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PREVALENCE AND INFLUENCING FACTORS OF DOMAIN-SPECIFIC COGNITIVE IMPAIRMENT IN MULTIPLE SCLEROSIS

Ph.D. Thesis

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Budapest

2025

„It always seems impossible until it's done."

Nelson Rolihlahla Mandela

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1 LIST OF ABBREVIATIONS

ACTRIMS	Americas Committee for Treatment and Research In MS
BDI	Beck Depression Inventory
BDI-FS	Beck Depression Inventory-Fast Screen
BDI-II	Beck Depression Inventory-II
BRB-N	Brief Repeatable Battery of Neuropsychological Tests
CDI	Cognitive Domain Impairment
CDs	Cognitive Domains
CI	Cognitive Impairment
CIS	Clinically Isolated Syndrome
CMi	Cognitive-Motor interference
CPI	Cognitive-Postural Interference
CNS	Central Nervous System
DMT	Disease-Modifying Therapy
DSI	Domain-Specific Impairment
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DTi	Dual-Task interference
ECTRIMS	European Committee for Treatment and Research In MS
EDSS	Expanded Disability Status Scale
FSS	Fatigue Severity Scale
HADS-D	Hospital Anxiety and Depression Scale – Depression score
HET	High-Efficacy Therapies
IPS	Information Processing Speed

JBI	Joanna Briggs Institute
MFIS	Modified Fatigue Impact Scale
MS	Multiple Sclerosis
MSIF	Multiple Sclerosis International Federation
MSSC	Multiple Sclerosis Society of Canada
NCD	Neurocognitive Disorders
NMSS	(US) National Multiple Sclerosis Society
OCEBM	Oxford Centre for Evidence-Based Medicine
PASAT3	Paced Auditory Serial Addition Test 3
PIRA	Progression Independent of Relapse Activity
POMS	Pediatric-Onset Multiple Sclerosis
PPMS	Primary Progressive Multiple Sclerosis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PwMS	People with MS
QoL	Quality of Life
RAW	Relapse-Associated Worsening
RIS	Radiologically Isolated Syndrome
RR	Relapse Rate
RRMS	Relapsing-Remitting Multiple Sclerosis
SDMT	Symbol Digit Modalities Test
SPART	10/36 Spatial Recall Test
SPART-DR	10/36 Spatial Recall Test Delayed Recall
SPMS	Secondary Progressive Multiple Sclerosis
SRT	Selective Reminding Test
SRT-CLTR	Selective Reminding Test Consistent Long-Term Retrieval

SRT-DR	Selective Reminding Test Delayed Recall
SRT-LTS	Selective Reminding Test Long-Term Storage
T9HP	Nine-Hole Peg Test
T25FW	Timed 25-Foot Walk Test
WLG	Word List Generation Test

2 STUDENT PROFILE

2.1 Vision and mission statement, specific goals

My vision is to ensure the sustained preservation of quality of life, functional independence, and active social and family participation in individuals with multiple sclerosis (MS).

I believe that by gaining a comprehensive understanding of cognitive impairment (CI) - a key contributor to disability progression - and integrating research findings directly into clinical practice, we can establish a preventive approach that ensures long-term functional stability for our patients.

My mission is to lay the scientific groundwork for a novel, proactive model of MS care that focuses on sustaining patients' well-being over time. My specific goal is to identify and evaluate the prevalence and influencing factors of CI in MS in order to develop targeted interventions aimed at improving the lasting stability of patients' conditions.

2.2 Scientometrics

Number of all publications:	5
Cumulative IF:	16,5
Av IF/publication:	3,3
Ranking (SCImago):	Q1: 4, Q4: 1
Number of publications related to the subject of the thesis:	2
Cumulative IF:	7,8
Av IF/publication:	3,9
Ranking (SCImago):	Q1: 2
Number of citations on Google Scholar:	39
Number of citations on MTMT (independent):	29
H-index:	3

The detailed bibliography of the student can be found on pages 64-65.

