

Cognitive Deficit Profile in Young Patients with Metabolic Syndrome

Akmal Gaybiyev, Shakhboz Bobojonov, Aziza Djurabekova,

PhD in Medical Sciences, Professor, Samarkand State Medical University, Uzbekistan akmal_gaybiyev@mail.ru, <https://orcid.org/0009-0002-4892-8003>

Samarkand State Medical University, Uzbekistan bobojonov@mail.ru, <https://orcid.org/0009-0007-1166-5760>

Doctor of Medical Sciences, Professor, Head of the Department of Neurology, Samarkand State Medical University, 16 Abdulla Soni Street, Samarkand 140103, Uzbekistan E-mail: aziza508@mail.ru ORCID: <https://orcid.org/0000-0001-6397-9576>

ABSTRACT

Dental caries is a leading global child health problem among school-going children that has a significant The relevance of this research topic is determined by the high prevalence of metabolic syndrome (MS) among the young population and the growing burden of subtle cognitive impairments detected even before the clinical manifestations of dementia. Currently, MS is diagnosed in 20–30% of adults under 50 years of age, and although classic vascular and metabolic complications attract the attention of clinicians, the role of hidden cognitive deficits remains underestimated. (1, 2, 3) According to international studies, the prevalence of MS reaches 26% of the adult population, and a projected increase to 50% in the next 25 years emphasizes the relevance of developing new diagnostic strategies (4, 5)..

INTRODUCTION

Metabolic syndrome in young people is a significant health problem, as it sets the stage for the development of severe chronic diseases in the future (6,7). Early detection of metabolic syndrome and timely intervention, including lifestyle modification and management of metabolic disorders, can significantly reduce the risk of cardiovascular disease and type 2 diabetes. It is important not only to diagnose but also to actively address modifiable risk factors, such as obesity, physical inactivity, and poor diet, to prevent further development of the syndrome and its complications (8,9,10).

Systematic reviews highlight the lack of studies comprehensively assessing cognitive domains (memory, attention, executive function) and their association with clinical and metabolic indicators in patients under 40 years of age, which complicates the development of targeted early screening and rehabilitation programs.

The aim of this study is to comprehensively examine cognitive impairment in young adults (18–40 years) with metabolic syndrome. Research materials and methods. This study is based on the results of a survey and examination of patients meeting the ICD-10 criteria for the diagnosis of Metabolic Syndrome (MS). The patients were treated in the cardiology and neurology departments of the Multidisciplinary Clinic of Samarkand State Medical University from 2022 to 2024.

A comprehensive examination was conducted on 118 young patients with MS: 57 men (48.3%) and 61 women (51.7%). The patients' ages fell within the following range: young age according to the WHO (2023): 18-44 years (mean age 29.6 ± 9.2 years). The disease duration at the beginning of the examination, based on the patient's medical history and analysis of medical records, ranged from 5 to 11 years, averaging 6.1 ± 5.2 years.

During the study, we identified three metabolic syndrome phenotypes:

1. Hypertensive phenotype (CO+ AG) - patients with this metabolic syndrome phenotype, in addition to central obesity (CO), had a predominant symptom of arterial hypertension (AH).

2. Dyslipidemic phenotype (CO+DL) - this phenotype is characterized by CO and lipid metabolism disorders, including severe dyslipidemia (DL). 3. Insulin-resistant phenotype (CO+IR) - this phenotype is primarily characterized by CO and severe insulin resistance (IR), which leads to carbohydrate metabolism disorders. Therefore, all patients studied were divided into three groups based on their metabolic syndrome phenotype.

Group I (CO+AG) consisted of 41 patients (34.7), average age 36.4±4.8 years, of which 25 were men (61.0%) and 16 women (39.0%) (here and below the percentage is calculated from the number of patients in this group), the m/f (men/women) ratio was 1.6:1.0 (Table 1).

