observed in patients older than 46.5 years. In younger athletes, the cognitive barrier was associated with higher fasting glucose levels (≥ 87.55 mg/dl). These results suggest that language-executive functioning in the studied group was more strongly associated with lifestyle factors and glycaemic control than with anthropometric parameters.

Semantic verbal fluency

In the domain of semantic fluency (category test), the regression model achieved a coefficient of determination of R^2 = 0.289 (Table 11). The structural analysis of the tree indicated the dominance of metabolic parameters over clinical variables, with fasting glucose concentration emerging as the key predictor differentiating cognitive performance (importance: 0.47). Indicators of body fat distribution also played a significant role in the model, including WHR (0.32) and BMI (0.21).The decision process in the model began with a split based on fasting glucose concentration, with a cut-off point of 195.05 mg/dl. Among patients exceeding this threshold, the highest predicted semantic fluency score (14.0) was observed, although this applied to a small number of cases. In the main part of the cohort (glucose ≤ 195.05 mg/dl), performance was determined by BMI with a threshold of 23.491. Among individuals with higher BMI, the model indicated a further relationship with WHR (threshold 0.976), where patients with greater abdominal obesity achieved poorer results (M = 5.25) than those with lower WHR (M = 6.692). In contrast, among patients with lower BMI, a low WHR (≤ 0.828) emerged as a significant predictor

and was associated with the lowest mean scores within this pathway (3.857). The obtained data suggest that the ability to retrieve words within semantic categories in the studied sample was closely associated with glycaemic homeostasis and the pattern of body fat distribution.

Table 11 . Predictor importance and overall model fit for semantic verbal fluency based on decision tree analysis.

Cognitive domain (Dependent variable)	Main predictor (Variable importance)	Model R^2
Semantic verbal fluency (category test)	BMI: 0.21 WHR: 0.32 Fasting glucose: 0.47	R^2 tree: 0.289

Discussion

Relative to studies of the general population, the most prominent problems in our group were hypercholesterolemia (elevated TC) and hypertriglyceridemia. We contrasted our findings with recent Polish population-based studies: NATPOL 2011 [9], PONS 2011 [10], and LIPIDOGRAM 2015 [11].

In LIPIDOGRAM, dyslipidemia was recorded in 82.4% of women and 88.7% of men [11] who were not taking lipid-lowering drugs, which is higher than in our sample (79.1% overall; 88.2% women; 67.5% men).

In NATPOL 2011, elevated TC was found in 54.3% of Poles (54.4% men; 54.4% women). In our study, 60.4% had elevated TC—75% of women and 45% of men [9]. The percentage of persons with elevated LDL-C was similar to national estimates (our study: 55% overall; 42.5% men; 64.7% women; NATPOL 2011: 57.8% overall; 58.3% men; 57.3% women). We observed a markedly lower prevalence of low HDL-C (7.7% overall; 9.8% women; 5% men) compared with NATPOL 2011 (35% of men; 22% of women).

In the PONS Study (2011), hypertriglyceridemia was noted in 21.2% versus 40.7% in our cohort, consistent with evidence that atypical antipsychotics substantially raise TG [10, 12].

Johansen et al. (2022) reported in 532 individuals with SMI that olanzapine and/or clozapine was associated with elevated TG and LDL-C and lower HDL-C. Contrary to our hypothesis that medication class would differentiate lipid levels (TG, TC, HDL-C, LDL-C), no significant differences were found across T+A, A, T, and P groups—possibly due to our pragmatic grouping reflecting real-world regimens and common polypharmacy [13].

We did, however, observe differences by diagnosis: TG were higher by 42 mg/dL in SMI versus non-SMI, which may help explain the high TG observed in our psychiatric sample relative to the general population. A meta-analysis by Pillinger et al. (2017) based on 20 studies (923 patients) found higher TG in first-episode psychosis (FEP) versus controls, with no differences in LDL-C, HDL-C, or TC; the findings align with hypotheses linking FEP to impaired glucose homeostasis and hypertriglyceridemia as a precursor to type 2 diabetes [14]. Similar results were reported in a meta-analysis of first-episode major depressive disorder (MDD), where 690 MDD participants were compared with 614 healthy controls: TG were higher and HDL-C lower in MDD [15]. Routine lipid monitoring in SMI is recommended to support lifestyle interventions and CVD prevention.

The application of the classical multiple linear regression model did not demonstrate statistically significant associations between BMI and cholesterol fraction concentrations and the results of cognitive tests ($p > 0.05$). The lack of significance in the linear models, together with the high coefficients of determination obtained in the decision tree models (C&RT), suggested that the relationships between metabolism and cognition in the studied patients were nonlinear and multifactorial. This indicated the greater usefulness of machine learning methods in analyzing complex biological interactions within this patient group. A detailed analysis of the relationships between all variables, including age, medications used, physical activity, engagement in sports, BMI, WHR, waist circumference, and body weight, did not demonstrate a negative effect of lipid-lowering medications on the examined cognitive domains: overall cognitive functioning, verbal fluency, and delayed memory.

In the model for delayed memory using decision tree models that achieved the highest predictive power, aripiprazole played a dominant role. Patients receiving this medication achieved significantly higher scores in memory performance, which is consistent with the findings of Bervoets et al., who reported significantly better results in the RAVLT test after four weeks of aripiprazole treatment in a group of patients with schizophrenia, as well as improved performance in the phonemic fluency test. This effect, however, was not observed in the present study [16].