2.3 Future plans

As a neurology specialist, I have been caring for MS patients for several years at the Bajcsy-Zsilinszky Hospital MS Center. Throughout my work, I have experienced that this "disease with a thousand faces" extends far beyond the "visible" neurological deficit symptoms, which themselves carry a societal stigma. During the comprehensive, thorough, and holistic care of patients, "invisible" symptoms - such as CI, fatigue, and depression – emerge as significant determinants of disability, leading to social, familial, and economic isolation, ultimately contributing to deepening stigmatization.

Based on my research findings, my future plan is to integrate these "invisible" symptoms - particularly the early detection of CI, the identification of at-risk groups, and the development of specialized care approaches - into professional guidelines through concrete, evidence-based recommendations.

Looking ahead, building on my clinical and research experience, I aim to further investigate the structural and functional foundations of MS-related cognitive neuroscience. My goal is to highlight the critical role of cognitive and affective factors in MS care, both nationally and internationally, and to promote a more integrated, multidimensional approach. By bridging cognitive neuroscience and patient-centered MS care, I hope to contribute to more holistic treatment strategies that balance the cognitive, emotional, and physical well-being of the affected patients.

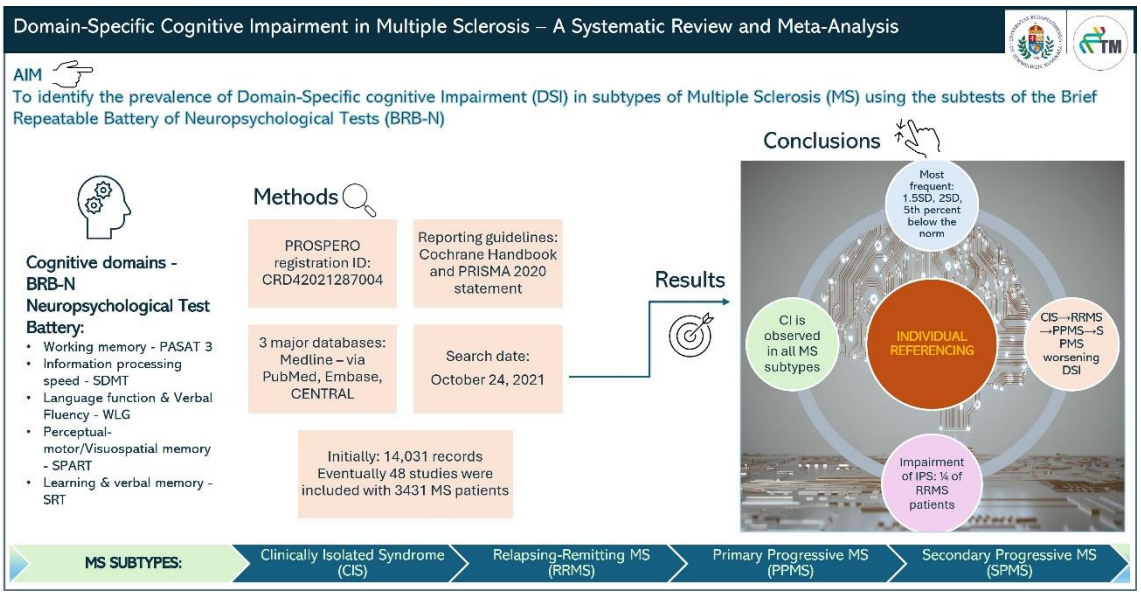
3 SUMMARY OF THE THESIS

Over the past two decades, preventing disability in MS has become achievable due to advances in pharmacological therapies, particularly early high-efficacy induction strategies, which reduced relapse rates (RR) and relapse-associated worsening (RAW). However, these improvements mainly address physical disability and radiological outcomes, while CI - a key contributor to overall disability and often linked to progression independent of relapse activity (PIRA) - remains insufficiently targeted. Internationally, the prevalence, characteristics, and determinants of domain-specific impairment (DSI) are not well defined, limiting targeted interventions. We conducted two meta-analyses to clarify DSI prevalence and identify its clinical and sociodemographic determinants across MS phenotypes. Study 1 analyzed observational studies using the Brief Repeatable Battery of Neuropsychological Tests (BRB-N) in clinically isolated syndrome (CIS), relapsing-remitting (RRMS), primary progressive (PPMS), and secondary progressive MS (SPMS), applying three common CI thresholds (1.5 SD, 2.0 SD below mean, and 5th percentile). CI was present in all phenotypes, including early CIS, and increased from CIS to RRMS, PPMS, and SPMS. Information processing speed (IPS) was impaired in about one-quarter of RRMS patients. Marked heterogeneity suggested that "*individual referencing*" may be preferable to rigid definitions. Study 2 examined clinical (disease duration, Expanded Disability Status Scale [EDSS], depression, mobility, treatment) and sociodemographic (age, sex, education) factors influencing Symbol Digit Modalities Test (SDMT) performance, using univariate and multivariate study-level analyses and meta-regressions. In mixed and, to a lesser extent, RRMS populations, EDSS showed the strongest negative effect, while education had a moderately strong positive effect. CI appears to result mainly from the interaction of physical disability and cognitive reserve (education), with additional modulation from sex, depression, and age.