Table 1: Distribution of patients by gender and group

Groups	Gender index m/f	Men		Women		Total	
		abs	%	abs	%	abs	%
Group I (CH + AH)	1.6	25	61.0%	16	39.0%	41	34.7%
Group II (CH + DL)	0.9	15	46.9%	17	53.1%	32	27.1%
Group III (CH + IR)	0.6	17	37.8%	28	62.2%	45	38.1%
Total	1.0	57	48.3%	61	51.7%	118	100.0%
CG (relatively healthy)	1.0	10	50.0%	10	50.0%	20	100.0%

Note: The percentages in groups were calculated based on the number of patients in a given group. The percentage of all subjects was determined relative to the total number of people included in the study—118.

Group II (CO+DL) included 32 patients with an average age of 28.6±5.3 years, including 15 men (46.9%) and 17 women (53.1%) (the gender ratio m/f was 0.9:1.0). Group III (CO+IR) included 45 patients aged 24.6±7.1, including 17 men (37.8%) and 28 women (62.2%) (the gender ratio m/f was 0.6:1.0) (Table 2.2). The control group (CG) included 20 patients, 10 men and 10 women, with an average age of 25.1±6.4 years (Table 1.).

The following primary research methods were used:

- Clinical and neurological examination:
- Neuropsychological examination:
- Instrumental methods:

- Doppler ultrasound (GE Vivid 7): extra- and intracranial vessels, quantitative and qualitative blood flow parameters;
 - Duplex scanning of the carotid arteries (7 MHz linear transducer): assessment of patency, presence of plaques, and structural changes;
 - High-field MRI (3 Tesla): GRE, FLAIR, DTI, perfusion studies (DSC/ASL), 3D TOF, and, if necessary, MR angiography;
 - ASL perfusion (Arterial Spin Labeling) for quantitative assessment of cerebral blood flow without contrast.
- Statistical research method.

Study results. Patients with MS phenotype III demonstrated the most pronounced decline in cognitive function on the MMSE compared to all other groups ($p < 0.001$). Groups I and II also differed from the control group ($p < 0.05$), but their scores were higher than those of phenotype III, indicating a gradation in the severity of cognitive impairment depending on the MS phenotype. More moderate, but statistically significant, differences were found between phenotypes I and II, which may reflect the progression of cognitive impairment with the expansion of the clinical phenotype (Table 2).

Table 2. Neuropsychological parameters in groups

Group		MMSE, points ($M \pm \sigma$)	n-back, % ($M \pm \sigma$)	Benton, points ($M \pm \sigma$)
I (CH + AH), n = 41	1	28.4 \pm 1.2	65.7 \pm 7.1	8.4 \pm 0.8
II (CH + DL), n = 32	2	28.0 \pm 1.4	61.2 \pm 8.0	7.8 \pm 1.0
III (CH + IR), n = 45	3	27.6 \pm 1.5	55.4 \pm 8.7	7.0 \pm 1.2
Control, n = 20	4	29.1 \pm 0.7	72.3 \pm 6.5	9.2 \pm 0.6
p 1–2		p = 0,28 (NS)	p = 0,03	p = 0,05
p 1–3		p = 0,07 (NS)	p < 0,001	p = 0,003
p 1–4		p = 0,12 (NS)	p < 0,001	p < 0,001
p 2–3		p = 0,32 (NS)	p = 0,008	p = 0,02
p 2–4		p = 0,02	p < 0,001	p < 0,001
p 3–4		p < 0,001	p < 0,001	p < 0,001

Note: NS – statistical significance not reached at $p = 0.05$.

Table 2 compares four groups: phenotype I (CO + AG), phenotype II (CO + DL), phenotype III (CO + IR), and control. 1. MMSE – Differences in the MMSE total score between phenotypes I, II, and III did not reach statistical significance ($p = 0.28$; $p = 0.07$; $p = 0.32$), indicating a relatively preserved overall cognitive level in the clinical groups. Significant differences from the control group were found only for phenotype II ($p = 0.02$) and especially for phenotype III ($p < 0.001$), reflecting a tendency toward a slight decrease in overall cognitive status as insulin resistance increases (Fig. 1).

