ASSOCIATION BETWEEN METABOLIC SYNDROME AND COGNITIVE DYSFUNCTIONS IN SCHIZOPHRENIA

Ph.D. Thesis

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Budapest

2026

„The key to happiness is not to get more, but to enjoy what we have and to fill the empty frame of our lives instead of enlarging it.”

Albert Szent-Györgyi

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS

ACE-III	Addenbrooke's cognitive examination
AGEs	Advanced glycation end products
AHA	American Heart Association
ANOVA	Analyses of variance
AVLT	Auditory Verbal Learning Test
BACS	The Brief Assessment of Cognition in Schizophrenia
BMI	Body mass index
C4	Complement component 4
CI	Confidence interval
CNS	Central nervous system
COWA	Controlled Oral Word Association test
CPT	Continuous Performance Test
CPZ	Chlorpromazine
CRP	C-reactive protein
D-KEFS	The Delis–Kaplan Executive Function System Test
DM	Diabetes mellitus
DNA	Deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DTI	Diffusion tensor imaging
FA	Fractional anisotropy
FBG	Fasting blood glucose
^{18}F-FDG PET	^{18}F-fluorodeoxyglucose positron emission tomography
GABA	Gamma-aminobutyric acid
GLP-1	Glucagon-Like Peptide-1
GWAS	Genome-wide association study
HbA1c	Hemoglobin A1c
HDL	High-density lipoprotein
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
HK	Hartung-Knapp adjustment
HPA	Hypothalamic-pituitary-adrenal

IL-1β	Interleukin-1 beta
IL-6	Interleukin-6
IL-10	Interleukin-10
IR	Insulin resistance
LDL	Low-density lipoprotein
LNS	Letter-Number Sequencing test
MANOVA	Multivariate analyses of variance
MCCB	MATRICS Consensus Cognitive Battery
MD	Mean difference
MHC	Major histocompatibility complex
MetS	Metabolic syndrome
NAD	Nicotinamide Adenine Dinucleotide
NADH	Nicotinamide Adenine Dinucleotide + Hydrogen
NCEP ATP III	National Cholesterol Education Program Adult Treatment Panel III
NMDA	N-methyl-D-aspartate
PANSS	Positive and Negative Syndrome Scale
^{31}P-MRS	Phosphorus-31 magnetic resonance spectroscopy
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PROSPERO	The International Prospective Register of Systematic Reviews
PSD-95	Postsynaptic density protein-95
QUIPS	Quality in Prognostic Studies
RAGE	Receptor for advanced glycation end products
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
SCZ	Schizophrenia
SD	Standard deviation
SE	Standard error
SMD	Standardized mean difference
T2DM	Type 2 diabetes mellitus
TG	Triglyceride
TICS-M	The Modified Telephone Interview for Cognitive Status

TMT	Trail Making Test A/B
TNF-α	Tumor Necrosis Factor-alpha
ToL	Tower of London
UK	United Kingdom
VSR	Vovk–Sellke p-ratios
WAIS-R	Wecshler Adult Intelligence Scale-Revised
WCST	Wisconsin Card Sorting Test
WCST-64	Wisconsin Card Sorting Test-64
WHR	Waist-to-hip ratio
WISC	Wechsler Intelligence Scale for Children
WMS-R	The Wechsler Memory Scale-Revised

2. STUDENT PROFILE

2.1. Vision and mission statement, specific goals

My vision is that schizophrenia will become an effectively treatable disorder in the future, allowing affected patients to live a fulfilling life. My mission is to contribute to this goal by investigating the effects of metabolic and immunological processes on cognitive functions, with the specific aim of identifying key metabolic–inflammatory pathways that contribute to cognitive impairment in schizophrenia and thereby supporting the development of more personalized and clinically relevant therapeutic approaches.

2.2. Scientometrics

Number of all publications:	3
Cumulative IF:	11.4
Av IF/publication:	3.8
Ranking (SCImago):	Q1:3
Number of publications related to the subject of the thesis:	2
Cumulative IF:	8
Av IF/publication:	4
Ranking (Sci Mago):	Q1:2
Number of citations on Google Scholar:	7
Number of citations on MTMT (independent):	2
H-index:	1

The detailed bibliography of the student can be found on page 77.

2.3. Future plans

My future plans include further expanding my expertise and pursuing additional experimental studies building on our current findings, with the aim of gaining deeper insight into the factors that facilitate cognitive decline in patients with schizophrenia. By advancing this line of research, I hope to contribute to the development of novel approaches and therapeutic interventions that may ultimately improve quality of life and long-term outcomes for affected individuals.

3. SUMMARY OF THE THESIS

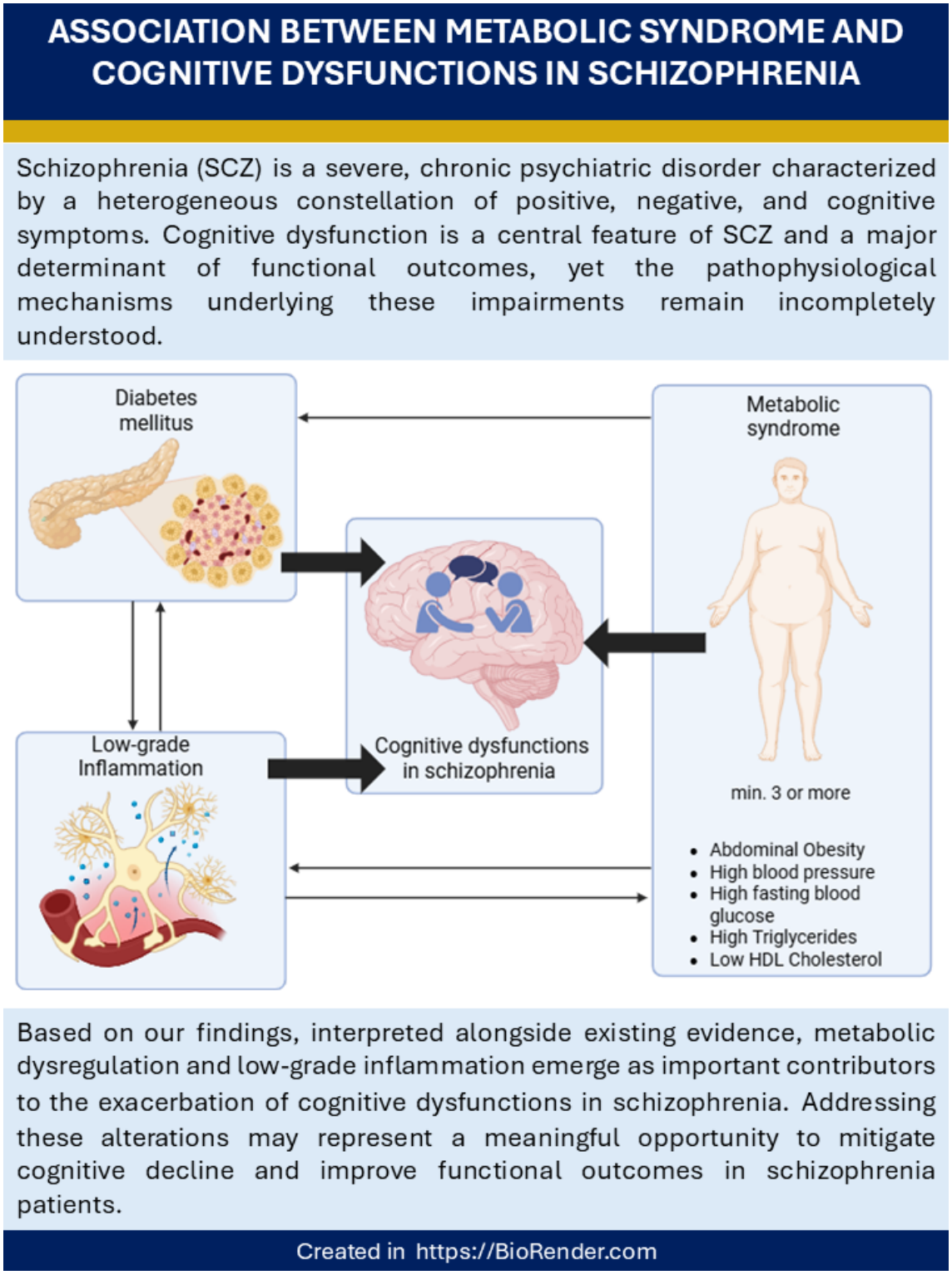
Cognitive dysfunction is a central feature of schizophrenia (SCZ) and a major determinant of functional outcomes, yet the pathophysiological mechanisms underlying these impairments remain incompletely understood. SCZ is also associated with a high burden of metabolic alterations and disorders, including metabolic syndrome (MetS), insulin resistance (IR), and diabetes mellitus (DM). The primary aim of this thesis was to investigate the impact of metabolic dysregulation and peripheral low-grade inflammation on cognitive functions in SCZ.

In our first study, we conducted a systematic review and meta-analysis to examine how different stages of impaired glucose homeostasis, including DM and IR, influence cognitive functions in SCZ. The results revealed a clear trend indicating that DM is associated with more severe cognitive dysfunction. (global cognition: SMD = −0.26; P = 0.1087), with particularly pronounced effects in the domains of reasoning (SMD = −0.40; P = 0.0109) and processing speed (SMD = −0.43; P = 0.0005). In contrast, findings related to IR were inconsistent and did not demonstrate a significant association with global cognitive performance (SMD = −0.12; P = 0.5890).

In the second study, we performed a cross-sectional analysis of adults with SCZ (N = 218), stratified into SCZ, SCZ+MetS, and SCZ+DM groups. IL-6 and CRP were measured, and their associations with RBANS cognitive domains and metabolic parameters were examined. Individuals with SCZ+DM showed significantly lower attention and delayed memory scores compared with SCZ+MetS, SCZ groups, whereas no differences were observed in other cognitive domains. Across the cohort, higher IL-6 and fasting glucose were associated with poorer attention and delayed memory, indicating that DM status and elevated IL-6 are key correlates of cognitive impairment in schizophrenia.

Our findings suggest that diabetes-related metabolic and inflammatory processes may play a central role in the exacerbation of cognitive dysfunctions in schizophrenia. Addressing these alterations may represent a meaningful opportunity to mitigate cognitive decline and improve functional outcomes in schizophrenia patients.

4. GRAPHICAL ABSTRACT



5. INTRODUCTION

5.1. Schizophrenia and cognitive dysfunctions

Schizophrenia (SCZ) is a severe, chronic psychiatric disorder characterized by a heterogeneous constellation of positive (e.g. delusions, hallucinations), negative (e.g. social withdrawal, anhedonia), and cognitive symptoms (1). The prevalence of the disorder worldwide is estimated to be between 0.85% and 1%; consequently, it imposes a substantial burden on patients, their families, and society alike (2). Cognitive dysfunction constitutes a core and persistent feature of SCZ, with patients exhibiting pronounced impairments in global cognitive performance, typically averaging around two standard deviations below that of the general population (3). Deficits are typically observed across multiple cognitive domains, including attention, working memory, processing speed, executive functions, learning and memory (4). Importantly, these impairments often emerge early in the course of the illness, may precede the onset of psychosis, and tend to persist throughout the lifespan, even during periods of symptomatic remission (5). Cognitive dysfunctions show robust associations with treatment non-adherence, more frequent and prolonged hospitalizations, reduced everyday productivity, diminished quality of life, poorer functional outcomes, and an overall less favorable prognosis (2).

5.2. Metabolic disturbances in schizophrenia

The widespread use of second-generation antipsychotics has drawn increasing attention to metabolic dysregulations in schizophrenia, including obesity, insulin resistance, and disturbances in glucose homeostasis. However, historically, the association between schizophrenia and metabolic dysfunctions predates the introduction of the first antipsychotic medication (chlorpromazine). In the 19th century, a British psychiatrist Sir Henry Maudsley stated in his book *The Pathology of Mind* that “diabetes is a disease which often shows itself in families in which insanity prevails” (6). Over the last decade, evidence from several studies and meta-analyses indicates that insulin resistance, diabetes and disturbances in glucose homeostasis occur more frequently among individuals with schizophrenia than in the general population (7). Epidemiological studies revealed that the prevalence of diabetes is approximately two- to threefold higher in individuals with

schizophrenia compared with the general population (8). Glucose homeostasis dysregulations are also observed in drug-naive patients with psychosis, suggesting that metabolic disturbances cannot be interpreted solely as a consequence of antipsychotic treatment (7). Notably, insulin resistance, beyond its well-established pathological effects in peripheral tissues, may also induce alterations in physiological processes within the central nervous system, thereby contributing to the manifestation of cognitive and behavioral symptoms (9-13).

Individuals with schizophrenia commonly present with broader metabolic abnormalities, such as metabolic syndrome, a condition closely linked to impaired glucose regulation and increased risk of T2DM. Findings from the CATIE study demonstrated that metabolic syndrome is highly prevalent among individuals with schizophrenia, with rates exceeding 40% (14). Metabolic syndrome is linked to an elevated risk of cardiovascular and cerebrovascular morbidity and to reduced life expectancy (15).

Historically, the metabolic syndrome (MetS) was first described by G.M. Reaven in 1988 as "Syndrome X," emphasizing the central role of insulin resistance (IR) and suggesting that the other components of the syndrome were consequences of disturbances in glucose homeostasis (16). Currently, according to the American Heart Association (AHA) criteria, MetS is defined by the presence of at least three of the following components: abdominal obesity, elevated blood pressure, impaired fasting glucose, high triglycerides, and low high-density lipoprotein (HDL) cholesterol (15,17). MetS is commonly characterized by chronic low-grade inflammation, reflecting a close and reciprocal interaction between metabolic abnormalities and inflammatory processes (18). Furthermore, chronic low-grade inflammation may contribute to neuroinflammatory mechanisms (19). Finally, both population-based and clinical studies suggest an association between metabolic syndrome and cognitive deficits in individuals with and without schizophrenia (20,21).