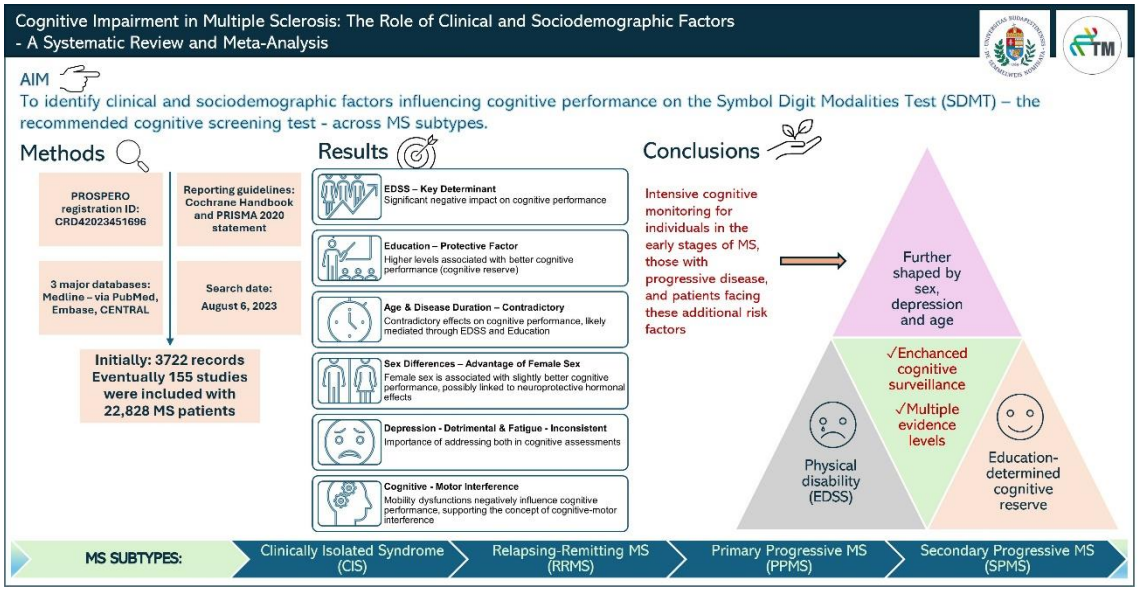
CI is common across all MS subtypes, worsens with progression, and is most likely in patients with higher EDSS and lower education, especially with other risk factors. Intensive cognitive monitoring and personalized care are essential, particularly for early-stage and progressive MS patients, and our findings provide a methodological framework for future CI association studies.

4 GRAPHICAL ABSTRACT

4.1 Study 1



4.2 Study 2



5 INTRODUCTION

5.1 Overview of the topic

5.1.1 What is the topic?

Multiple sclerosis (MS) is a chronic inflammatory and degenerative disease of the central nervous system (CNS) with varying degrees of demyelination and axonal damage. MS typically begins in young adults and is a key factor contributing to the leading causes of disability in this population [1]. Cognitive impairment (CI) is one of the most common, life-altering consequences of MS, with an estimated prevalence ranging from 43-70% [2].

In my thesis, I examine the prevalence of CI across different cognitive domains (CDs) and the influencing factors that are essential for the prevention, early detection, and development of targeted treatment strategies for the major contributor to disability in young adulthood.