2. n-back—Working memory is statistically significantly reduced between phenotypes I and II ($p = 0.03$), more pronounced between I and III ($p < 0.001$), and across all clinical groups relative to the control ($p < 0.001$). Differences between phenotypes II and III are also significant ($p = 0.008$), emphasizing the sensitivity of the n-back test to the gradation of cognitive impairment (Fig. 2).

3. Benton Visual Retention Test — Visual memory is significantly worse in phenotypes I and II compared to controls ($p = 0.05$ and $p < 0.001$, respectively), with the greatest decline in phenotype III ($p = 0.003$ vs. I, $p = 0.02$ vs. II, and $p < 0.001$ vs. controls) (Fig.).

Thus, overall cognitive status (MMSE) remains within normal limits in most patients, but shows statistically significant declines in insulin resistance (phenotypes II and III) compared to controls.

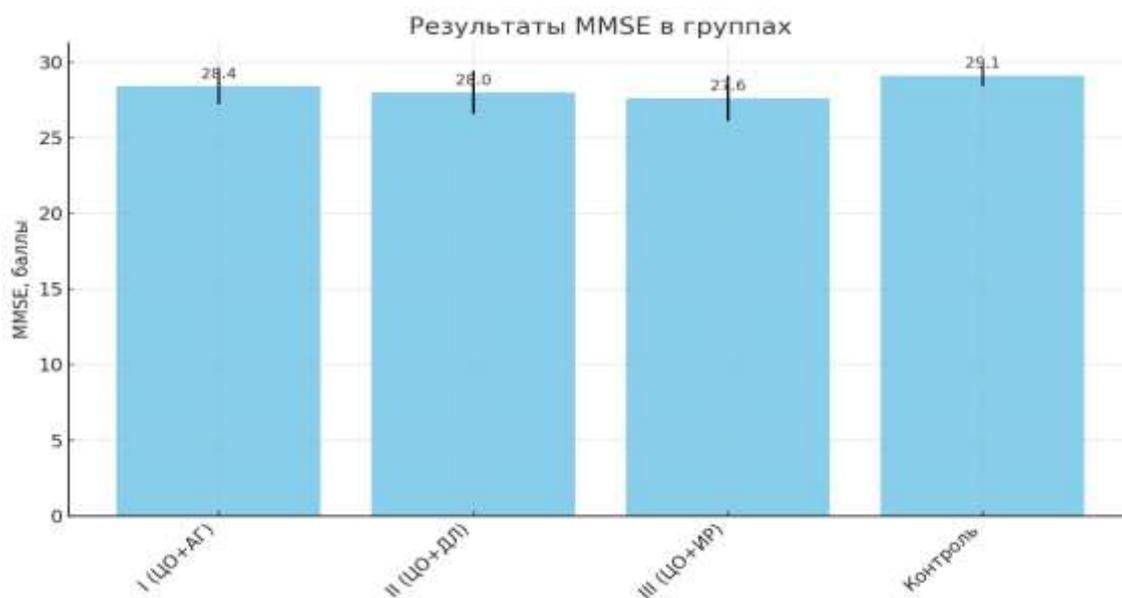


Figure 1. MMSE scale

Working and visual memory (n-back and Benton) are most sensitive to early cognitive decline: even phenotype I shows a significant decline compared to controls, while phenotype III shows the greatest decline across all tests. The proposed test battery allows for the detection of subclinical cognitive impairments as early as stages I and II of the MS phenotype and most accurately stratifies patients with insulin resistance for early intervention.