Futhermore, the applied decision tree model identified body weight as a key moderator of the relationship between aripiprazole use and delayed memory. In individuals with higher body weight, the benefits of treatment were attenuated by age and elevated LDL-C levels, leading to the conclusion that obesity limited the pro-cognitive effects of the applied pharmacotherapy.

Decision tree analysis showed that triglyceride concentration was the most important predictor of overall cognitive performance. The identified cut-off point (58.7 mg/dl) indicated that even values considered clinically low (within the laboratory reference range) differentiated the neuropsychological performance of the participants.

This relationship was consistent with reports suggesting that elevated triglyceride levels may negatively affect the blood–brain barrier and promote leptin and insulin resistance in the central nervous system, which in turn leads to a global decline in cognitive functioning [17].

Furthermore, the observed interaction between elevated triglyceride levels, abdominal obesity (WHR), and smoking, which in this study reduced the mean STMS score, confirmed the negative impact of metabolic disturbances and oxidative stress on brain neurobiology. These findings are consistent with a body of research demonstrating that the accumulation of vascular risk factors markedly accelerates cognitive decline, particularly in brain regions dependent on cerebral microcirculation [18], [19].

High TG, particularly in midlife, are linked not only to CVD risk but also to cognitive impairment, including progression to mild cognitive impairment (MCI) as a potential harbinger of dementia [20]. Elevated TG may contribute via atherosclerotic risk mechanisms, blood–brain barrier dysfunction, amyloid metabolism disturbance [21], endothelial dysfunction, inflammation, and cytokine dysregulation [22]. A meta-analysis by Zhao et al. (2024) suggested that high TC increases the risk of cognitive decline, especially in older men [23].

Conversely, some studies report opposing patterns. In a cohort of 1,336 adults, Yu et al. (2023) found that high TG reduced the risk of cognitive decline in older urban men, and further analyses indicated that this protective association was specific to older men living in cities [24]. The China Health and Retirement Longitudinal Study (CHARLS) identified a nonlinear inverse-U relationship between TG and cognition, suggesting that both too-low and too-high TG may be unfavorable for cognition [25]. Age likely moderates lipid–cognition associations: Lv et al. (2016) observed that higher TC, LDL-C, and HDL-C were linked to a lower risk of cognitive impairment among the "oldest old" (≥80 years) but not among younger elders (65–79 years) [26].

The positive association we observed between TG and attention (and between TG and STMS Counting in women) is difficult to interpret and mirrors current debates about TG and cognition. One possible explanation relates to triglyceride chain length—from short-chain triglycerides (SCTs) to very long-chain triglycerides (VLCTs). Detailed lipidomics (fatty acid profiling) could help identify which species may be beneficial or detrimental for cognition. Previous work suggests medium-chain triglycerides (MCTs) may benefit working memory and verbal memory and processing speed [27,28].

In the present study, the presence of type 2 diabetes mellitus and, consequently, metformin use were taken into account. Statistical analyses demonstrated that in the group of individuals with type 2 diabetes mellitus treated with metformin, no significant associations were observed between triglyceride (TG) concentrations and cognitive functioning. This finding is consistent with the results reported by Ma et al., who likewise did not observe associations between total cholesterol (TC), TG, HDL-C, LDL-C, or apolipoprotein B and the assessed cognitive functions. Their study population consisted of individuals with type 2 diabetes mellitus without mental disorders. Interestingly, serum apolipoprotein A1 levels were significantly negatively correlated with overall cognitive functioning. In the present study, apolipoproteins A and B were not assessed [29].

We also found a very weak positive association between LDL-C and visuospatial/motor functions. Similar mixed patterns have been reported longitudinally in Parkinson's disease (PD), where higher LDL-C was associated with better visuospatial/motor function but worse language performance at baseline; authors speculated that cholesterol might facilitate compensatory repair of damaged neural pathways [30]. At the same time, LDL-C is an established CVD risk factor and has been linked to dementia. A meta-analysis by Zhou et al. (2020) reported higher LDL-C in Alzheimer's disease (AD) versus controls, suggesting LDL-C as a potential risk factor for AD [31]; higher pre-diagnosis LDL-C was related to faster memory loss in AD. In a 25-year longitudinal study, Mefford et al. (2021) found that LDL-C was associated with small adverse changes in RAVLT memory scores [32]. Although we did not detect similar effects in RAVLT, we noted a statistical trend ($p = 0.09$).

Limitations of the study

The present study is not without limitations. The study group was heterogeneous with respect to the types of mental disorders as well as the psychotropic medications used. In addition, the participants differed in terms of age and co-occurring somatic conditions. Nevertheless, it is noteworthy that the actual distribution of psychotropic medications used by the participants was taken into account, as many individuals were receiving medications from different psychotropic drug classes.

Conclusions

In summary, the analysis showed that the association between metabolic parameters and on cognitive functions in individuals with mental disorders is nonlinear, which confirmed the superiority of decision tree models over traditional linear regression. The key predictor of overall cognitive performance was triglyceride (TG) concentration, which, even at relatively low levels (58.7 mg/dl), significantly differentiated the results, supporting the hypothesis of their negative impact on the blood–brain

barrier.

The study also confirmed the pro-cognitive effect of aripiprazole in the domain of delayed memory; however, these benefits were found to be attenuated by excessive body weight and elevated LDL-C levels.

Ultimately, the results suggested that strict control of the lipid profile and body weight is an essential prerequisite for the effectiveness of pharmacotherapy and the preservation of patients' cognitive functioning.

Conflict of Interest

The authors declare no financial or personal relationships with other persons or organizations that could negatively influence the content of the publication.

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