5.1.2 What is the problem to solve?

Traditionally, clinical perspectives have focused on the degree of physical impairment in MS, with the primary mechanisms of relapse rate (RR) and ” relapse-associated worsening (RAW)” determining daily functioning, workability, and quality of life (QoL) [3]. However, studies over the past 20 years have shown that CI – through ”progression independent of relapse activity” (PIRA) - can also be both a contributing factor and a primary cause of overall disability in people with MS (PwMS) [2,4,5]. However, there is a gap in our knowledge regarding the extent of cognitive dysfunction across different MS subtypes, as comprehensive and up-to-date meta-analyses are lacking. Although some evidence suggests that more severe CI is associated with progressive MS forms, with domains like attention and working memory being most affected early on, results remain inconsistent [6-9]. Additionally, factors such as age, sex, education, and EDSS score have been shown to influence cognitive performance, but the limited number of studies and the lack of analysis on the interdependencies between these factors hinder the reliability of these findings [10-13].

5.1.3 What is the importance of the topic?

According to WHO data, approximately 2.8 million people worldwide are living with MS, and this number has been continuously increasing over the past three decades

[14]. In Hungary, the prevalence varies, with estimates ranging between 6,000 and 8,000 cases and a prevalence of 101,8 per 100,000 in Csongrád County, which translates to around 10,000 patients nationwide [15]. The most recent data indicate that between 2010 and 2015 in Hungary, the age-standardized prevalence of multiple sclerosis rose from 105.2 to 127.2 per 100,000, showing a higher national prevalence than previously reported. Over the same period, the age-standardized incidence declined from 6.7 to 5.1 per 100,000, with a stable male rate and a significant decrease among women [16]. Given all of this, investigating the significance, prevalence, causes, and influencing factors of MS-associated cognitive impairment, as a leading cause of disability in young adults, is essential not only for healthcare professionals aiming to maintain the long-term QoL of patients but also for both micro- and macroeconomic perspectives.

5.1.4 What would be the impact of our research results?

By identifying key CDs most affected in different MS subtypes, and the factors that contribute to disability of our patients, these findings could inform the development of targeted diagnostic and treatment strategies. Ultimately, the research could improve the long-term QoL for PwMS while also offering valuable insights into healthcare policies and economic planning related to MS care.

5.2 International phenotypic classification of MS

In 1996, a consensus paper defined four clinical courses of MS: relapsing-remitting, primary progressive, secondary progressive, and progressive-relapsing MS [17]. Since then, advances in MS research, including the identification of fluid biomarkers and MRI features, have led to a reevaluation of these classifications. This re-examination, supported by various international organizations like the International Advisory Committee on Clinical Trials in Multiple Sclerosis of the European Committee for Treatment and Research in MS (ECTRIMS), US National Multiple Sclerosis Society (NMSS), Americas Committee for Treatment and Research in MS (ACTRIMS), Multiple Sclerosis International Federation (MSIF), and Multiple Sclerosis Society of Canada (MSSC), resulted in revised MS phenotypes. The updated classification, published in 2014, remains the globally accepted system [18].

Based on this, the following clinical phenotypes can be distinguished within the MS spectrum:

- **Clinically Isolated Syndrome (CIS):** a monophasic, first clinical episode characterized by diverse neurological symptoms persisting for at least 24 hours. Although the diagnostic criteria for MS (as defined by the McDonald criteria [19]) are not fulfilled at this stage, there is a high risk for subsequent development of MS, particularly when demyelinating lesions are detectable on MRI. CIS can be *active* or *not active* based on MRI characteristics.
- **Relapsing-Remitting MS (RRMS):** characterized by episodes of neurological dysfunction (relapses) followed by partial or complete remission. This is the most common form of MS at the time of diagnosis, accounting for approximately 85% of cases. RRMS can be *active* (with clinical relapses occurring and/or new or contrast-enhancing lesions appearing on MRI) or *not active* (with no relapses or new MRI lesions within a defined period).
- **Primary Progressive MS (PPMS):** characterized by a gradual neurological decline from disease onset, without distinct relapses. Disease progression is continuous, although periods of stabilization may occur. Based on disease activity, PPMS can be classified as *active* (with clinical and/or radiological activity) or *not active* (with neither clinical nor radiological evidence of activity).
- **Secondary Progressive MS (SPMS):** initially follows a relapsing-remitting course, but over time a steady neurological decline develops, regardless of the presence of relapses. Disease progression can be classified as *active* (with new relapses and/or new or enlarging lesions on MRI) or *not active* (with no evidence of new relapses and/or radiological activity).