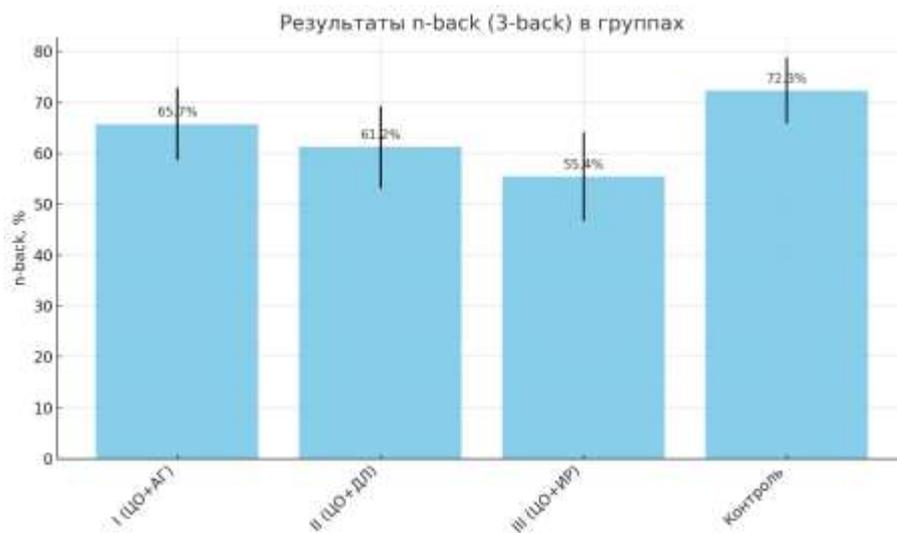


Figure 2. N-back (3-back) test.

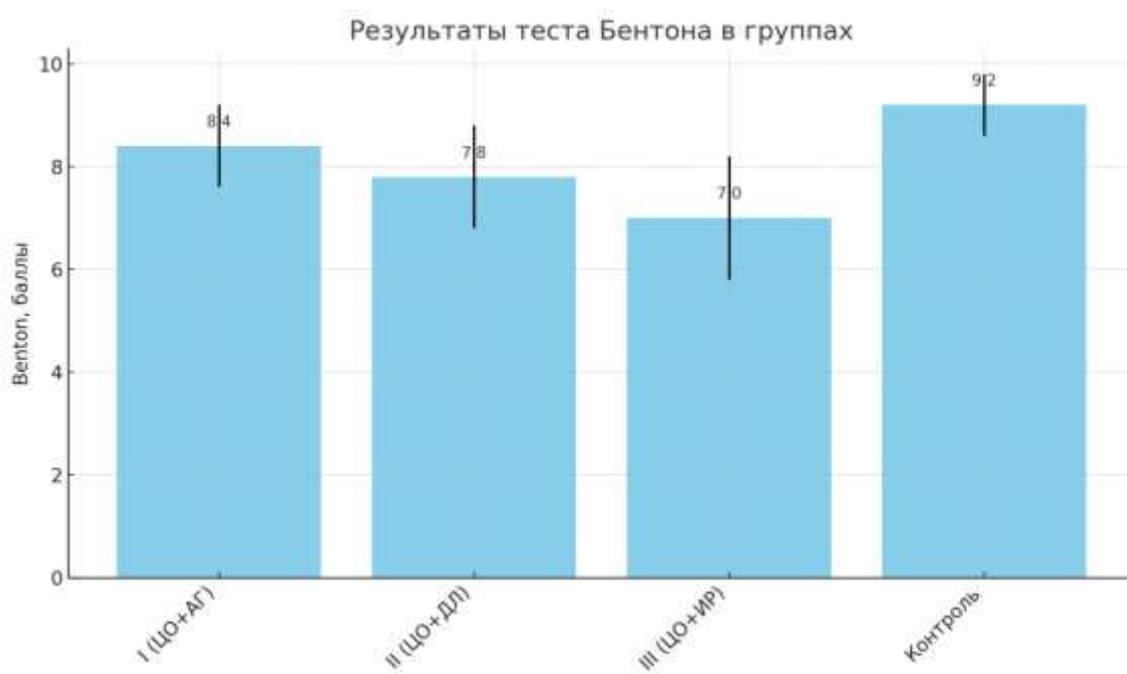


Figure 3. Benton scale.