5.3. Genetic and environmental factors associated with metabolic disturbances in schizophrenia

Given the frequent co-occurrence of schizophrenia and metabolic syndrome, there has been growing attention to shared risk factors between these disorders, along with possible

overlaps in genetic loci (22). Although numerous genetic investigations have sought to clarify a possible biological connection between these conditions, the available evidence remains inconclusive. For example, a large-scale genome-wide association study (GWAS) found a high level of genetic overlap between body mass index (BMI) and SCZ with opposite direction associations (23). In contrast, other studies found a possible association between the genetic predisposition of SCZ, diabetes mellitus (DM) and MetS (24,25).

The inconsistent findings of genetic studies suggest that non-genetic, particularly environmental factors may contribute to the increased prevalence of metabolic syndrome among individuals with schizophrenia (23). Patients with SCZ are more likely to have experienced childhood trauma and are exposed to greater psychosocial stress throughout their lives compared to the general population (26). This may contribute to later dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis, thereby leading to the development of subsequent metabolic disorders and immune dysregulation (27). In addition, individuals with schizophrenia frequently exhibit lifestyle patterns, including low levels of physical activity, unhealthy dietary habits, and substance use, which collectively contribute to an elevated risk of metabolic disturbances (28). These observations indicate that metabolic abnormalities in schizophrenia are unlikely to be explained by a single factor, pointing to the involvement of multiple biological and environmental influences.

5.4. Immune dysregulation in schizophrenia

The complex pathophysiology of schizophrenia is often interpreted through the immune hypothesis, which serves as a traditional, conceptual framework for understanding the illness (29). The underlying mechanisms involve both adaptive immune pathways driven by lymphocytes and innate processes mediated by microglia and macrophages, with additional hypotheses suggesting that disturbances in the relative balance between these immune components may contribute to the pathogenesis (29). Evidence from longitudinal cohorts suggests that inflammation during neurodevelopment, reflected in increased IL-6 and CRP levels, is associated with a higher likelihood of psychotic outcomes and later schizophrenia (30). Consistently, individuals with SCZ exhibit increased concentrations of proinflammatory cytokines in peripheral blood as well as in cerebrospinal fluid (31,32).

Furthermore, the role of inflammatory processes in the disease's pathomechanism has been supported by genetic studies (33). For example, a Mendelian randomization study, which utilized data from the UK Biobank of 20,688 subjects, found that genetically predicted interleukin-6 (IL-6) levels were associated with the gray matter volume of the medial temporal gyrus and fusiform gyrus, as well as the cortical thickness of the superior frontal gyrus, suggesting a strong link between IL-6 and changes in brain structure (34). The involvement of the innate immune system is further supported by findings showing that higher percentages of TLR4-positive monocytes correlate with the severity of cognitive dysfunction in drug-naïve patients with schizophrenia (35). Finally, peripheral inflammatory dysregulation may ultimately drive central neuroinflammatory processes, leading to structural brain changes that contribute to cognitive deficits (36,37). These findings underscore the relevance of investigating the relationship between inflammatory processes and cognitive dysfunction in schizophrenia, as immune dysregulation may represent an important biological contributor to neurocognitive alterations associated with the disorder.

5.5. Rationale for an integrative research approach

The evidence reviewed above indicates that cognitive dysfunctions in schizophrenia may arise from the interplay of multifaceted biological mechanisms, rather than from isolated pathophysiological processes.

In clinical practice, antipsychotic medications, which form the cornerstone of schizophrenia treatment, are effective in alleviating positive symptoms; however, they exert little to no therapeutic benefit on cognitive functions (38). As a result, cognitive dysfunction remains a major unmet therapeutic need in the clinical management of schizophrenia. This issue is further complicated by evidence that antipsychotic medications, especially second-generation agents, are commonly associated with metabolic side effects, potentially mediated by changes in the gut microbiome, impaired central glucose sensing, weight gain, and disturbances in peripheral glucose and lipid metabolism (39-42). Notably, both inflammation and metabolic dysregulation, such as insulin resistance, have been implicated in treatment response and the development of therapeutic resistance (43-45).

The evidence presented above highlights a complex interaction between metabolic dysregulation, inflammatory pathways, and the potential worsening of pre-existing cognitive impairments in schizophrenia. Addressing these multifaceted relationships requires an integrative research approach that bridges psychiatry, endocrinology, and immunology. By adopting a multidimensional perspective, this thesis aims to advance a more comprehensive understanding of schizophrenia as a systemic disorder and to emphasize the clinical relevance of early identification and management of metabolic abnormalities and immune activation. Prompt recognition and treatment of these comorbid conditions may, in turn, create opportunities to attenuate cognitive decline and improve functional outcomes in individuals with schizophrenia.

6. OBJECTIVES

6.1. Study I. – Glucose homeostasis and cognitive functions in schizophrenia: a systematic review and meta-analysis

The aim of this study was to systematically review the existing literature and to perform a meta-analysis to examine the impact of different stages of glucose homeostasis dysregulation -ranging from insulin resistance and prediabetes to manifest diabetes mellitus- on cognitive functions in individuals with schizophrenia.

6.2. Study II. – Association between metabolic syndrome, diabetes mellitus, inflammation and cognitive dysfunctions in schizophrenia: a cross-sectional analysis

In this cross-sectional study, we aimed to comprehensively investigate the impact of metabolic abnormalities, including metabolic syndrome and diabetes mellitus, as well as systemic inflammatory markers -specifically interleukin-6 (IL-6) and C-reactive protein (CRP)- on cognitive functions in individuals with schizophrenia. In addition to examining their overall effects on cognitive performance, we sought to identify which specific metabolic and inflammatory parameters are associated with the severity of cognitive dysfunctions across different cognitive domains. The following hypotheses were formulated: (I) patients with diabetes mellitus (DM) would show the most severe cognitive dysfunctions; (II) fasting blood glucose levels would be inversely associated with cognitive performance; (III) inflammatory markers would be highest in the SCZ + DM and SCZ + MetS groups; and (IV) elevated inflammatory markers would be associated with worse cognitive functions.

7. METHODS

7.1. Study I. – Glucose homeostasis and cognitive functions in schizophrenia: a systematic review and meta-analysis

7.1.1. Methodology and Protocol

This systematic review and meta-analysis was reported based on the recommendation of the PRISMA 2020 guideline, while we followed the guidance of the Cochrane Handbook. The protocol of the study was registered on PROSPERO (registration number CRD42023481556) and we completely adhered to it.

7.1.2. Eligibility Criteria

The meta-analysis incorporated observational studies that investigated associations among schizophrenia spectrum disorders, cognitive impairment, and disturbances in glucose homeostasis. Eligible studies included individuals diagnosed with schizophrenia spectrum disorders presenting with diabetes mellitus or insulin resistance, who were compared to patients without impaired glucose homeostasis. Cognitive performance was required to be evaluated using standardized and validated neuropsychological instruments. Global cognitive functioning was defined as the primary outcome measure, while domain-specific cognitive outcomes were additionally analyzed when sufficient data were available. For the review part, studies examining associations between markers of glucose metabolism and cognitive functions in schizophrenia spectrum disorders were also considered.

7.1.3. Information Sources and Search Strategy

A comprehensive literature search was performed across five electronic databases—PubMed, Embase, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL). The initial search was conducted on November 23, 2023, and subsequently updated on April 2, 2025, ensuring coverage of all eligible studies published up to that date. No database-specific filters or search restrictions were applied, with the sole exception of limiting records to studies involving human participants. To enhance the identification of relevant evidence, supplementary searches of the grey literature were undertaken using Google Scholar, and corresponding authors of included

studies were contacted to obtain additional unpublished data for potential inclusion in the review.

The search strategy was structured around three core conceptual domains and employed the following sets of keywords: (schizophren* OR “psychosis” OR “psychotic” OR “schizophreniform” OR “schizoaffective”) AND (“glucose” OR “insulin” OR “diabetes” OR “HbA1c” OR “HOMA-IR” OR (“blood” AND “sugar”)) AND (cogn* OR “neuropsychological” OR neuropsych*).

7.1.4. Study Selection and Data Extraction

All retrieved records were organized and processed using EndNote X9 reference management software. Duplicate entries were systematically identified and removed prior to screening. Study selection was carried out independently by two reviewers (A.K. and E.V.-T.), who initially screened titles and abstracts, followed by full-text assessment of potentially eligible articles. Any discrepancies arising during the selection process were resolved through consultation with a third reviewer (M.E.). Eligibility was determined in accordance with the PECO (Population, Exposure, Comparator, and Outcomes) framework.

Data extraction from studies meeting the eligibility criteria was conducted independently by two reviewers (A.K. and E.V.-T.) and systematically recorded using a predefined Microsoft Excel data extraction form. When available, the following information was collected: first author and year of publication, study duration and setting, study design, characteristics of the study population, duration of illness, severity of psychopathology assessed using the Positive and Negative Syndrome Scale (PANSS), antipsychotic treatment status and dosage expressed as chlorpromazine equivalents (CPZ mg/day), participants’ educational attainment, cognitive performance measures, and metabolic parameters reported as means with corresponding standard deviations (SD). For studies presenting data exclusively in graphical format, numerical values were extracted using WebPlotDigitizer (46).

7.1.5. Risk of Bias and Quality of Evidence Assessment

Assessment of methodological quality and risk of bias was conducted independently by two reviewers (A.K. and E.V.-T.) using the Quality in Prognostic Studies (QUIPS) tool (47). Any discrepancies in judgments were resolved through consensus. The results of the

risk of bias evaluation were summarized and presented in graphical form, with visualizations generated using the Robvis application (48).

7.1.6. Data Synthesis and Analysis

The included studies were stratified into two comparison groups: individuals with SCZ with versus without DM, and patients with SCZ with versus without IR. Given the heterogeneity of cognitive assessments employed across studies, effect sizes were primarily reported as standardized mean differences (SMDs). In addition, a subgroup analysis was performed within the SCZ with DM group, limited to studies utilizing the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), for which, outcomes were reported as mean differences (MDs).

When studies reported cognitive outcomes in quartiles only, established statistical methods described by Luo et al. and Shi et al. were applied to estimate corresponding means and standard deviations (49,50). In the study by Guo (2011), a global cognitive score was derived by calculating SMDs for individual cognitive subtests and subsequently averaging these values, employing a conservative approach for the estimation of the associated standard error (51).

Meta-analytic results were synthesized using random-effects models and are presented as forest plots with 95% confidence intervals (95% CI). P-values were calculated to evaluate the overall effects of diabetes mellitus and insulin resistance on cognitive functions. All statistical analyses were conducted using R software (version 4.3.2), applying the meta package (version 6.5.0) (52,53).

7.1.7. Classification of cognitive domains

To address potential domain misclassification bias, we applied a predefined manual domain-allocation framework, independent double-coding by expert neuropsychologists with consensus adjudication, targeted sensitivity analyses for ambiguous classifications, and random-effects model. Sensitivity analyses demonstrated that reassignment of a single RBANS subtest between the “Processing Speed” and “Reasoning” domains resulted in a change in the pooled standardized mean difference of ≤ 0.03, remaining well within the meta-analytic confidence intervals. Classification of cognitive domains is presented in ***Table 1.***

Table 1. *Classification of cognitive domains and tests included in the analysis*

Cognitive domains	Tests
Reasoning/ problem-solving	• Wisconsin Card Sorting Test (WCST) • Tower of London (ToL)
Working memory	• Digit span • Computerized test of visuospatial working memory • Letter-Number Sequencing test (LNS)
Speed of processing	• Controlled Oral Word Association test (COWA) • Category instances • Grooved pegboard • Wecshler Adult Intelligence Scale-Revised (WAIS-R) • Digit symbol test • Trail Making Test A/B (TMT) • Verbal fluency • Symbol coding

7.2. Study II. – Association between metabolic syndrome, diabetes mellitus, inflammation and cognitive dysfunctions in schizophrenia: a cross-sectional analysis

7.2.1. Participants and psychiatric assessment

A total of 218 patients diagnosed with schizophrenia (SCZ) were enrolled from three psychiatric institutions in Hungary: National Institute of Psychiatry, Budapest; University of Szeged, Szeged; Bács-Kiskun County Hospital, Kecskemét. Participant recruitment took place between 2012 and 2023. Inclusion criteria comprised a diagnosis of SCZ according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (54), age between 18 and 65 years, and a clinically stable condition under antipsychotic treatment. Exclusion criteria included a history of neurological disorders or head trauma, as well as substance misuse within the preceding six months. Comprehensive clinical documentation and complete medical histories were available for all participants.

Diagnostic assessments were conducted using the Structured Clinical Interview for DSM-5 (55), administered by trained psychiatrists or clinical psychologists. Symptom severity was evaluated with the Positive and Negative Syndrome Scale (PANSS) (56), a clinician-

rated instrument consisting of 30 items scored on a 7-point Likert scale. The PANSS includes three subscales assessing positive symptoms (7 items, e.g., delusions, hallucinatory behavior, conceptual disorganization), negative symptoms (7 items, e.g., blunted affect, emotional withdrawal, passive/apathetic social withdrawal), and general psychopathology (16 items, e.g., anxiety, tension, hostility, depression). Ratings are based on structured interviews and direct clinical observation, with higher scores reflecting more severe psychopathology.

7.2.2. Ethics and Patient Consent

Ethical approval was granted by the National Medical Research Council (ETT-TUKEB 18814, Budapest, Hungary), and the study was conducted in accordance with the Declaration of Helsinki. All subjects gave their written informed consent.