5.3 Cognition, neurocognitive disorders, cognitive domains

Cognition and cognitive performance/function are key concepts in psychology, neuroscience, education, and medicine. While there is no single, universally agreed-upon ”official” definition, several widely accepted scientific interpretations are available. According to the American Psychological Association, cognition refers to „all forms of knowing and awareness, such as perceiving, conceiving, remembering, reasoning, judging, imagining, and problem solving. Along with affect and conation, it is one of the three traditionally identified components of mind” [20]. The DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) does not define “cognitive performance” explicitly, but identifies six cognitive domains (complex attention,

executive function, learning and memory, language, perceptual-motor function, and social cognition) that may deteriorate in *neurocognitive disorders* (NCD), including in MS. Impairments should be identified through patient-reported symptoms, clinical observations, and objective neuropsychological assessment [21].

5.4 Definition of neurocognitive disorders in MS

Neurocognitive disorders (NCD) in the DSM-5 refer to a group of conditions characterized by acquired cognitive decline due to brain pathology, distinct from primary mental illnesses. NCDs include Delirium, *Mild* Neurocognitive Disorder (Mild NCD), and *Major* Neurocognitive Disorder (formerly known as dementia).

Mild NCD is defined by the following criteria:

- A modest decline in cognitive performance in one or more domains compared to a previous level of functioning, based on concerns expressed by the individual, a knowledgeable informant, or the clinician.
- Objective evidence is provided by neurocognitive testing showing performance typically between one and two standard deviations below appropriate norms (i.e., between the third and sixteenth percentile)
- Cognitive deficits do not significantly interfere with independence in everyday activities, such as managing bills or medications, although maintaining independence may require extra effort, use of compensatory strategies, or accommodations.
- The cognitive impairment is not primarily caused by other mental disorders, for example, major depressive disorder or schizophrenia.

In MS, according to DSM-5, CI is classified under "*mild* NCD due to another condition".

5.5 Neurocognitive testing

Neurocognitive testing, also known as neuropsychological testing, is used to comprehensively evaluate and interpret cognitive functioning and to help determine the presence and extent of potential cognitive impairment. These assessments rely on standardized tasks, which may be administered orally, in writing, or via digital/computerized platforms. They allow for comparisons either to normative population data or to an individual's previous performance. Targeted neuropsychological

evaluation of specific CDs, as previously discussed, is possible; however, to assess overall performance across multiple domains, comprehensive test batteries are typically used.

In MS, three major neuropsychological batteries have been developed for this purpose: the Brief International Cognitive Assessment for MS (BICAMS) [22], the Minimal Assessment of Cognitive Function in MS (MACFIMS) [23], and Rao's Brief Repeatable Battery of Neuropsychological Tests (BRB-N) [10].

BRB-N is one of the most sensitive, specific (71% sensitivity and 94% specificity) and widely used, validated testing tools, which consists of several subtests, collectively detecting five key measurable parts of the six main CDs: the Paced Auditory Serial Addition Test 3 (PASAT3) [24] measures working memory, the Symbol Digit Modalities Test (SDMT) [25] measures information processing speed (IPS) and complex attention, the Word List Generation Test (WLG) [26] measures language function and verbal fluency; the 10/36 Spatial Recall Test (SPART) [27] measures perceptual-motor/visuospatial memory and refers to some aspects of executive functions, and the Selective Reminding Test (SRT) [28] measures learning and verbal memory.

In our first study, we chose the subtests of the BRB-N battery because they have been widely validated in multiple countries and demonstrate relatively high sensitivity and specificity. Using this approach, the DSI was assessed with the same neurocognitive measurements. Due to its ease of administration and characteristics such as reliability, validity, predictive validity, sensitivity, and specificity, in our second study, we have chosen SDMT as a primary cognitive target variable outcome, a test widely recognized as an indicator of overall cognitive functioning.