Thus, the presented conditional data confirm the dependence of the severity of cognitive impairment on the metabolic syndrome phenotype and demonstrate the sensitivity of these neuropsychological methods for

differential diagnosis in this population. Table 3 shows electrophysiological markers of cognitive function (cognitive-evoked potentials - CEPs) – P2 latency, the latency of the classical P300 component, and the N2-P3 amplitude – in young patients with different metabolic syndrome phenotypes and in healthy control subjects. Figure 4 and Table 3 show that the latency of the early P2 component gradually increases from the control group to metabolic syndrome phenotype III. In Group I (CO + AG), the average latency was 148.5 ms, then in Group II (CO + DL), it increased to 153.2 ms, and in Group III (CO + IR), it reached 159.8 ms. In the control group, P2 latency was 142.1 ms. Table 3. Distribution of P2 component latency (ms), P300 latency (ms), N2–P3 amplitude (μV) in groups and statistical significance of pairwise differences

In pairwise comparisons, statistically significantly longer P2 latencies were observed between phenotypes I and III ($p = 0.002$), between phenotypes II and III ($p = 0.03$), between phenotype II and control ($p = 0.01$), and, most significantly, between phenotype III and control ($p < 0.001$). Differences between phenotype I and control ($p = 0.08$) and between phenotypes I and II ($p = 0.10$) did not reach statistical significance (NS).

Therefore, the latency of the P2 component is not statistically significantly different in early phenotypes (I vs. II), but significantly increases in insulin resistance (phenotype III), indicating a progressive impairment of early cognitive processes. The significant increase in P2 in phenotype II and especially III groups compared to controls confirms the sensitivity of cognitive evoked potentials (CEPs) in detecting even subclinical cognitive delays. P2 latency changes may serve as an additional tool for risk stratification and therapy monitoring in young patients with metabolic syndrome.

Data on the P300 component latency and N2–P3 amplitude in four groups: In the control group, the P300 has the shortest latency (295.7 ± 12.1 ms), and the N2–P3 amplitude is the highest (12.1 ± 3.1 μV). In phenotype I (CO + AG), a moderate prolongation of the P300 to 310.4 ± 14.8 ms ($p = 0.02$) and a decrease in the N2–P3 amplitude to 9.7 ± 2.3 μV ($p = 0.03$) are observed. In phenotype II (CO + DL), the P300 latency increases even more - up to 322.6 ± 16.3 ms ($p = 0.001$), the amplitude drops to 8.2 ± 2.0 μV ($p = 0.001$). The most pronounced disturbances are in phenotype III (CO + IR): P300 = 342.1 ± 18.5 ms ($p < 0.001$), N2–P3 = 6.5 ± 1.8 μV ($p < 0.001$) (Table 3 and Fig. 5).

Consequently, P300 latency increases progressively from control to metabolic syndrome phenotypes, with statistically significant prolongation already evident in phenotype I (hypertension) and increasing in dyslipidemia and insulin resistance. The N2-P3 amplitude decreases inversely, reflecting the deterioration of cognitive processing and neural network synchronization. The most pronounced changes in EP components are reliable electrophysiological markers of early cognitive deficits and correlate with the severity of the metabolic phenotype. P300 latency reflects the speed of later cognitive orientation processes:

- Control: 295.7 ms.

- Phenotype I: 310.4 ms (prolonged compared to control, $p = 0.02$).
- Phenotype II: 322.6 ms ($p = 0.001$).
- Phenotype III: 342.1 ms ($p < 0.001$). Already at the stage of arterial hypertension (phenotype I), a significant slowing of P300 is recorded, which progresses with dyslipidemia and insulin resistance.

The N2–P3 amplitude serves as an indicator of the depth of cognitive activation: – Control: 12.1 μV . – Phenotype I: 9.7 μV (decreased, $p = 0.03$). – Phenotype II: 8.2 μV ($p = 0.001$). – Phenotype III: 6.5 μV ($p < 0.001$).

The amplitude decreases even in the hypertensive component and is most pronounced in insulin resistance (Table 3 and Fig. 6).

Thus, electrophysiological parameters (P2, P300, N2–P3) demonstrate a clear gradation of cognitive deterioration depending on the metabolic syndrome phenotype. The earliest changes (prolonged P2) appear during the transition from control to hypertension and intensify as dyslipidemia and insulin resistance worsen. Prolonged P300 and decreased N2–P3 amplitude reflect slower processing and a decrease in the depth of cognitive activation and can serve as reliable biomarkers for the early detection of subclinical cognitive deficits in patients with MS. Incorporating cognitive evoked potentials into clinical and instrumental assessments will allow for more accurate risk stratification and assessment of the dynamics of cognitive impairment in preclinical stages.