7.2.3. Metabolic status and laboratory measures

Metabolic status was evaluated in all participants. Sixty-two patients met the criteria for metabolic syndrome (MetS) according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), defined by the presence of at least three of the following five components: (I) abdominal obesity, indicated by a waist circumference >102 cm in men or >88 cm in women; (II) hypertriglyceridemia, with triglyceride levels ≥1.7 mmol/L; (III) reduced high-density lipoprotein cholesterol (HDL), <1.03 mmol/L in men and <1.29 mmol/L in women; (IV) elevated blood pressure, defined as systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg; and (V) elevated fasting plasma glucose, ≥5.6 mmol/L (57).

In addition, 53 patients were diagnosed with diabetes mellitus (DM), whereas the remaining patients with MetS did not meet criteria for DM. Accordingly, participants were categorized into three groups: SCZ patients without MetS or DM, SCZ with MetS without DM (SCZ+MetS), and SCZ with DM (SCZ+DM). These groups were characterized using laboratory indicators of lipid metabolism, including triglycerides (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL), as well as measures of glucose regulation, namely fasting blood glucose (FBG) and hemoglobin A1c (HbA1c). C-reactive protein (CRP) and interleukin-6 (IL-6) levels were also assessed.

Diagnoses of MetS and DM were established immediately prior to cognitive and clinical assessments; consequently, none of the patients were receiving pharmacological treatment specifically targeting MetS or DM at the time of testing.

7.2.4. Evaluation of cognitive functions

Cognitive functions were assessed using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (58). The RBANS is a standardized neuropsychological battery that evaluates multiple cognitive domains and can be administered within approximately 20–30 minutes. It comprises 12 subtests yielding five core index scores.

The Attention index, derived from the Digit Span and Coding subtests, reflects sustained attention, processing speed, and working memory. Immediate Memory assesses the encoding and immediate recall of verbal information and is measured using the List Learning and Story Memory subtests. Delayed Memory evaluates the retention and retrieval of information following a delay and is based on performance on the List Recall, List Recognition, Story Recall, and Figure Recall subtests. Visuospatial/Constructional abilities are assessed through the Figure Copy and Line Orientation subtests and reflect visual perception and constructional praxis. The Language index, calculated from the Picture Naming and Semantic Fluency subtests, captures aspects of language production and semantic access.

All subtests were administered by trained examiners in accordance with standardized testing procedures. Raw scores were converted into age-adjusted scaled scores using published normative data, which were subsequently used to compute the five index scores (normative mean = 100, SD = 15). The RBANS has been extensively validated and demonstrates high reliability and sensitivity for the detection of cognitive impairments (58).

7.2.5. Statistical Analysis

Statistical analyses were performed using Spotfire Data Science Workbench version 14.2.0 (TIBCO), JASP version 0.19.1, and the R-package.

After verifying the normality of the data distribution of all variables at the group level using the Shapiro–Wilk test, multivariate analyses of variance (MANOVA) were conducted, with group specified as the between-subjects factor (SCZ, SCZ+MetS, and

SCZ+DM) and RBANS cognitive domains as the within-subjects factors (attention, immediate memory, delayed memory, visuospatial function, and language). The dependent measure comprised RBANS scores across individual cognitive domains. Effect sizes were calculated using eta squared (η^2). For the Bayesian interpretation of p-values, Vovk–Selke p-ratios (VSRs) were calculated. (VSR > 1: evidence against the null hypothesis; VS-ratio > 10: the evidence in favor of the alternative hypothesis is strong; VS-ratio < 1: the null hypothesis is more supported). If the sphericity or homogeneity of variance was violated, Huynh-Feldt or Welch corrections were applied, respectively. Post hoc comparisons were performed using t-tests with Holm correction. Demographics, clinical scales, and laboratory parameters were entered into one-way ANOVA, followed by post-hoc tests. Where appropriate, Cohen's effect size values were also calculated.

To examine the association between cognitive dysfunctions (RBANS domain scores) and laboratory parameters (IL-6, FBG, HbA1c, TG, HDL, and LDL), multiple regression analyses were conducted, with adjustment for age, sex, education, clinical symptom severity, social functioning, chlorpromazine-equivalent antipsychotic dose, and duration of illness. We also calculated the strength and direction of the relationship between cognitive scores and laboratory measures using Pearson's product-moment coefficients with VSR for Bayesian statistics. To provide context for subgroup-level precision, we report the minimum detectable within-group correlations (two-sided $\alpha = 0.05$, 80% power): $r = 0.38$ (SCZ + DM, $n = 53$), $r = 0.35$ (SCZ+MetS, $n = 62$), $r = 0.27$ (SCZ, $n = 103$).

8. RESULTS

8.1. Study I: Glucose homeostasis and cognitive functions in schizophrenia: a systematic review and meta-analysis

8.1.1. Study Search and Selection

The systematic literature search yielded 11,789 records. Following the removal of duplicate entries, 6,806 articles were screened based on titles and abstracts. Of these, 107 publications underwent full-text evaluation, resulting in the inclusion of 26 studies in the qualitative synthesis (51, 59-83). Among the included articles, nine studies were eligible for quantitative synthesis and were incorporated into the meta-analysis (51, 59-64, 76, 83). Specifically, seven studies examined cognitive functions in patients with schizophrenia and comorbid diabetes, while three studies investigated the impact of insulin resistance on cognitive performance in individuals with schizophrenia.

The meta-analysis focusing on schizophrenia with comorbid diabetes comprised a total of 3,214 participants, including 563 patients with diabetes and 2,651 schizophrenia patients without diabetes serving as controls. The meta-analysis addressing insulin resistance included 552 participants, of whom 163 were identified as having insulin resistance, while 389 participants constituted the control group. The study selection and screening process is summarized in a PRISMA flow diagram (***Figure 1***). Baseline characteristics of the enrolled studies are detailed in **Table 2.**

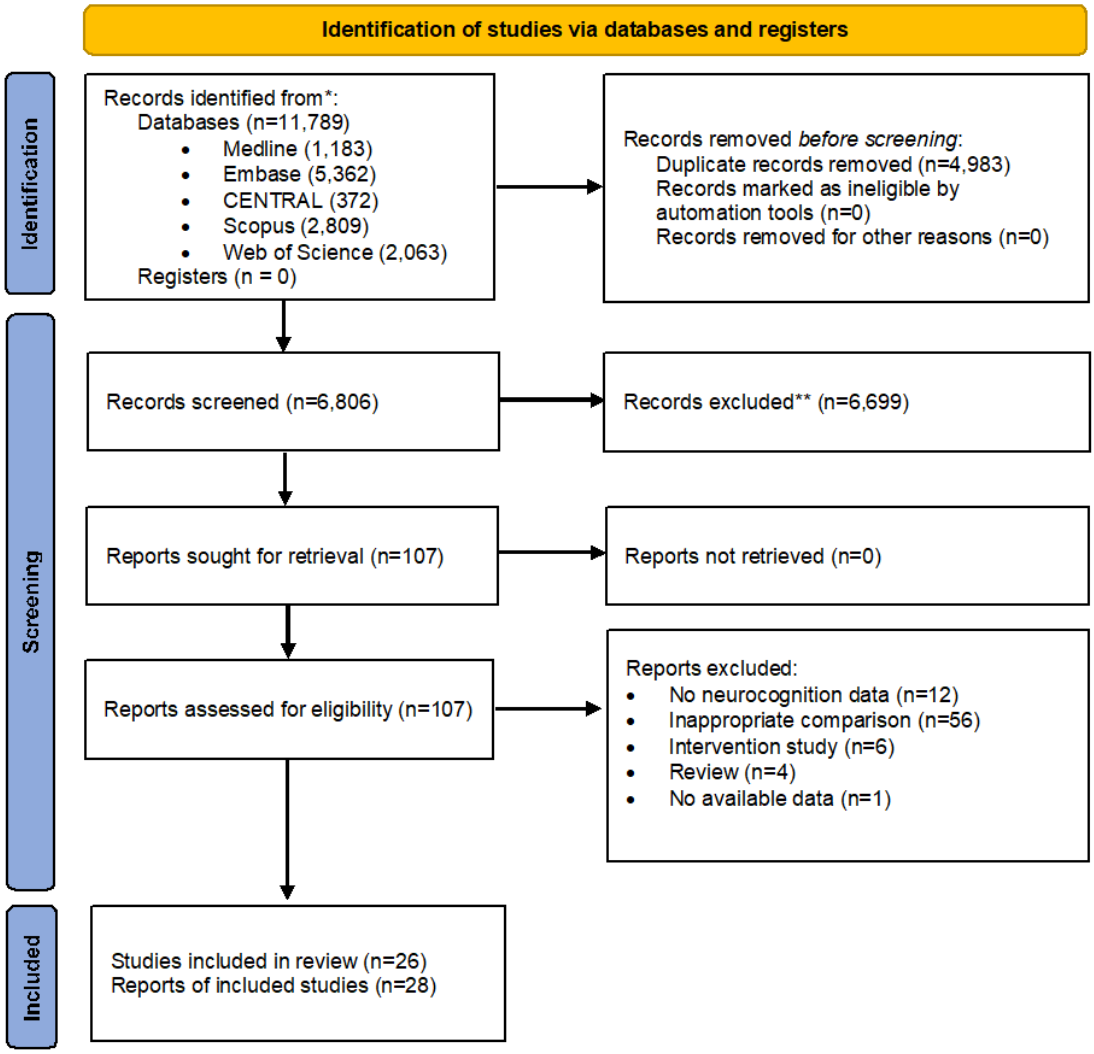


Figure 1. *PRISMA 2020 flowchart showing the study selection process*

Table 2. *Basic characteristics of studies included*

	Author (year)	Study site	Study design	Number of analyzed patients Exposed (female %)	Number of analyzed patients Unexposed (female %)	Total number of analyzed patients	Age (year) mean (SD) Exposed/ unexposed	Exposed patients (exposure type) % of total	PANSS Mean/SD Exposed	Educational Years Exposed/unexposed Mean (SD)	Duration of illness (Y/M) Mean/SD Exposed	Cognitive battery	Treatment status (CPZ EQ.mg/Day) Exposed Mean/SD
1	Dickinson et. al. 2008	USA	cross-sectional	97 (42)	575 (32)	672	48.1(8.9)/40.5(9.7)	14.4 (D)	NA	NA	NA	RBANS	NA
2	Guo et. al. 2011	China	cross-sectional	78 (46.2)	118 (44.1)	196	44.6(7.6)/43.0(7.2)	39.8 (D)	63/12.8	12.5(2.7)/12.2(2.9)	8.2/3.0(Y)	WAIS-R digit symbol, WAIS-R digit span TMT-A, TMT-B, WCST-128, WMS-R (visual reproduction)	NA
3	Han et. al. 2013	China	case-control	55 (38.2)	127 (35.4)	182	54.4(8.1)/53.3(8.3)	30.22 (D)	59.2/15.0	9.8(2.5)/9.7(2.4)	11.6/9.3 (Y)	RBANS	385.7/257.1
4.1	Zhang et. al. 2015	China	cross-sectional	67 (0)	125 (0)	192	52.1(8.8)/50.9(8.1)	34.9 (D)	60.6/13.9	9.1(2.1)/9.7(2.4)	27.0/9.8 (Y)	RBANS	410.8/188.8
4.2	Zhang et. al. 2015	China	cross-sectional	34 (100)	37 (100)	71	53.8(6.8)/51.2(6.4)	47.89 (D)	62.7/18.6	9.7(1.8)/9.9(2.4)	25.2/9.6 (Y)	RBANS	438.2/270.0
5	Li et. Al. 2021	China	cross-sectional	54 (26)	418 (11.2)	472	52.72(8.31)/46.5(8.69)	11.44 (D)	57.87/12.98	9.35(2.6)/8.71(2.37)	28.26/8.22 (Y)	RBANS	589.50/782.09

6	Takayanagi et. al. 2012	USA	cross-sectional	161 (31)	1128 (24)	1289	45.9(8.7)/39.6(11.1)	12.49 (D)	71.4/15.2	12.0(2.0)/12.2(2.2)	NA	controlled oral word, category instances, grooved pegboard, WAIS-R digit symbol, WCST-64, WISC-mazes, Hopkins verbal learning, comp. test of visuospatial working memory, letter-number seq, CPT, facial emotion discrimination test	NA
7	Lin et. al. 2020	China	cross-sectional	73 (39.73)	120 (42.5)	193	49.26(8.57)/51.05(6.8)	37.82 (IR)	75.60/14.72	11.15(2.73)/10.73(2.38)	289.05/123.05 (M)	RBANS	334.52/203.01
8	Kowalski et. al. 2023	Poland	cross-sectional	100 (40)	55 (45.5)	155	43.7(12.0)/42.3(15.0)	64.5 (SCH)	N: 16.0/9.1	NA	18.8/12.3 (Y)	RBANS	608/373.5
9	Liu et. al. 2018	China	cross-sectional	80 (NA)	70 (NA)	150	NA	53.3 (DN-SCH)	NA	NA	NA	MCCB	Drug naïve
10	Montalvo et. al. 2020	Spain	cross-sectional	60 (35)	50 (44)	110	24.5(5.4)/23.8(4.8)	54.5 (SCH-SP)	NA	11.3(2.8)/13.4(2.7)	NA	MCCB	371.1/334.0
11	Qi Tao et. al. 2020	China	cross-sectional	90 (51.1)	70 (54.3)	160	21.5(7.7)/23.4(5.4)	56.3 (DN-SCH)	84.2/12.7	10.4(2.6)/11.1(2.4)	5.9/6.3 (M)	MCCB	Drug naive
12	Lis et. al. 2020	Poland	cross-sectional	35 (48.6)	65 (64.6)	100	34.2(12.5)	35.0 (SCH-SP)	P:15/5.3, N:19.3/8.0	13.7(3.0)	NA	RBANS	347.2/174.2
13	Pang et. al. 2023	China	cross-sectional	142 (51)	140 (49)	282	25.0(4.0)/26.0(4.0)	50.4 (DN-SCH)	80.0/6.0	12.0(3.0)	6.0/4.0 (M)	MCCB	Drug naive
14	Peng et. al. 2021	China	cross-sectional	172 (56)	-	172	24.32(6.69)	100 (DN-SCH)	97.01/15.68	10.95(2.61)	15.03/12.68 (M)	MCCB	Drug naive
15	Soontornniyomkij et. al. 2019	USA	cross-sectional	145 (46)	140 (54)	285	48.3(10.1)/48.7(11.2)	50.9 (SCH)	NA	12.4(2.3)/14.5(2.3)	25.0/11.1 (Y)	TICS-M, D-KEFS	NA
16	Tang et. al. 2022	USA	cross-sectional	245 (33)	165 (45)	410	32.5(10.4)/32.0(10.4)	59.8 (SCH)	NA	NA	NA	MCCB	NA
17	Nandeesha et. a. 2020	India	cross-sectional	200 (44)	169 (36.1)	369	35.66(9.44)/36.53(8.34)	54.2 (DN-SCH)	29.18/12.81	NA	3.5 (Y)	ACE-III	Drug naive