6 OBJECTIVES

6.1 Study 1 – Domain-specific cognitive impairment in multiple sclerosis

We aimed to identify the prevalence of DSI in subtypes of MS by conducting a meta-analysis and using subtests of the Brief Repeatable Battery of Neuropsychological Tests (BRB-N), analyzing the different cut-offs used to define pathological.

6.2 Study 2 – Cognitive impairment in multiple sclerosis: the role of clinical and sociodemographic factors

We aimed to examine the clinical and sociodemographic variables impacting the cognitive screening Symbol Digit Modalities Test (SDMT) performance across MS subtypes, identifying subgroups at greater risk of cognitive impairment.

7 METHODS

Both studies were conducted with full adherence to the Cochrane Handbook for Systematic Reviews of Interventions [29] and were structured following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement [30]. Additionally, both were prospectively registered on the International Prospective Register of Systematic Reviews (PROSPERO), under the following identifiers for the first and second review, respectively: CRD42021287004 and CRD42023451696.

7.1 Study 1

7.1.1 Literature search strategy

The systematic search was performed within three major databases (Medline – via PubMed, Embase, CENTRAL - The Cochrane Central Register of Controlled Trials), without restrictions, on October 24, 2021. The following search key was applied: „multiple sclerosis" AND (cognitive OR cognition OR neurocognitive OR neurocognition) AND (impairment OR decline OR dysfunction).

7.1.2 Eligibility criteria

The selection criteria were defined using the "CoCoPop" framework (i.e., condition – context – population) [31]. The population consisted of adult patients of both sexes (age ≥ 18 years) diagnosed with MS in the context of MS subtypes, according to the Lublin classifications [18], with the condition of distinct DSI measured by subtests of the BRB-N battery. Studies were excluded if they involved pediatric or pediatric-onset MS (POMS) populations, if they used computerized versions of BRB-N subtests (given the differences in normative data, the lack of comparability, and concerns about measurement equivalence), or tested patients during relapse/steroid administration, due to the potential impact on cognitive performance [32].

MS diagnosis was based on the McDonald criteria [19], and as this was first established in 2001, studies published before 2001 were eventually excluded.

Only observational studies were included in the analysis. The primary outcome was the reported prevalence (%) of DSI across different MS subtypes, as measured by BRB-N subtests. Since the literature reports varying cut-off thresholds for identifying

abnormal performance on these subtests, all reported cut-off values were considered separately in the analysis.

7.1.3 Study selection process

The selection was performed using EndNote 20 (Clarivate Analytics, Philadelphia, PA, USA) software. After automatic and manual removal of duplicates, two independent reviewers screened the records in a two-phase process: first by title and abstract, then by full-text review, with any disagreements resolved by a third reviewer. The degree of inter-reviewer agreement was quantified by Cohen's kappa statistic. A Kappa value of more than 0.8 was considered sufficient to complete each stage of the selection process.

7.1.4 Data extraction

Data extraction was also performed independently by two reviewers and compared by a third. Key baseline characteristics, outcome measures, and their definitions for studies and populations were extracted using a pre-designed Excel spreadsheet (Microsoft Corporation, Redmond, Washington, USA).

The Selective Reminding Test (SRT) allows differentiation between short-term and long-term memory processes through indices such as Long-Term Storage (SRT-LTS), Consistent Long-Term Retrieval (SRT-CLTR), and Delayed Recall (SRT-DR) – as the latter refers to the total number of words remembered following a delay.

The 10/36 Spatial Recall Test (SPART) includes both immediate (SPART) and delayed recall (SPART-DR) components. Whenever studies reported results for these subtests, such data were likewise extracted and included in the analysis.

7.1.5 Data synthesis and statistical analysis

The statistical analysis of the data was conducted using the R programming language [33]. We used the meta [34] package for calculations and plots.

For each MS subtype, test, and cut-off value, we extracted the number of MS patients and the number of those who were found to be impaired in the given CD. To conduct the statistical analysis, we applied the three most widely adopted cut-off values: a cut-off of ≤1.5 standard deviations (SD) and ≤2.0 SD below the normative value, and ≤5th percentile of the normative population (i.e., compared to the healthy control group).