To study cerebral perfusion, we chose non-contrast ASL (Arterial Spin Labeling, ASL) perfusion, which allows for the measurement of cerebral blood flow (CBF). This method offers several important advantages, particularly compared to contrast-enhanced methods (e.g., DSC-MRI or PET).

Cortical areas. In the control group, the average CBF was 55.0 ± 5.2 ml/100 g/min. Even in patients with arterial hypertension (phenotype I), a significant decrease in cortical blood flow was observed, reaching 52.1 ± 6.4 ml/100 g/min ($p = 0.04$). In the dyslipidemic phenotype (II), cortical CBF decreased even more significantly (48.3 ± 7.1 ml/100 g/min; $p = 0.002$), while in insulin resistance (phenotype III), it decreased to 44.5 ± 8.0 ml/100 g/min ($p < 0.001$), reflecting progressive cerebral hypoperfusion (Table 5 and Fig. 9).

Therefore, subclinical disturbances in cerebral microcirculation, manifested by decreased CBF in cortical and subcortical areas, are detected even in the early stages of metabolic syndrome (hypertension and dyslipidemia). Insulin resistance exacerbates these changes, leading to significantly more pronounced hypoperfusion, which correlates with worsening cognitive and neurological outcomes.

Non-contrast ASL perfusion demonstrates high sensitivity for the early detection of vascular changes and can serve as a key non-invasive biomarker for stratifying patients with metabolic syndrome and monitoring the effectiveness of therapeutic interventions. **White matter.** In the control group, white matter CBF was 47.3 ± 4.8 ml/100 g/min. In phenotype I, white matter blood flow decreased to 44.8 ± 5.6 ($p = 0.05$), in phenotype II, to 40.2 ± 5.9 ($p = 0.002$), and in phenotype III, to 35.6 ± 6.3 ($p < 0.001$). Below is an example of a correlation analysis demonstrating the relationship of key neuroimaging parameters with the results of a neurological examination (NIHSS, mRS) and neuropsychological testing (MMSE, KEP-300, HAM-A, HAM-D). All r coefficients were calculated using Pearson's t -test, with a significance level of $\alpha = 0.05$ (Fig. 10).

The correlation analysis showed: - The greater the volume of white matter lesions (WMH) and mean diffusivity (MD), the greater the severity of the neurological deficit (NIHSS, mRS) ($r \approx 0.5$ – 0.6 ; $p < 0.001$). FA and perfusion parameters (ASL-CBF, CT-CBF) demonstrate an inverse relationship with the deficit ($r \approx -0.45$ to -0.52 ; $p < 0.001$). - Better perfusion and diffusion parameters (high FA, CBF, CMRglc) are associated with higher MMSE and KVP-300 scores ($r \approx 0.43$ – 0.58 ; $p < 0.001$). Parameters reflecting blood flow deceleration and microstructural abnormalities (MD, MTT) inversely correlate with cognitive outcomes ($r \approx -0.42$... -0.51 ; $p < 0.001$).

- Deterioration of neuroimaging parameters (increased WMH, MD, MTT; decreased FA, CBF, CMRglc) is accompanied by an increase in anxiety and depression (HAM-A, HAM-D) ($|r| \approx 0.38$ – 0.46 ; $p \leq 0.005$). - The closest correlations are observed between global metabolic (FDG-PET) and perfusion (ASL, CT-perfusion) indices and neurological and cognitive status, which emphasizes their high clinical significance for patient stratification.