18	Ali et. al. 2020	Egypt	cross-sectional	40 (NA)	20(NA)	60	NA	66.7 (SCH)	NA	NA	NA	TMT-A, TMT-B, WMS-R	NA
19.1	John et. al. 2023	Australia	cross-sectional	17 (41.2)	123(26.8)	140	35.71(10.42)/31.51(10.4)	12.14 (D)	NA	NA	11.9/7.35 (Y)	BACS	NA
19.2	John et. al. 2023	Australia	cross-sectional	47 (36.2)	123(26.8)	170	34.43(9.66)/31.51(10.4)	27.65 (IR)	NA	NA	10.34/7.83 (Y)	BACS	NA
20	Zhang et. al. 2020	China	cross-sectional	39 (59)	30 (56.7)	69	26.5(6.3)/27.5(7.9)	56.5 (DN-SCH)	NA	12.4(3.1)	23.3/25.1 (M)	MCCB	NA
21	Jakobsen et. al. 2018	Denmark	cohort	428 (55)	-	428	38.6(12.4)	100 (SCH-SP)	NA	NA	NA	BACS	473.5/397.9
22	Salaj et. al. 2014	NA	NA	27 (44)	-	27	23.9(6.0)	100 (DN-SCH)	NA	9.6(2.8)	NA	WCST	Drug naive
23	Chen et. al. 2020	China	cross-sectional	158 (50.6)	-	158	NA	100 (SCH)	NA	NA	NA	MCCB	NA
24	Grover et. al. 2019	India	cross-sectional	121 (45.5)	-	121	33.89(9.86)	100 (SCH)	59.28/17.71	13.37(3.05)	NA	TMT-A, TMT-B, COWA, Stroop, AVLT, Tower of London	NA
25	Zhang et. al 2017	China	cross-sectional	216 (47)	-	216	28.71(3.72)	100 (SCH)	NA	9.83(1.97)	NA	RBANS	NA
26	Yuan et. al. 2025	China	cross-sectional	43(58.1)	146(56.8)	189	NA	22.75 (IR)	82.79/15.90	NA	NA	MCCB	Drug naive

Abbreviations: *D: schizophrenia with diabetes; IR: schizophrenia with insulin resistance; SCH: schizophrenia; DN-SCH: drug naive or drug free schizophrenia; SCH-SP: schizophrenia spectrum; P/N: PANSS negative or positive subscore (when PANSS total score is unavailable); NA: not applicable; M: months; Y: years; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; AVLT: Auditory Verbal Learning Test; COWA: Controlled Oral Word Association Test; TMT-A/B: Trail Making Test-A/B; MCCB: MATRICS Consensus Cognitive Battery; BACS: The Brief Assessment of Cognition in Schizophrenia; WMS-R: The Wechsler Memory Scale; ACE-III: Addenbrooke's cognitive examination; TICS-M: The Modified Telephone Interview for Cognitive Status; D-KEFS: The Delis–Kaplan Executive Function System Test; CPT: Continuous Performance Test; WAIS-R: Wechsler Adult Intelligence Scale; WCST-64: Wisconsin Card Sorting Test-64; WISC: Wechsler Intelligence Scale for Children; WMS-R: The Wechsler Memory Scale-Revised*

8.1.2. Diabetes mellitus and cognition

Regarding global cognitive performance, six of the seven included studies demonstrated a consistent pattern indicating that the coexistence of diabetes and schizophrenia is associated with greater cognitive impairment. Although the pooled effect size did not reach statistical significance, the direction of effects across studies suggested a clear trend: ($n = 3214$; SMD=−0.26; 95% CI −0.59 to 0.08; $P = 0.1087$; I^2=80% [95% CI 59–90%]). (***Figure 2***)

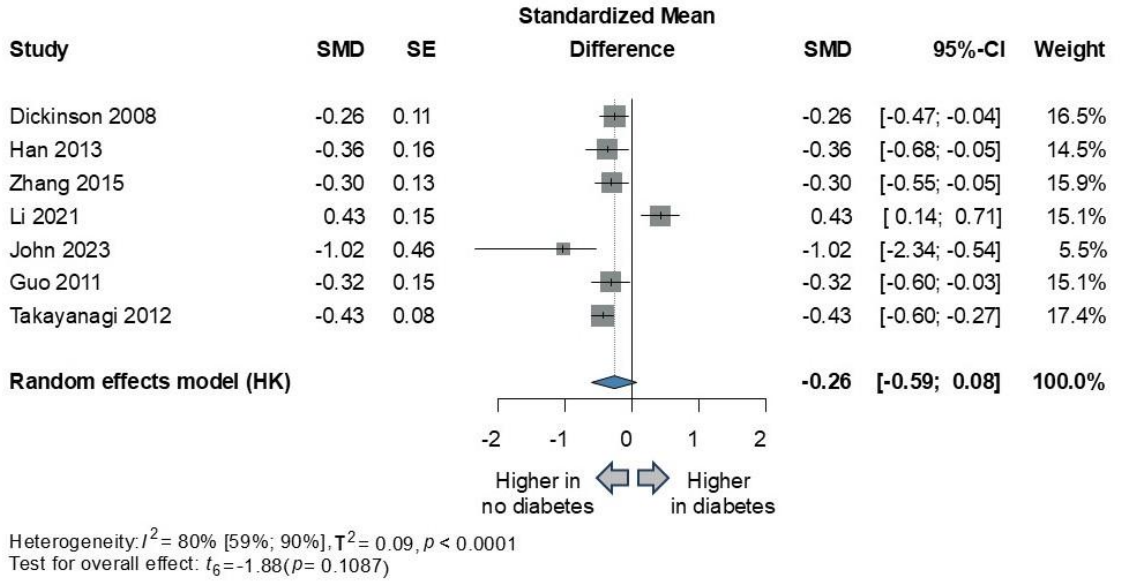


Figure 2. *Comparison of global cognitive functions in schizophrenia with and without diabetes. SMD standardized mean difference, SE standard error, CI confidence interval, HK Hartung-Knapp adjustment.*

8.1.3. Comparison of cognitive functions by different cognitive domains in schizophrenia with and without diabetes

The following results were obtained for each cognitive domain: reasoning (3 studies; SMD= -0.40; 95% CI, -0.58 to -0.22; P=0.0109; I^2=0% [95% CI, 0% to 90%]); working memory (4 studies; SMD=-0.17; 95% CI, -0.47 to 0.14; P=0.1824; I^2=54% [95% CI, 0% to 85%]); processing speed (4 studies; SMD=-0.43; 95% CI, -0.52 to -0.35; P=0.0005; I^2=0% [95% CI, 0% to 85%]). (***Figure 3***)

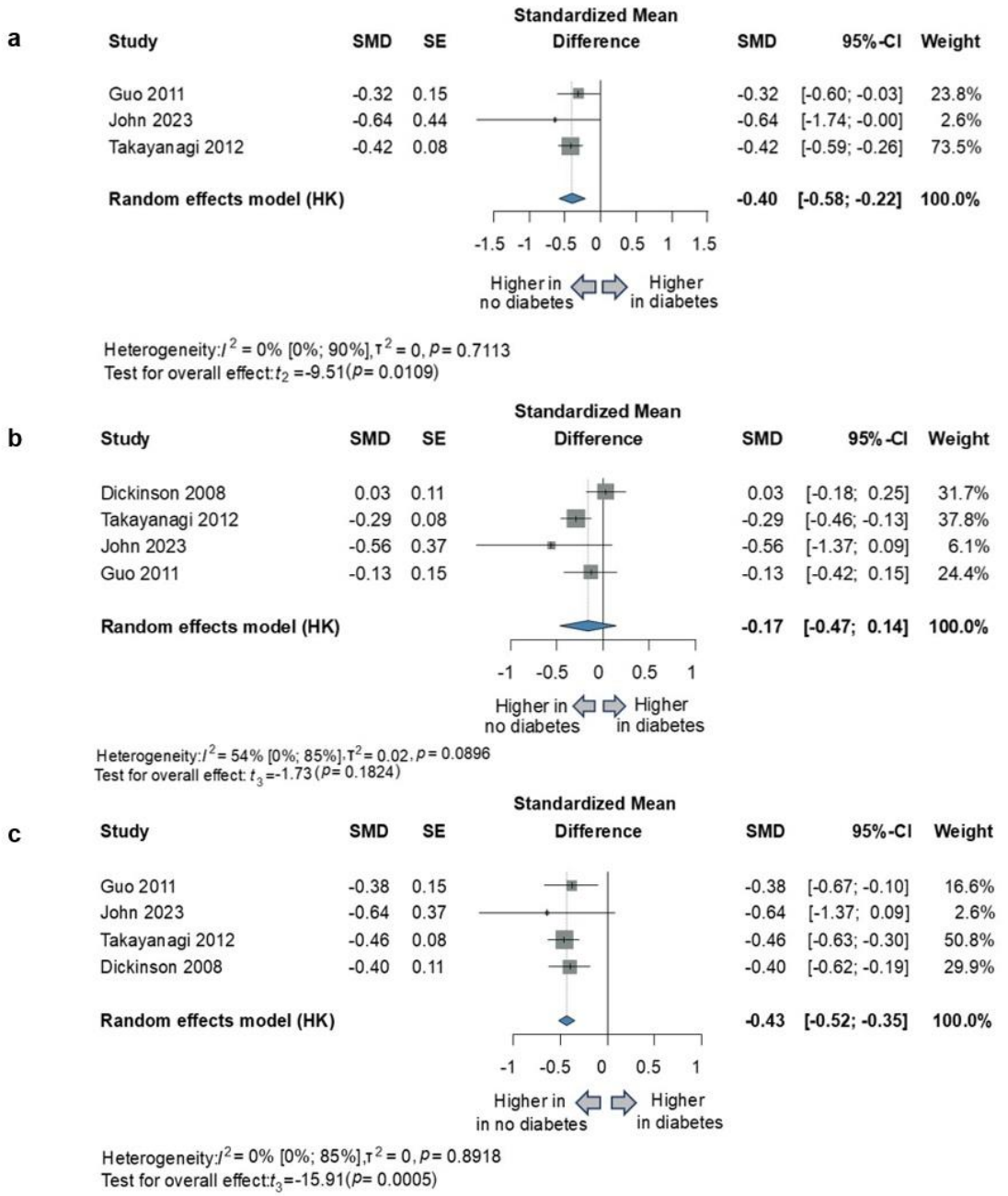


Figure 3. *Comparison of cognitive functions by different cognitive domains in schizophrenia with and without diabetes.* ***A:*** *reasoning/problem-solving* ***B:*** *working memory* ***C:*** *processing speed. Abbreviations: SMD: standardized mean difference; SE: standard error; CI: confidence interval; HK: Hartung-Knapp adjustment*

8.1.4. Comparison of cognitive functions in schizophrenia with diabetes versus without diabetes in studies where cognitive functions were assessed using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).