Patients with MS who fell below these cut-off values on a given test were classified as impaired in the given CD. Raw prevalences from the included studies were transformed to the logit scale, then pooled using a random-effects model, and then transformed back to the original scale for data presentation [35]. I.e., prevalence data were universally logit-transformed to stabilize variances, and a random-effects model was chosen to account for the substantial heterogeneity across studies. T^2 was estimated using the restricted maximum likelihood method [36]. To assess statistical heterogeneity across the studies, we used the Cochrane Q statistic test and calculated the I^2 values [37]. Results were graphically summarized via forest plots. Where appropriate, we reported the 95% prediction intervals (i.e., the estimated range that contains 95% of true prevalence) following the recommendations [38].

7.1.6 Risk of bias and certainty of evidence assessment

The risk of bias was evaluated according to the Joanna Briggs Institute (JBI) Quality Assessment Tool for Prevalence Studies [39,40] by two independent reviewers, with any disagreements resolved through consultation with a third reviewer. The certainty of the evidence was determined following the framework provided by the modified OCEBM Levels of Evidence Working Group [41].

7.2 Study 2

7.2.1 Literature search strategy

A systematic literature search was performed in three major databases (Medline – via PubMed, Embase, CENTRAL - The Cochrane Central Register of Controlled Trials) on August 6, 2023. The following search key was applied: (SDMT OR „Symbol Digit Modalities Test" OR „Symbol Digits Modalities Test" OR „Symbol Digits Modality Test" OR „Symbol Digit Modality Test" OR „Single Digit Modalities Test" OR „Single Digits Modalities Test" OR „Single Digit Modality Test" OR „Single Digits Modality Test") AND „multiple sclerosis".

7.2.2 Eligibility criteria

Our selection criteria were structured based on the "CoCoPop" framework [31]. The population consisted of adult MS patients of both sexes (age ≥ 18 years), in the context of their clinical and sociodemographic variables, including at minimum the

Expanded Disability Status Scale (EDSS) [42] score and disease duration, with the condition of SDMT raw score test results. The inclusion of EDSS and disease duration as a minimum baseline criterion was justified by a preliminary literature search, based on feasibility considerations. However, according to the PROSPERO protocol, due to sufficient data availability, additional population characteristics such as age, sex, education level, depression, fatigue, mobility assessments, and treatment status were also analyzed. Studies focusing on pediatric or pediatric-onset MS (POMS), those utilizing smartphone-based, digital/computerized, or modified versions of the SDMT (given the differences in normative data, the lack of comparability, and concerns about measurement equivalence), as well as patients assessed during relapse phases, recovery from relapse, or under steroid treatment, were excluded, given the potential confounding effects on cognitive test performance [32]. Only studies reporting raw SDMT scores (the number of correct responses within 90 seconds) were included; those presenting adjusted scores such as z-scores or t-scores were excluded due to their derived nature and possible bias in association analyses. No limitations were applied to the diagnostic criteria for MS, and all MS subtypes [18] were considered eligible except for patients with radiologically isolated syndrome (RIS) and those classified as having "benign MS." RIS was excluded due to its uncertain conversion to MS, while "benign MS" was excluded because of the absence of a universally standardized definition.

All included articles were observational in design. For eligible longitudinal studies, baseline data were extracted and used as cross-sectional observations.

7.2.3 Study selection process

The selection process was carried out using EndNote 20 (Clarivate Analytics, Philadelphia, PA, USA). Following automatic and manual removal of duplicates, two independent reviewers performed screening in two stages: initially based on titles and abstracts, followed by a full-text assessment. Discrepancies between reviewers were settled by involving a third reviewer. Agreement between reviewers was measured using Cohen's kappa statistic. A Kappa value of more than 0.8 was considered sufficient to complete each stage of the selection process.

7.2.4 Data extraction

Data extraction was performed by three reviewers independently and compared by a fourth reviewer. Baseline study data (first author, study site, year of publication, study design, study population), clinical-sociodemographic parameters of the populations (age in years, sex: rate of females, education in years, disease durations in years, EDSS, depression, fatigue, and mobility/gait function scores, disease-modifying therapy/DMT use) and outcomes (SDMT raw scores, intra-study direct correlations and multivariable regression coefficients with the statistical method applied) were extracted into a pre-designed Excel (Microsoft Corporation, Redmond, Washington, USA) spreadsheet.