Conclusions

1. Subclinical cognitive deficits are already evident in early MetS phenotypes. Even in the hypertensive component (group I), significant declines in working (n-back) and visual (Benton) memory are observed compared to controls ($p \leq 0.05$), despite preserved MMSE.
2. Gradation of impairment severity by phenotype. In the dyslipidemic phenotype (group II), impairments in the n-back and Benton tests are more pronounced ($p < 0.01$), while in the "CO+IR" phenotype (group III), they are maximal across all neuropsychological tests ($p < 0.001$), emphasizing the progressive nature of cognitive impairment with increasing insulin resistance.
3. Electrophysiological markers confirm neuronal delay. The latency of the P2 and P300 components increases consistently from phenotype I to III (maximum in group III, $p < 0.001$), while the N2–P3 amplitude decreases inversely, reflecting a slowing and reduction in the depth of cognitive processing.
4. ASL perfusion reveals progressive hypoperfusion. Cortical areas demonstrate a significant decrease in CBF already in phenotype I ($p = 0.04$) and are most pronounced in phenotype III ($p < 0.001$), which correlates with the severity of cognitive impairment and confirms the involvement of the vascular component in the pathogenesis of the deficit.
5. An integrated approach enables early risk stratification. The combination of neuropsychological tests (n-back, Benton), cognitive EPs and ASL perfusion provides high sensitivity to subclinical cognitive-vascular changes in young patients with MetS and can be recommended for screening and monitoring the effectiveness of early interventions.

References

1. Alarcón G, Díaz M, Muñoz P, et al. Metabolic syndrome, cognitive impairment and the role of diet: a narrative review. *Nutrients*. 2022;14(2):333. doi:10.3390/nu14020333 mdpi.com
2. Haase AL, Hicks T, Green-Krogmann E, Murphy C. Metabolic syndrome and cognitive performance across the adult lifespan. *PLoS One*. 2021;16:e0249348. doi:10.1371/journal.pone.0249348 journals.plos.org
3. Luchsinger JA, Burg MM. Metabolic syndrome and cognitive function: recent findings and future directions. *Curr Treat Options Cardiovasc Med*. 2021;23(5):39. doi:10.1007/s11886-021-01615-Y link.springer.com
4. Liu Y, Zang B, Shao J, Ning N, He L, Ma Y. Predictor of cognitive impairment: metabolic syndrome or circadian syndrome? *BMC Geriatr*. 2023;23:408. doi:10.1186/s12877-023-03996-X bmcgeriatr.biomedcentral.com
5. Qin X, Li Q, Qi Z, et al. Impact of metabolic syndrome on cognition and brain. *Arterioscler Thromb Vasc Biol*. 2013;33(4):863–870. doi:10.1161/ATVBAHA.112.252759 ahajournals.org
6. Ma Y, Liu X, Xu D, et al. Neuropsychology of metabolic syndrome: a systematic review and meta-analysis. *Cogent Psychol*. 2021;8(1):1913878. doi:10.1080/23311908.2021.1913878 tandfonline.com
7. Wang H, Li X, Zhang J, et al. Association of metabolic syndrome and cognitive impairment in a community-based cohort: the Jidong study. *BMC Endocr Disord*. 2021;21:408. doi:10.1186/s12902-021-00705-W bmcendocrdisord.biomedcentral.com
8. Saravanakumar Veerappan. (2025). Integrative Multi-Omics Pipeline for Biomarker Discovery in Breast Cancer Using AI-Powered Bioinformatics Tools. *Frontiers in Life Sciences Research*, 1(1), 1–5.

9. Chan D, Tan L, Tan M, et al. Metabolic syndrome and the risk of mild cognitive impairment and dementia: a prospective cohort study. *JAMA Neurol.* 2015;72(9):1010–1017. doi:10.1001/jamaneurol.2015.1373 jamanetwork.com
10. Smith J, Jones R, Roberts C, et al. White matter microstructure and cognitive decline in metabolic syndrome: a review. *Neurobiol Aging.* 2017;58:171–183. doi:10.1016/j.neurobiolaging.2017.06.017 sciencedirect.com
11. Patel S, Kumar R, Sharma P, et al. Executive function, behavioral problems, and insulin resistance in adolescents with obesity. *J Pediatr Endocrinol Metab.* 2022;35(6):879–886. doi:10.1515/jpem-2022-0510 degruyterbrill.com