Studies that employed the RBANS cognitive test battery for the assessment of cognitive functions were additionally examined in a separate analysis, yielding the following results: global cognition (4 studies; MD=-1.90; 95% CI, -10.71 to 6.91; P=0.542; I^2=86% [95% CI, 64% to 94%]); attention (4 studies; MD=-2.33; 95% CI, -13.58 to 8.92; P=0.557; I^2=90% [95% CI, 76% to 95%]); delayed memory (4 studies; MD=0.75; 95% CI, -10.65 to 12.16; P=0.847; I^2=87% [95% CI, 69% to 95%]); immediate memory (4 studies; MD=-3.66; 95% CI, -10.39 to 3.08; P=0.183; I^2=70% [95% CI, 14% to 90%]); language (4 studies; MD=0.06; 95% CI, -5.70 to 5.82; P=0.976; I^2=67% [95% CI, 4% to 89%]); and visuospatial skills (4 studies; MD=-3.35; 95% CI, -12.40 to 5.69; P=0.323; I^2=79% [95% CI, 45% to 92%]). ***(Figures 4 and 5)***

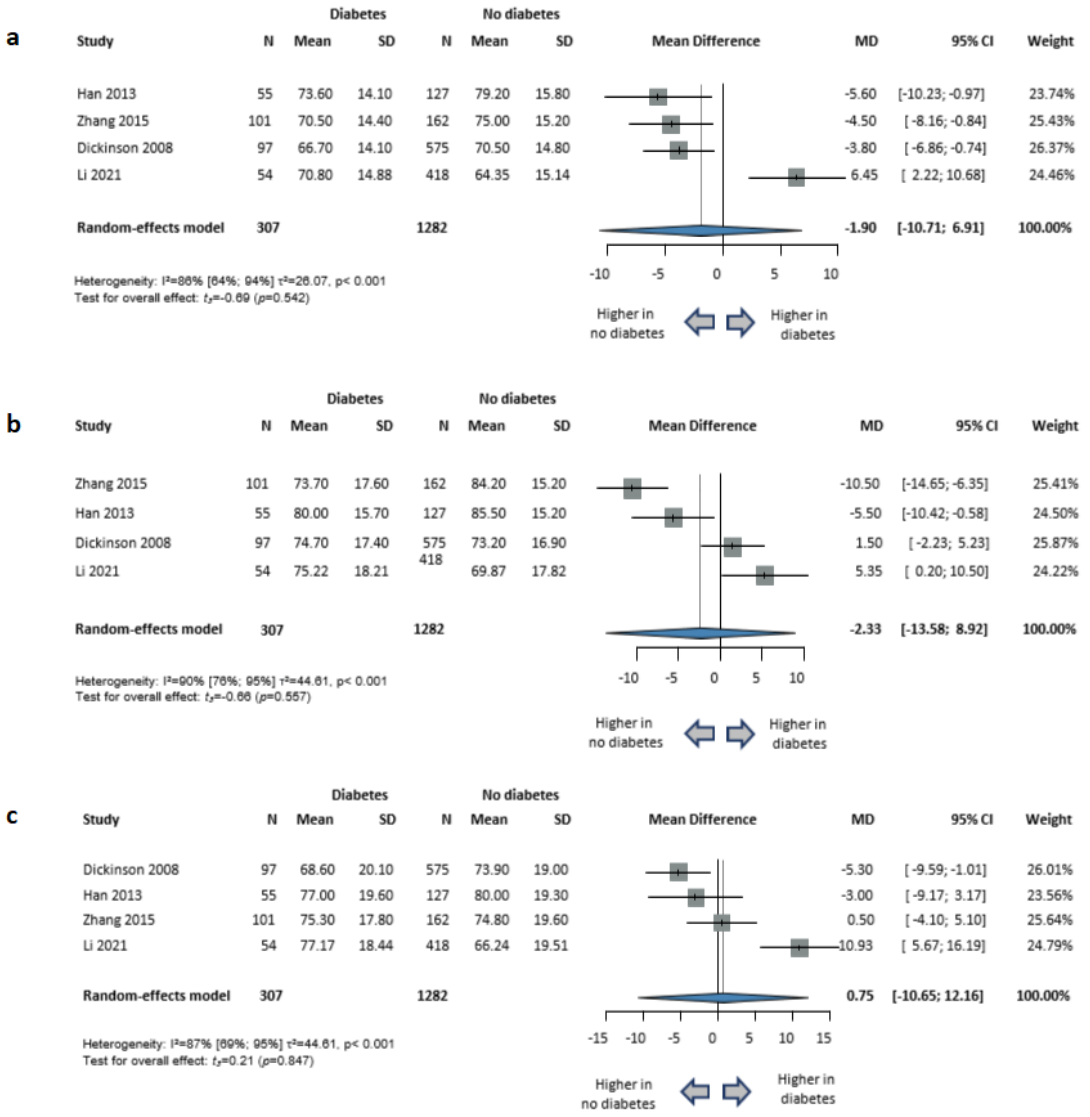


Figure 4. *Comparison of cognitive functions in schizophrenia with diabetes versus without diabetes in studies where cognitive functions were assessed using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).* ***A:*** *global cognition;* ***B:*** *attention;* ***C:*** *delayed memory. Abbreviations****:*** *CI: confidence interval; SD: standard deviation; MD: mean difference; N: sample size*

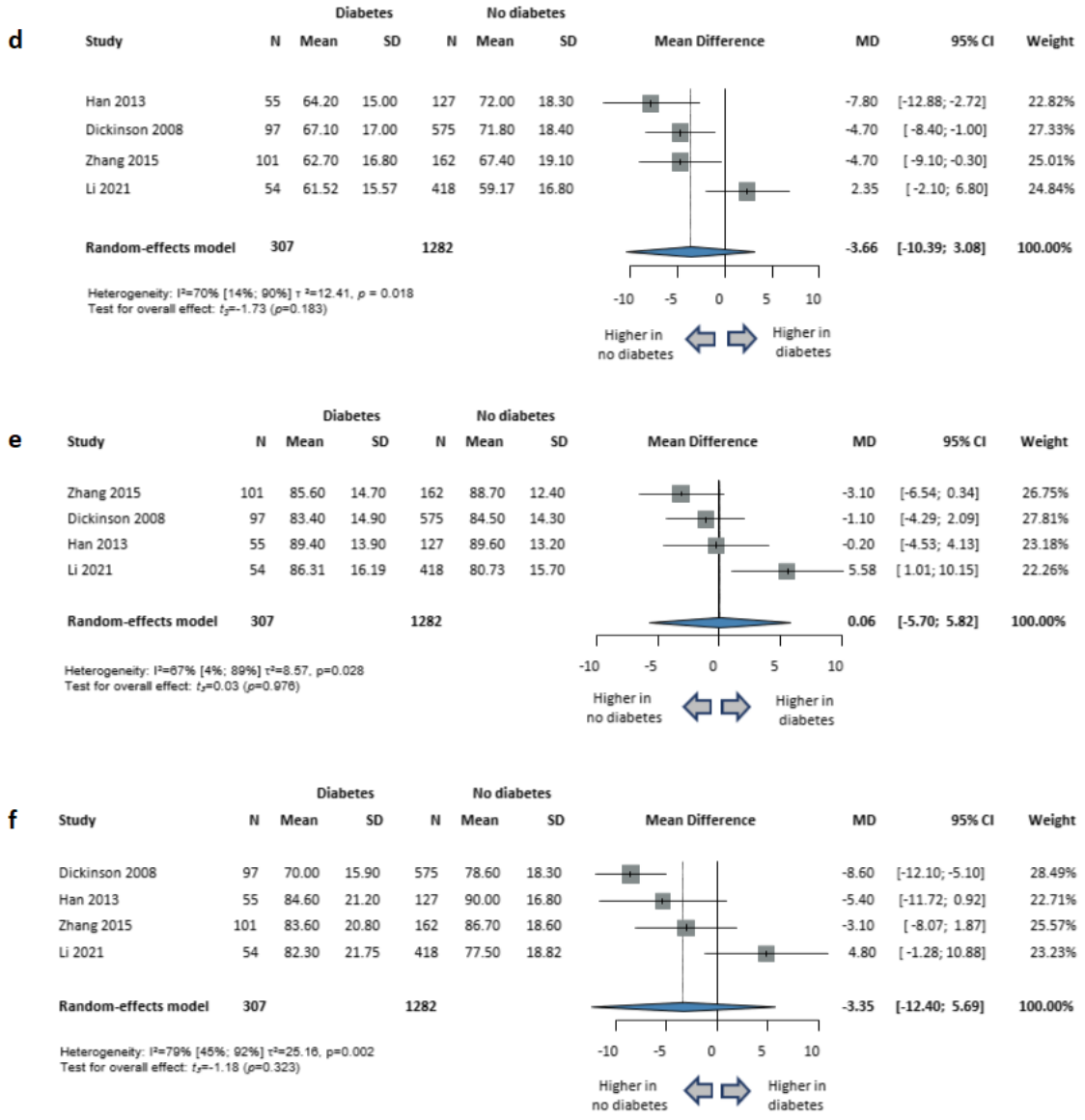


Figure 5. *Comparison of cognitive functions in schizophrenia with diabetes versus without diabetes in studies where cognitive functions were assessed using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).* ***D****: immediate memory;* ***E:*** *language;* ***F****: visuospatial. Abbreviations****:*** *CI: confidence interval; SD: standard deviation; MD: mean difference; N: sample size*

8.1.5. Insulin resistance and cognition

The three studies examining the effect of insulin resistance on cognitive functions yielded conflicting results. (n=552; SMD=-0.12; 95% CI, -0.91 to 0.68; P=0.5890; I^2=70% [95% CI, 0% to 91%]) ***(Figure 6)***

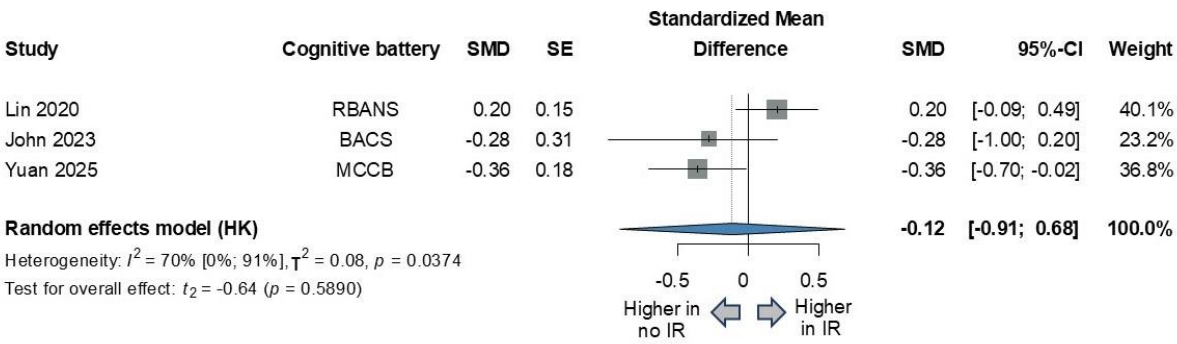


Figure 6. *Comparison of global cognitive functions in schizophrenia with and without insulin resistance. Abbreviations: SMD: standardized mean difference; SE: standard error; CI: confidence interval; IR: insulin resistance; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; BACS: The Brief Assessment of Cognition in Schizophrenia; MCCB: MATRICS Consensus Cognitive Battery*

8.1.6. Correlation between glucose homeostasis parameters and cognitive functions

Among the 26 studies included in the review, 21 provided data on correlations or associations between parameters of glucose metabolism and cognitive performance: 11 studies on fasting glucose, 5 on HbA1c, 7 on HOMA-IR, and 5 on fasting insulin. Significant negative correlations or associations are shown in ***Table 3.*** Among the included studies, only one reported a significant positive correlation between fasting glucose levels and performance on both the Continuous Performance Test (CPT) and the digit sequencing test. (77). Due to different types of correlation coefficients and lack of raw data, we were unable to perform a meta-analysis of these studies.

Table 3. *Summary of significant negative correlations or associations between glucose metabolism parameters and cognitive functions.*

A	B	C	D
HbA1c	Montalvo et al. 2020	processing speed, reasoning/problem-solving visual learning, attention	MCCB
	Tang et al. 2022	visual and verbal learning	MCCB
	Jakobsen et al. 2018	global cognition	BACS
HOMA-IR	Soontornniyomkij et al. 2019	global cognition	TICS-M, D-KEFS
	Qi Tao et al. 2020	global cognition	MCCB
	Liu Y. F. et al. 2018	attention, visual and verbal learning	MCCB
Insulin	Lis M. et al. 2020	language	RBANS
	Liu Y. F. et al. 2018	attention, visual and verbal learning	MCCB
Glucose	Nandeesha et al. 2020	memory, fluency, global cognition	ACE-III
	Grover et al. 2019	attention, executive functions, verbal memory	TMT-A, TMT-B, COWA, Stroop, AVLT, ToL
	Zhang et al. 2017	global cognition	RBANS
	Salaj et al. 2014	executive functions	WCST
	Chen et al. 2020	fluency, working memory	MCCB
	Ali D. et al. 2020	processing speed, memory	TMT-A, TMT-B, WMS-R

A: *glucose metabolism parameter;* ***B:*** *Study (author, year);* ***C:*** *cognitive domains with significant negative correlation;* ***D:*** *cognitive battery, test used in the study. Abbreviations: HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; AVLT: Auditory Verbal Learning Test; COWA: Controlled Oral Word Association Test; TMT-A/B: Trail Making Test-A/B; MCCB: MATRICS Consensus Cognitive Battery; BACS: The Brief Assessment of Cognition in Schizophrenia; TICS-M: The Modified Telephone Interview for Cognitive Status; D-KEFS: The Delis–Kaplan Executive Function System Test; CPT: Continuous Performance Test; WAIS-R: Wechsler Adult Intelligence Scale; WCST: Wisconsin Card Sorting Test; ToL: Tower of London; ACE-III: Addenbrooke's cognitive examination; WMS-R: The Wechsler Memory Scale-Revised*

8.1.7. Risk of Bias Assessment

The assessment of risk of bias across the included studies indicated that eight investigations were classified as having a low risk of bias, while one study was judged to be at moderate risk. The overall moderate risk of bias was primarily attributable to limited reporting on confounding variables, prognostic factor assessment, outcome measurement procedures, study attrition, and aspects of statistical analysis and reporting. (***Figure 7***)

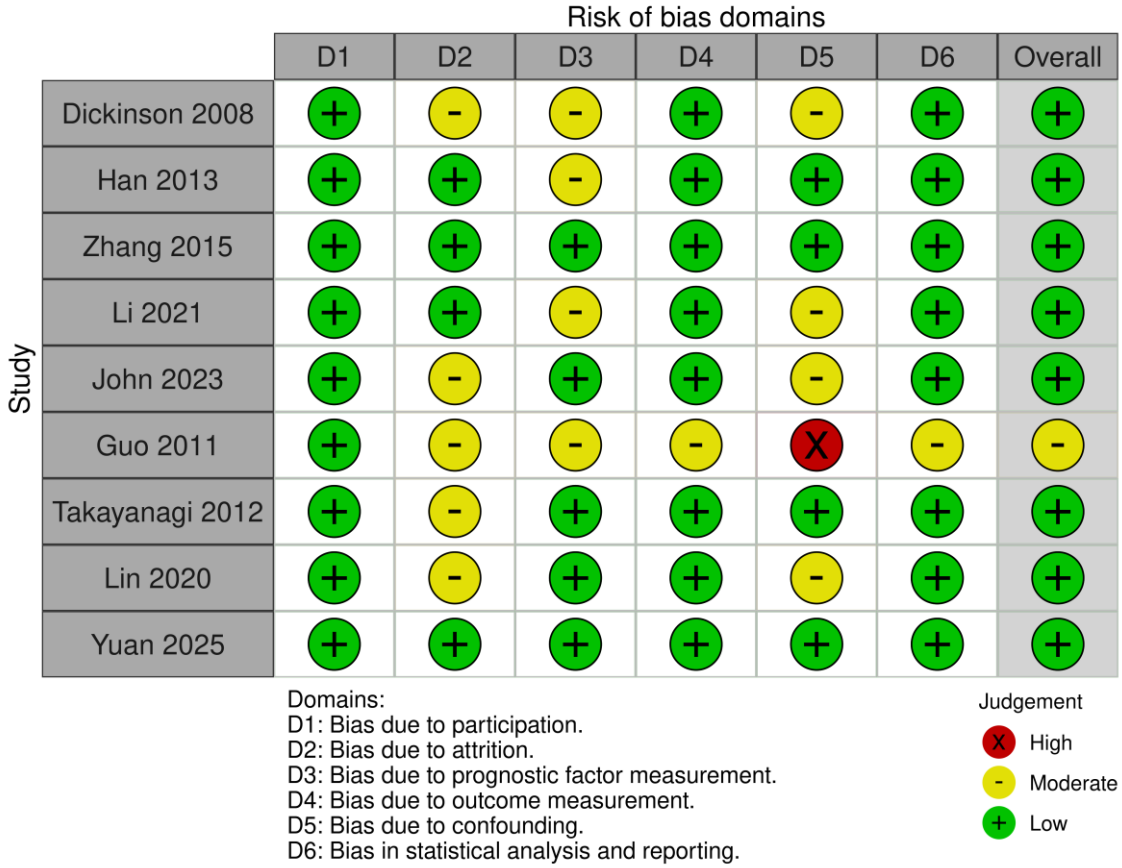


Figure 7. *Risk of bias assessment across included studies.*

8.2. Study II: Association between metabolic syndrome, diabetes mellitus, inflammation and cognitive dysfunctions in schizophrenia: a cross-sectional analysis

8.2.1. Demographics and clinical characteristics

We found no significant differences in age, education, sex, PANSS, illness duration, or general functioning. Patients with SCZ+MetS and SCZ+DM exhibited higher BMIs and WHRs than those with SCZ, but there was no significant difference between SCZ+MetS and SCZ+DM. Demographic and clinical characteristics of the three SCZ groups (SCZ, SCZ+MetS, and SCZ+DM) are summarized in ***Table 4.***

Table 4. *Demographic and clinical characteristics*

	SCZ (n=103)	SCZ+MetS (n=62)	SCZ+DM (n=53)
Age (years)	43.3 ± 11.3	43.4 ± 11.5	44.0 ± 10.0
Sex (male/female)	69/34	41/21	37/16
Education (years)	11.7 ± 3.2	11.0 ± 2.8	12.2 ± 3.3
Illness duration (years)	14.8 ± 4.7	15.4 ± 5.2	16.1 ± 4.1
BMI	23.7 ± 3.2	33.8 ± 4.2*	34.5 ± 4.5*
Waist-to-hip ratio	0.7 ± 0.1	1.0 ± 0.07*	1.0 ± 0.08*
PANSS-P	21.5 ± 7.2	21.9 ± 9.0	22.1 ± 8.0
PANSS-N	24.3 ± 6.9	24.8 ± 8.7	25.7 ± 7.2
PANSS-G	49.5 ± 10.3	49.4 ± 11.3	50.5 ± 10.6
PSP	50.8 ± 8.6	53.2 ± 7.4	51.2 ± 8.9
Antipsychotic dose (CPZ-equivalent, mg/day)	409.7 ± 160.3	401.1 ± 159.3	443.9 ± 187.7
Antipsychotic type	olanzapine (n=35) risperidone/paliperidone (n=39) clozapine (n=11) aripiprazole (n=9) quetiapine (n=8) haloperidol (n=1)	olanzapine (n=20) risperidone (n=14) quetiapine (n=10) aripiprazole (n=11) flupentixol (n=5) clozapine (n=2)	olanzapine (n=12) risperidone/paliperidone (n=23) quetiapine (n=10) aripiprazole (n=7) zuclopenthixol (n=1)

Data are mean (± standard deviation) except for sex and antipsychotic type. SCZ-schizophrenia, MetS – metabolic syndrome, DM – diabetes mellitus, BMI – body mass index, PANSS – Positive and Negative Syndrome Scale, P – positive symptoms, N – negative symptoms, G – general symptoms, PSP – Personal and Social Performance scale, CPZ – chlorpromazine

**SCZ < SCZ+MetS = SCZ+DM, p < 0.01, one-way ANOVA followed by Holm-corrected t-tests*

8.2.2. Laboratory measures

Patients with SCZ+MetS and SCZ+DM displayed increased TG, LDL, and lower HDL than patients with SCZ, but there was no significant difference between SCZ+MetS and SCZ+DM. In terms of FBG, the highest level was measured in SCZ+DM, followed by SCZ+MetS and SCZ. HbA1c was significantly elevated in SCZ+DM relative to SCZ+MetS and SCZ. IL-6 was significantly elevated in SCZ+DM relative to SCZ and SCZ+MetS, with no significant difference between SCZ and SCZ+MetS. Finally, there were no significant between-group differences in CRP. Laboratory measures are shown in ***Table 5***.

Table 5. *Laboratory measures*

	SCZ (n=103)	SCZ+MetS (n=62)	SCZ+DM (n=53)	Group comparisons
IL-6 (pg/mL)	8.3 ± 3.7	9.7 ± 4.5	13.8 ± 4.6	• SCZ < MetS, $p = 0.03$, $d = 0.35$ • SCZ < DM, $p < 0.001$, $d = 1.4$ • DM > MetS, p = 0.001, d = 0.9
CRP (mg/mL)	1.8 ± 1.0	1.8 ± 0.9	2.0 ± 1.2	• SCZ = MetS, $p = 1$, $d = 0$ • SCZ = DM, $p = 0.3$, $d = 0.19$ • DM = MetS, p = 0.3, d = 0.19
TG (mmol/L)	1.0 ± 0.4	2.1 ± 0.9	2.4 ± 1.0	• SCZ < MetS, $p < 0.001$, $d = 1.7$ • SCZ < DM, $p < 0.001$, $d = 2.1$ • DM = MetS, p=0.1, d = 0.32
HDL (mmol/L)	1.8 ± 0.5	1.2 ± 0.4	1.2 ± 0.5	• SCZ > MetS, $p < 0.001$, $d = 1.3$ • SCZ > DM, $p < 0.001$, $d = 1.2$ • DM = MetS, $p = 1$, $d = 0$
LDL (mmol/L)	2.4 ± 0.7	2.8 ± 0.8	2.7 ± 0.8	• SCZ < MetS, $p < 0.001$, $d = 0.54$ • SCZ < DM, $p = 0.02$, $d = 0.41$ • DM = MetS, $p = 0.5$, $d = 0.13$
FBG (mmol/L)	4.0 ± 0.8	5.6 ± 1.2	7.6 ± 1.7	• SCZ < MetS, $p < 0.001$, $d = 1.7$ • SCZ < DM, $p < 0.001$, $d = 3.0$ • DM > MetS, $p < 0.001$, $d = 1.4$
HbA1c (%)	4.9 1.3	5.4 ± 1.5	7.1 ± 1.6	• SCZ < MetS, $p = 0.03$, $d = 0.36$ • *SCZ* < DM, $p < 0.001$, $d = 1.6$ • DM > MetS, $p < 0.001$, d = 1.1

Data are mean (± standard deviation) except sex and antipsychotic type. SCZ-schizophrenia, MetS – metabolic syndrome, DM – diabetes mellitus, IL-6 – interleukin 6, CRP – C-reactive protein, TG – triglyceride, HDL – High Density Lipoprotein, LDL – Low Density Lipoprotein, FBG – fasting blood glucose, HbA1c – Hemoglobin A1c

Group comparisons: one-way ANOVA followed by Holm-corrected t-tests, $p < 0.05$; The "<" and ">" signs denote significant differences between the groups, whereas the "=" sign indicates no significant between-group difference.

8.2.3. Cognitive performance

The MANOVA conducted on the RBANS domain scores indicated a significant main effect of group ($F(2,115) = 18.0$, $p < 0.001$, $\eta^2 = 0.03$, $VSR = 372010.54$) and RBANS domain scores ($F(3.9, 838.3) = 3.47$, $p < 0.05$, $\eta^2 = 0.01$, $VSR = 8.97$). The two-way interaction between the group and RBANS domain scores was also significant ($F(7.8, 838.3) = 5.80$, $p < 0.001$, $\eta^2 = 0.04$, $VSR = 58250.54$). Post-hoc tests revealed that patients with SCZ+DM scored lower on the attention domain than those with SCZ ($t = 6.0$, $SE = 2.25$, $p_{Holm} < 0.001$, $d = 1.0$) and SCZ+MetS ($t = 4.78$, $SE = 2.49$, $p_{Holm} < 0.001$, $d = 0.98$). However, no significant difference was observed between SCZ and SCZ+MetS ($p_{Holm} = 1$, $d = 0.11$). Similar results were obtained for delayed memory (SCZ+DM < SCZ, $t = 5.39$, $SE = 2.50$, $p_{Holm} < 0.001$; $d = 0.97$; SCZ+DM < SCZ+MetS, $t = 3.72$, $SE = 2.49$, $p_{Holm} < 0.05$, $d = 0.70$; SCZ = SCZ+MetS, $p_{Holm} = 1$, $d = 0.2$). No significant between-group differences were observed for immediate memory, visuospatial functions, and language ($ps_{Holm} > 0.05$). The RBANS results are shown in ***Table 6***.

Table 6. *Cognitive performance*

RBANS	SCZ (n=103)	SCZ+MetS (n=62)	SCZ+DM (n=53)
Attention	80.6 ± 14.5	79.0 ± 13.0	67.2 ± 10.8*
Immediate memory	74.8 ± 11.7	76.2 ± 11.6	74.4 ± 10.6
Delayed memory	77.5 ± 13.3	74.7 ± 15.3	65.4 ± 10.5*
Visuospatial	75.0 ± 12.0	75.1 ± 10.9	71.2 ± 11.3
Language	75.4 ± 11.4	76.8 ± 12.0	77.4 ± 12.4

Data are mean (± standard deviation). SCZ- schizophrenia, MetS – metabolic syndrome, DM – diabetes mellitus, RBANS - Repeatable Battery for the Assessment of Neuropsychological Status

**SCZ = SCZ+MetS > SCZ+DM, p < 0.01, one-way ANOVA followed by Holm-corrected t-tests*

8.2.4. Laboratory measures and cognitive performance

In the whole sample, multiple regression analyses identified IL-6 as the sole significant predictor of the RBANS attention score. (β = -0.37, t = -5.34, $p < 0.001$, R^2 = 0.19, *VSR* = 94017.2). For the RBANS delayed memory score, there were two predictors: IL-6 (β = -0.16, t = -2.11, $p < 0.05$, R^2 = 0.08, *VSR* = 3.1) and FBG (β = -0.22, t = -2.58, $p < 0.05$, R^2 = 0.08, *VSR* = 7.6). For the remaining RBANS domain scores (immediate memory, language, and visuospatial functions), we found no significant predictors from the laboratory measures (ps > 0.2).

In the entire sample, numerous significant correlations were observed between laboratory parameters and the RBANS attention scores: IL-6 (r = -0.42, $p < 0.001$, *VSR* = 1.1x 10^8), FBG (r = -0.27, $p < 0.001$, *VSR* = 520.8), TG (r = -0.19, $p < 0.05$, *VSR* = 13.5), and HDL (r = 0.20, $p < 0.05$, *VSR* = 17.7). However, in SCZ+MetS, the sole significant correlation was found between RBANS attention scores and IL-6 (r = -0.45, $p < 0.001$, *VSR* = 207.5). This correlation was consistently significant in SCZ+DM (r = -0.42, $p < 0.01$, *VSR* = 31.8), but not in SCZ (r = -0.14, p = 0.15, *VSR* = 1.3).

For the RBANS delayed memory domain, several significant correlations were also observed in the overall sample, including IL-6 (r = -0.28, $p < 0.001$, *VSR* = 985.8) and FBG (r = -0.28, $p < 0.001$, *VSR* = 897.1). Significant correlation between RBANS delayed memory and IL-6 was also observed in SCZ+DM (r = -0.40, $p < 0.01$, *VSR* = 20.2), but not in SCZ+MetS and SCZ. (ps > 0.1) For detailed correlation analyses, see ***Table 7-14***.

***Table** 7. Pearson's Correlations for the RBANS attention domain in the entire schizophrenia sample.*

			Pearson's r	p	VS-MPR†	Lower 95% CI	Upper 95% CI
Attention	-	LDL	0.030	0.669	1.000	-0.106	0.165
Attention	-	HbA1c	-0.128	0.066	2.058	-0.259	0.008
Attention	-	IL-6	-0.416***	< .001	$1.095\times10^{+8}$	-0.521	-0.300
Attention	-	Fasting GLU	-0.269***	< .001	520.792	-0.390	-0.139
Attention	-	TG	-0.192**	0.005	13.529	-0.319	-0.058
Attention	-	HDL	0.199**	0.004	17.658	0.066	0.326
Attention	-	CRP	-0.081	0.233	1.084	-0.212	0.052

IL-6 – interleukin 6, CRP – C-reactive protein, TG – triglyceride, HDL – High Density Lipoprotein, LDL – Low Density Lipoprotein, Fasting GLU – fasting blood glucose, HbA1c – Hemoglobin A1c

** p < .05, ** p < .01, *** p < .001*

† Vovk-Sellke Maximum p -Ratio: Based on the p-value, the maximum possible odds in favor of H_1 over H_0 equals 1/(-e p log(p)) for p ≤ .37 (Sellke, Bayarri, & Berger, 2001).

Table 8. *Pearson's Correlations for the RBANS attention domain in schizophrenia patients with metabolic syndrome.*

			n	Pearson's r	p	VS-MPR†	Lower 95% CI	Upper 95% CI
Attention	-	LDL	62	0.067	0.603	1.000	-0.186	0.312
Attention	-	HbA1c	62	0.172	0.182	1.187	-0.081	0.404
Attention	-	IL-6	62	-0.454***	<.001	207.528	-0.632	-0.231
Attention	-	Fasting GLU	62	0.134	0.300	1.019	-0.120	0.371
Attention	-	TG	62	0.142	0.271	1.040	-0.112	0.378
Attention	-	CRP	62	0.076	0.558	1.000	-0.177	0.320
Attention	-	HDL	62	-0.130	0.315	1.011	-0.368	0.124

IL-6 – interleukin 6, CRP – C-reactive protein, TG – triglyceride, HDL – High Density Lipoprotein, LDL – Low Density Lipoprotein, Fasting GLU – fasting blood glucose, HbA1c – Hemoglobin A1c

** p < .05, ** p < .01, *** p < .001*

† Vovk-Sellke Maximum p *-Ratio: Based on the* p *-value, the maximum possible odds in favor of* H_1 *over* H_0 *equals 1/(-e* p *log(*p *)) for* p ≤ *.37 (Sellke, Bayarri, & Berger, 2001).*

Table 9. *Pearson's Correlations for the RBANS attention domain in schizophrenia patients with diabetes mellitus.*

			n	Pearson's r	p	VS-MPR†	Lower 95% CI	Upper 95% CI
Attention	-	LDL	53	0.184	0.188	1.172	-0.091	0.433
Attention	-	HbA1c	52	0.229	0.103	1.575	-0.047	0.472
Attention	-	IL-6	53	-0.418**	0.002	31.762	-0.618	-0.167
Attention	-	Fasting GLU	53	-0.046	0.743	1.000	-0.313	0.227
Attention	-	TG	53	-0.181	0.195	1.154	-0.430	0.094
Attention	-	CRP	53	-0.153	0.273	1.038	-0.407	0.122
Attention	-	HDL	53	0.046	0.745	1.000	-0.227	0.312

IL-6 – interleukin 6, CRP – C-reactive protein, TG – triglyceride, HDL – High Density Lipoprotein, LDL – Low Density Lipoprotein, Fasting GLU – fasting blood glucose, HbA1c – Hemoglobin A1c

** p < .05, ** p < .01, *** p < .001*

† Vovk-Sellke Maximum p *-Ratio: Based on the* p*-value, the maximum possible odds in favor of* H_1 *over* H_0 *equals 1/(-e* p *log(*p *)) for* p ≤ *.37 (Sellke, Bayarri, & Berger, 2001).*

Table 10. *Pearson's Correlations for the RBANS attention domain in schizophrenia patients without metabolic syndrome or diabetes mellitus.*

			n	Pearson's r	p	VS-MPR†	Lower 95% CI	Upper 95% CI
Attention	-	LDL	94	0.070	0.503	1.000	-0.135	0.269
Attention	-	HbA1c	94	0.020	0.851	1.000	-0.184	0.221
Attention	-	IL-6	103	-0.143	0.150	1.294	-0.327	0.052
Attention	-	Fasting GLU	96	0.040	0.702	1.000	-0.162	0.238
Attention	-	TG	96	-0.041	0.693	1.000	-0.239	0.161
Attention	-	CRP	103	-0.084	0.397	1.000	-0.273	0.111
Attention	-	HDL	95	0.183	0.076	1.875	-0.019	0.371

IL-6 – interleukin 6, CRP – C-reactive protein, TG – triglyceride, HDL – High Density Lipoprotein, LDL – Low Density Lipoprotein, Fasting GLU – fasting blood glucose, HbA1c – Hemoglobin A1c

** p < .05, ** p < .01, *** p < .001*

† Vovk-Sellke Maximum p *-Ratio: Based on the* p*-value, the maximum possible odds in favor of* H_1 *over* H_0 *equals 1/(-e* p *log(*p *)) for* p ≤ *.37 (Sellke, Bayarri, & Berger, 2001).*

Table 11. *Pearson's Correlations for the RBANS delayed memory domain in the whole schizophrenia sample.*

			n	Pearson's r	p	VS-MPR†	Lower 95% CI	Upper 95% CI
Delayed Memory	-	LDL	209	0.041	0.553	1.000	-0.095	0.176
Delayed Memory	-	HbA1c	208	-0.176*	0.011	7.317	-0.304	-0.041
Delayed Memory	-	IL-6	218	-0.276***	< .001	985.746	-0.394	-0.148
Delayed Memory	-	Fasting GLU	211	-0.279***	< .001	897.102	-0.399	-0.149
Delayed Memory	-	TG	211	-0.168*	0.015	5.886	-0.296	-0.033
Delayed Memory	-	CRP	218	-0.048	0.480	1.000	-0.180	0.085
Delayed Memory	-	HDL	210	0.083	0.230	1.089	-0.053	0.216

IL-6 – interleukin 6, CRP – C-reactive protein, TG – triglyceride, HDL – High Density Lipoprotein, LDL – Low Density Lipoprotein, Fasting GLU – fasting blood glucose, HbA1c – Hemoglobin A1c

** p < .05, ** p < .01, *** p < .001*

† Vovk-Sellke Maximum p *-Ratio: Based on the* p*-value, the maximum possible odds in favor of* H_1 *over* H_0 *equals 1/(-e* p *log(*p *)) for* p ≤ *.37 (Sellke, Bayarri, & Berger, 2001).*

Table 12. *Pearson's Correlations for the RBANS delayed memory domain in schizophrenia patients with metabolic syndrome.*

			n	Pearson's r	p	VS-MPR†	Lower 95% CI	Upper 95% CI
Delayed Memory	-	LDL	62	0.094	0.465	1.000	-0.159	0.336
Delayed Memory	-	HbA1c	62	-0.018	0.891	1.000	-0.266	0.233
Delayed Memory	-	IL-6	62	-0.210	0.101	1.588	-0.437	0.042
Delayed Memory	-	Fasting GLU	62	-0.011	0.932	1.000	-0.260	0.239
Delayed Memory	-	TG	62	0.028	0.826	1.000	-0.223	0.276
Delayed Memory	-	CRP	62	0.114	0.376	1.000	-0.139	0.354
Delayed Memory	-	HDL	62	-0.162	0.208	1.126	-0.396	0.091

IL-6 – interleukin 6, CRP – C-reactive protein, TG – triglyceride, HDL – High Density Lipoprotein, LDL – Low Density Lipoprotein, Fasting GLU – fasting blood glucose, HbA1c – Hemoglobin A1c

** p < .05, ** p < .01, *** p < .001*

† Vovk-Sellke Maximum p *-Ratio: Based on the* p *-value, the maximum possible odds in favor of H_1 over H_0 equals 1/(-e* p *log(*p *)) for* p ≤ *.37 (Sellke, Bayarri, & Berger, 2001).*

Table 13. *Pearson's Correlations for the RBANS delayed memory domain in schizophrenia patients with diabetes mellitus.*

			n	Pearson's r	p	VS-MPR†	Lower 95% CI	Upper 95% CI
Delayed Memory	-	LDL	53	0.184	0.188	1.171	-0.091	0.433
Delayed Memory	-	HbA1c	52	0.289*	0.038	2.983	0.018	0.521
Delayed Memory	-	IL-6	53	-0.398**	0.003	20.163	-0.603	-0.143
Delayed Memory	-	Fasting GLU	53	-0.038	0.785	1.000	-0.306	0.234
Delayed Memory	-	TG	53	-0.192	0.168	1.227	-0.440	0.082
Delayed Memory	-	CRP	53	-0.166	0.235	1.080	-0.417	0.109
Delayed Memory	-	HDL	53	-0.097	0.490	1.000	-0.358	0.178

IL-6 – interleukin 6, CRP – C-reactive protein, TG – triglyceride, HDL – High Density Lipoprotein, LDL – Low Density Lipoprotein, Fasting GLU – fasting blood glucose, HbA1c – Hemoglobin A1c

** p < .05, ** p < .01, *** p < .001*

† Vovk-Sellke Maximum p *-Ratio: Based on the* p *-value, the maximum possible odds in favor of* H_1 *over* H_0 *equals 1/(-e* p *log(*p *)) for* p ≤ *.37 (Sellke, Bayarri, & Berger, 2001).*

Table 14. *Pearson's Correlations for the RBANS delayed memory domain in schizophrenia patients without metabolic syndrome or diabetes mellitus.*

			n	Pearson's r	p	VS-MPR†	Lower 95% CI	Upper 95% CI
Delayed Memory	-	LDL	94	0.081	0.437	1.000	-0.123	0.279
Delayed Memory	-	HbA1c	94	-0.101	0.332	1.005	-0.298	0.104
Delayed Memory	-	IL-6	103	0.043	0.663	1.000	-0.151	0.235
Delayed Memory	-	Fasting GLU	96	-0.042	0.682	1.000	-0.241	0.159
Delayed Memory	-	TG	96	0.190	0.063	2.112	-0.010	0.377
Delayed Memory	-	CRP	103	-0.050	0.619	1.000	-0.241	0.145
Delayed Memory	-	HDL	95	0.005	0.958	1.000	-0.196	0.207

IL-6 – interleukin 6, CRP – C-reactive protein, TG – triglyceride, HDL – High Density Lipoprotein, LDL – Low Density Lipoprotein, Fasting GLU – fasting blood glucose, HbA1c – Hemoglobin A1c

** p < .05, ** p < .01, *** p < .001*

† Vovk-Sellke Maximum p *-Ratio: Based on the* p *-value, the maximum possible odds in favor of H_1 over H_0 equals 1/(-e* p *log(*p *)) for* p ≤ *.37 (Sellke, Bayarri, & Berger, 2001).*

9. DISCUSSION

9.1. Summary of Findings (including all studies)

In our meta-analysis, a clear trend was observed in the relationship between DM and global cognitive functions (SMD=-0.26; p=0.1087), suggesting that the presence of diabetes may be associated with lower cognitive performance in individuals with schizophrenia. Although statistical significance was not reached, the observed trend was consistent with earlier meta-analytic findings and was considered clinically relevant (20, 84). Six of the seven included studies yielded statistically significant findings consistent with this pattern, whereas a single study reported results in the opposite direction. A possible explanation for the lack of statistical significance may be related to the inclusion of a large-sample study by Li S. et al., which was published subsequent to the appearance of the two previously mentioned meta-analyses (62). In this study patients with diabetes demonstrated better cognitive performance compared to non-diabetic controls (62). Furthermore, patients with diabetes required higher doses of antipsychotic medication, had a greater number of lifetime hospitalizations, and were of higher mean age -factors that would typically be expected to adversely affect cognitive outcomes (62). Based on the available data, we identified statistically significant associations between diabetes and exacerbation of cognitive dysfunctions in particular domains, including reasoning (SMD=-0.40; p=0.0109) and processing speed (SMD=-0.43; p=0.0005). While the pooled estimate for global cognition did not reach statistical significance, the predominance of studies reporting poorer global scores with diabetes and the robust domain specific associations indicate that early metabolic dysregulation may exert measurable cognitive effects.

Findings regarding insulin resistance were inconsistent across the three available studies (64,76,83). This discrepancy may be attributable to differences in the diagnostic thresholds used to define insulin resistance across the studies, for example HOMA-IR values of 1.7 versus 2.5. This raises the possibility of a dimensional approach to insulin resistance, according to which impairments in cognitive function emerge only beyond a certain threshold.

In the review section of our work, we collated studies that demonstrated statistically significant negative correlations or associations between laboratory markers commonly used to monitor glucose homeostasis (e.g. fasting insulin, fasting glucose, HOMA-IR, and HbA1c) and cognitive performance. However, due to the different correlation coefficients reported by the authors, we were unable to perform a meta-analysis of these studies.

Our cross-sectional study revealed that diabetes mellitus exhibited the most robust association with cognitive impairment, particularly in the domains of attention and delayed memory. Cognitive performance was significantly lower in patients with DM compared to SCZ+MetS and SCZ groups. Additionally, fasting glucose levels showed negative correlation with cognitive performance across these domains in the whole cohort.

We also examined the association between different metabolic disturbances, peripheral levels of inflammatory markers (IL-6 and CRP) and cognition. Results revealed that IL-6 levels were highest in patients with DM, intermediate in those with MetS, and lowest in patients without metabolic abnormalities. By contrast, no statistically significant differences were observed in CRP levels across groups. IL-6 levels showed a significant negative correlation with attention and delayed memory in the whole sample. Although two previous meta-analyses have established that metabolic dysregulations contribute to the deterioration of cognitive functions in schizophrenia (20,84), our findings refine these results by demonstrating that such alterations are domain-specific -most prominently affecting attention and delayed memory- and are closely associated with elevated IL-6 levels.

9.1.1. Pathophysiological mechanisms linking diabetes and insulin resistance to cognitive dysfunction

The observed findings may be explained by several neurobiological and pathophysiological factors. IR plays a key role in the development of type 2 diabetes mellitus (T2DM), which is particularly relevant given that, beyond its well-established peripheral effects, insulin modulates several physiological processes within the central nervous system (CNS) that are essential for normal cognitive functions (9,11,85). These processes include the modulation of synaptic plasticity, neuronal survival, neurotransmission, oxidative stress regulation, and mitochondrial function (9-12). Based on preclinical studies, insulin has been implicated in the trafficking, activity, and stabilization of NMDA receptors, which play a critical role in neural plasticity (86-88). Evidence further indicates that insulin plays a significant role in the regulation of multiple neurotransmitter systems and their associated neural circuits, including dopamine, gamma-aminobutyric acid (GABA), and glutamate (9). This is of particular relevance given that these neurotransmitter systems play a critical role in maintaining the integrity and synchronization of neuronal networks (e.g. excitation–inhibition (E/I) balance), thereby supporting neural representations and computational processes that form the foundation of cognitive functions (4). In light of the mechanisms discussed above, impaired insulin signaling may contribute to cognitive dysfunctions.

On the other hand, hyperglycemia resulting from severe insulin resistance may lead to vascular pathology, thereby contributing to the development of micro- and macrovascular damage as well as endothelial dysfunction. Furthermore, chronic hyperglycemia may ultimately compromise blood–brain barrier integrity through disruption of tight junctions, resulting in increased permeability (89,90).

The observed negative correlations between fasting glucose levels and scores in the attention and delayed memory domains suggest that hyperglycemia and insulin resistance may affect brain regions and neural networks critical for cognitive functions. Specifically, these alterations may involve the prefrontal cortex and frontoparietal networks subserving attentional processes, as well as the hippocampus and hippocampal -cortical circuits underlying memory functions. These findings are further supported by neuroimaging

evidence indicating that IR and DM may adversely affect the structural integrity of multiple brain regions and neural networks (91-94). Consequently, alterations in white matter integrity have been reported, with diffusion tensor imaging (DTI) studies demonstrating reduced fractional anisotropy (FA) in association with T2DM (95). Finally, T2DM is associated with reduced hippocampal neurogenesis, decreased neuronal survival, and hippocampal atrophy (96,97).

Neuroimaging evidence further supports the potential relationship between altered glucose metabolism and cognitive dysfunctions: positron emission tomography studies using ^{18}F-fluorodeoxyglucose have demonstrated reduced glucose metabolism in the frontal cortex of patients with chronic schizophrenia, which may partly account for observed cognitive impairments (98). In addition, studies employing phosphorus-31 magnetic resonance spectroscopy (^{31}P-MRS) have shown that cognitive dysfunction in both affective and non-affective psychotic disorders is associated with a reduced NAD^+/NADH ratio and decreased creatine kinase activity in the brain, findings that potentially implicate cellular-level metabolic dysregulation, impaired insulin signaling, and mitochondrial dysfunction in the development of cognitive impairment (99,100).

9.1.2. Inflammation as a potential mediator between metabolic dysregulation and cognitive dysfunctions

Related to peripheral inflammatory markers, in our cohort, IL-6 showed a negative correlation with attention and delayed memory performance, and multiple regression analyses indicated that IL-6 significantly predicted outcomes in these cognitive domains. These findings suggest that low-grade inflammation may potentially act as a mediator between metabolic dysregulation and the severity of cognitive dysfunctions.

Various forms of metabolic dysregulation -including individual components of metabolic syndrome such as dyslipidaemia, obesity, insulin resistance and, in more advanced stages, diabetes mellitus- are bidirectionally associated with chronic low-grade inflammation (18). Obesity and visceral adipose tissue play a central role in this interaction (18). Adipocyte hypertrophy within white adipose tissue promotes macrophage infiltration, which in turn leads to increased secretion of pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α (18). In addition to cytokine production, adipocytes secrete several

adipokines with pro-inflammatory properties (e.g. leptin) (18). At the same time, the secretion of anti-inflammatory adipokines (e.g. adiponectin) are reduced, further contributing to a pro-inflammatory milieu (18). Elevated levels of these pro-inflammatory cytokines may contribute, on the one hand, to increased blood-brain-barrier permeability through several mechanisms, including impairment of tight junction integrity and endothelial dysfunction (101). On the other hand, after crossing the blood–brain barrier, these cytokines may induce pathological activation patterns of microglia and astrocytes, which play a key role in the development of neuroinflammation (102-105). Neuroinflammation can trigger a cascade of detrimental processes, including glutamatergic excitotoxicity, oxidative stress, mitochondrial DNA damage, synaptic pathology, and neuronal cell death. Over time, these alterations may lead to profound disturbances in brain cytoarchitecture, affect both grey and white matter integrity, and ultimately contribute to cerebral atrophy (37, 106, 107). Moreover, there is a bidirectional relationship between metabolic dysregulation and neuroinflammation within the central nervous system (108). For example, chronic hyperglycaemia leads to the formation and accumulation of advanced glycation end products (AGEs), which can exert direct neurotoxic effects and activate inflammatory signaling pathways through their interaction with the receptor for advanced glycation end products (RAGE) (108). Activation of the AGE–RAGE axis induces downstream pro-inflammatory cascades, leading to increased production of cytokines and reactive oxygen species (108,109). These processes may further amplify microglial and astrocytic activation, thereby sustaining neuroinflammation and contributing to neuronal dysfunction and cognitive impairment (108).

Finally, it is important to consider the extent to which the observed metabolic-cognitive associations reflect between-group contrasts (i.e., categorical DM status) versus within-group dose-response relationships. In our cohort, fasting glucose showed robust negative associations with attention and delayed memory when the full sample was analyzed. However, these relationships were weaker when correlations were examined within the metabolic subgroups. This pattern is consistent with the threshold model in which cognitive impairments become pronounced when glucose dysregulation exceeds a critical level, rather than worsening linearly across the entire range of fasting glucose values. Future work should therefore test non-linear effects and group-by-metabolic marker

interactions, which may help distinguish categorical (diagnosis-related) from dimensional (severity-related) models.

Our findings also highlight low-grade inflammation (IL-6) as a mechanistic link between diabetes and cognitive impairment in schizophrenia. IL-6 levels were markedly elevated in patients with DM. In contrast, CRP did not differ between metabolic groups, suggesting that IL-6 may capture clinically relevant inflammatory variance not reflected by more general acute-phase markers. Notably, IL-6 was the strongest laboratory correlate and predictor of cognitive performance. Although the cross-sectional design does not provide causal conclusions, this convergent pattern supports longitudinal and interventional studies that jointly target glycemic control and inflammatory pathways, characterized by a more complex cytokine profile.

9.2. Strengths

Our studies have several strengths. To the best of our knowledge, our meta-analysis is the most comprehensive study to date investigating the associations between the different stages of impaired glucose homeostasis and cognitive functions among patients with schizophrenia. The study was conducted in accordance with a pre-registered protocol, and all methodological procedures adhered to the recommendations of the Cochrane Collaboration.

To our knowledge, our second study constitutes the most extensive examination to date of the relationships between diabetes mellitus, metabolic syndrome, inflammatory markers, and cognition in schizophrenia. Metabolic syndrome and diabetes mellitus had not been previously diagnosed in the examined patients, and participants had not received antidiabetic medication before assessment, reducing potential treatment-related confounding. Finally, in addition to conventional statistical approaches, Bayesian analyses were used to improve the reliability and interpretability of the findings.

9.3. Limitations

Both of our studies have some limitations. With respect to the meta-analysis, it should be noted that none of the included studies were longitudinal and were limited to

nonrandomized studies; therefore, causal inferences cannot be drawn, and the findings should be interpreted as reflecting associations rather than causality. The observed results may have been influenced by several confounding factors, including the effects of different pharmacological treatments, such as antipsychotics, antidiabetic agents, and benzodiazepines. In addition, other potential confounding factors may have contributed to the observed findings, including sleep quality, dietary habits, physical activity, and smoking status. Moreover, among the three studies meta-analyzed with respect to insulin resistance, differing operational definitions were applied (e.g., HOMA-IR cutoffs: 1.7 versus 2.5). The use of non-uniform criteria may have introduced misclassification bias, thereby limiting the interpretability of the pooled estimates. Finally, the use of different cognitive assessment instruments across studies complicated the quantitative synthesis; however, given the overlapping psychometric properties of these measures, a meaningful analysis could still be performed using standardized mean differences.

The second study has several limitations that should be mentioned. First, due to the cross-sectional study design, definitive causal relationships cannot be established from the obtained results. Consequently, future longitudinal studies are necessary to further interpret the findings. Second, in our study, only IL-6 was measured among the proinflammatory cytokines. Therefore, a more comprehensive analysis of inflammatory processes, including additional pro-inflammatory (e.g., IL-1β, TNF-α) and anti-inflammatory cytokines (e.g., IL-4, IL-10), is warranted.

10. CONCLUSIONS

Based on our findings, interpreted alongside existing evidence, metabolic dysregulation and low-grade inflammation emerge as important contributors to the exacerbation of cognitive impairment in schizophrenia. These observations underscore the clinical relevance of systematically monitoring and managing metabolic and inflammatory risk factors as part of routine psychiatric care, rather than treating them as secondary comorbidities. Our findings support the need for integrated and multidisciplinary treatment approaches enabling prompt identification and targeted management of metabolic vulnerability. Addressing these alterations may represent a meaningful opportunity to mitigate cognitive decline and improve functional outcomes in schizophrenia patients.

11. IMPLICATIONS FOR PRACTICE

Routine clinical practice should place strong emphasis on the systematic monitoring and early management of metabolic abnormalities and inflammatory markers in both psychiatric and primary care settings. When initiating antipsychotic treatment, the selection of agents with a more favourable metabolic side-effect profile should be prioritised whenever clinically feasible. The promotion of a healthy lifestyle, including increased physical activity and adherence to a balanced diet, is of particular importance in this patient population, as these non-pharmacological interventions can be highly effective in improving both metabolic abnormalities and inflammatory processes (110, 111). In addition, pharmacological therapies targeting disturbances in glucose regulation and broader metabolic abnormalities—such as metformin or GLP-1 receptor agonists—warrant consideration, given their potential to alleviate cognitive impairment by modulating metabolic dysfunction and attenuating neuroinflammatory pathways (112-114). Overall, the management of schizophrenia requires an integrative and holistic approach, with increasing emphasis on the development and implementation of personalized therapeutic strategies in the future.

12. IMPLICATIONS FOR RESEARCH

Advancing the field will require well-powered, longitudinal studies -preferably with randomized controlled designs- that include antipsychotic-naïve participants, systematically assess glycemic and cognitive measures over time, and integrate neuroimaging approaches with broader inflammatory marker analyses.

13. IMPLICATIONS FOR POLICY MAKERS

Sustained support for further research is essential from a policy perspective, as deeper characterization of metabolic and immune dysregulation may open new avenues for improving cognitive functions in individuals with schizophrenia, thereby contributing to a reduction in the associated socioeconomic burden. Equally important is the translation of research findings into clinical guidelines and the potential prioritization of funding for diagnostic approaches that may enable personalized therapeutic strategies.

Investment in such translational research frameworks has the potential to improve long-term functional outcomes, optimize resource allocation within mental health services, and support evidence-based decision-making at the healthcare system level.

14. FUTURE PERSPECTIVES

This thesis highlights several priorities for future research, with a primary emphasis on achieving deeper mechanistic insight. Longitudinal studies will be essential to clarify the causal pathways through which metabolic and inflammatory processes influence brain function, and to determine how these interactions contribute to alterations in neuronal network organization and cognitive outcomes in severe mental illness. Integrative approaches combining, for example multi-omics profiling with advances in neuroimaging may provide a powerful framework for linking molecular signatures to in vivo measures of brain structure, connectivity, and function. Ultimately, such efforts could facilitate the identification of clinically relevant biomarkers for patient stratification and the development of more personalized therapeutic strategies.

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16. BIBLIOGRAPHY

16.1. Publications Related to the Thesis

Glucose homeostasis and cognitive functions in schizophrenia: a systematic review and meta-analysis.

Kancsev, A., Virág-Tulassay, E. É., Engh, M. A., Kiss-Dala, S., Horváth, A. A., Hegyi, P., Kéri, S.

Sci Rep, **15**(1), 22898. (2025)

DOI: 10.1038/s41598-025-06225-0

IF: 3.9 (2024)

Association between metabolic syndrome, diabetes mellitus, inflammation and cognitive dysfunctions in schizophrenia: a cross-sectional analysis.

Kancsev, A., Engh, M.A., Horváth, A.A., Hegyi, P., Kelemen, O., Kéri, S.

Schizophr **11**, 148 (2025).

DOI: 10.1038/s41537-025-00694-y

IF: 4.1 (2024)

16.2. Publications not Related to the Thesis

Algorithm-Based Modular Psychotherapy Alleviates Brain Inflammation in Generalized Anxiety Disorder.

Kéri, S., **Kancsev, A**., Kelemen, O. (2024).

Life (Basel, Switzerland), **14**(7), 887.

DOI: 10.3390/life14070887

IF: 3.4 (2024)

17. ACKNOWLEDGEMENTS

First and foremost, I would like to express my deepest and most sincere gratitude to my supervisor, Professor Szabolcs Kéri, whose outstanding mentorship, continuous support, and genuine dedication were fundamental to the successful completion of my doctoral studies. His scientific insight, patience, and constant availability provided invaluable guidance at every stage of this work. Beyond his academic excellence, his intellectual openness, and human approach profoundly shaped my way of thinking, influencing not only my development as a researcher but also as a person. His trust, encouragement, and belief in my abilities were a continuous source of motivation.

I would also like to express my sincere appreciation to Professor Péter Hegyi, Director of the Centre for Translational Medicine (CTM), for his substantial support, encouragement, and personal commitment throughout my PhD studies. His guidance and efforts in creating a supportive and inspiring research environment were essential to my academic progress and professional development.

Furthermore, I am sincerely grateful to my co-authors for their collaboration, scientific contributions, and constructive discussions, which greatly enriched this work.

Finally, I would like to express my heartfelt thanks to my family for their unconditional support, patience, and understanding throughout this journey.