7.2.5 Data synthesis and statistical analysis

Statistical analyses were performed using packages 'meta' and 'PerformanceAnalytics' of the R statistical software (version 4.1.2). The statistical analyses followed the advice of Harrer et al. [35]. For all statistical analyses, a *p*-value of less than 0.05 was considered significant. All meta-analyses performed included random effect terms.

In the absence of randomized data, deriving robust conclusions from observational studies can be difficult. Confounding can lead to spurious results in univariate analyses. In multivariate settings, collinearity and interdependence among predictors further complicate interpretation. When the meta-regression is based on aggregated variables, results should be interpreted cautiously due to the potential for ecological bias, also known as aggregation bias, as outlined by Schmid et al. [43]. To ensure a comprehensive and reliable understanding, we used four types of analysis separately for mixed MS (including various phenotypes), RRMS, PPMS, and SPMS populations. The first two analyses represent the two key meta-analyses; the third corresponds to the systematic review component; and the fourth addresses the interdependence among the examined parameters, aiming to assess the reliability of the final results.

I. **Univariate study-level correlation results:** We meta-analyzed correlation coefficients (Pearson and Spearman) separately. These represent univariate, study-level association estimates. We pooled Fisher's z-transformed correlations using the classical inverse variance approach with REML tau estimator and Hartung-Knapp adjustment. We visualized the pooled correlations and their 95%

confidence intervals in forest plots. Heterogeneity was assessed by calculating the I^2 measure and its confidence interval and by performing the Cochrane Q test.

II. **Univariate meta-regression results:** We extracted mean and standard deviation (SD) values of SDMT performance from included studies. When studies only reported medians and dispersion statistics (e.g., quartiles, minimum, maximum), we estimated the mean and SD using the default algorithm implemented in the metamean() function in R. We then performed univariate meta-regression of SDMT, using the mean or median values of clinical and demographic variables as predictors. The resulting associations were presented in bubble/scatter plots.

III. **Study-level multivariable regression models' results:** due to the heterogeneity in multivariable analytical methods across studies, direct pooling of adjusted regression coefficients was not feasible. Differences were observed in covariate selection strategies, multicollinearity diagnostics, and regression models applied. Therefore, we synthesized this information narratively by compiling a summary table of the reported multivariable models, providing an overview of the study-level findings as part of the systematic review.

IV. **Meta-level multivariate regression analyses of the investigated clinical and sociodemographic factors (covariates) – interdependence analyses:** We carried out multivariate meta-level regression analyses based on commonly reported covariates across studies. Following the methodological guidance of Harrer et al. [35], we used the PerformanceAnalytics R package to explore pairwise associations between predictors. For simplicity, we did not check interdependence among variable triples and quadruples. The resulting correlations between predictors were only simple correlations between the means/medians reported, i.e., meta-weighting was not used in the calculations. However, along with the visualization provided, the results were useful to avoid multicollinearity in the meta-level regression. Finally, we fitted several multivariate models involving only predictors that were not too strongly correlated. The different runs served as sensitivity analyses of each other.

For univariate study-level correlations, a minimum of three eligible studies was required. If fewer studies were available, or if correlation metrics other than Pearson or Spearman

were reported, the results were still visualized but excluded from the meta-analytic synthesis. Univariate meta-regressions were only performed when at least eight studies contributed data. However, the Cochrane Handbook [29] does not recommend performing meta-regression when the number of studies is less than ten. For this reason, results based on eight and nine studies should be interpreted with caution.

7.2.6 Risk of bias and certainty of evidence assessment

The risk of bias was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Tool for Analytical Cross-Sectional Studies [39,40] framework by two independent reviewers, with disagreements resolved by a third reviewer. Level of evidence rated by the modified Oxford 2011 Levels of Evidence [41].

8 RESULTS

8.1 Study 1 – Domain-specific cognitive impairment in multiple sclerosis

8.1.1 Systematic Literature Search, Selection, and Study Characteristics

The systematic search initially identified 14,031 articles, and eventually 48 studies were included in the synthesis (both in the systematic review and in the meta-analysis). The detailed record of the complete selection process is presented in Figure 1.

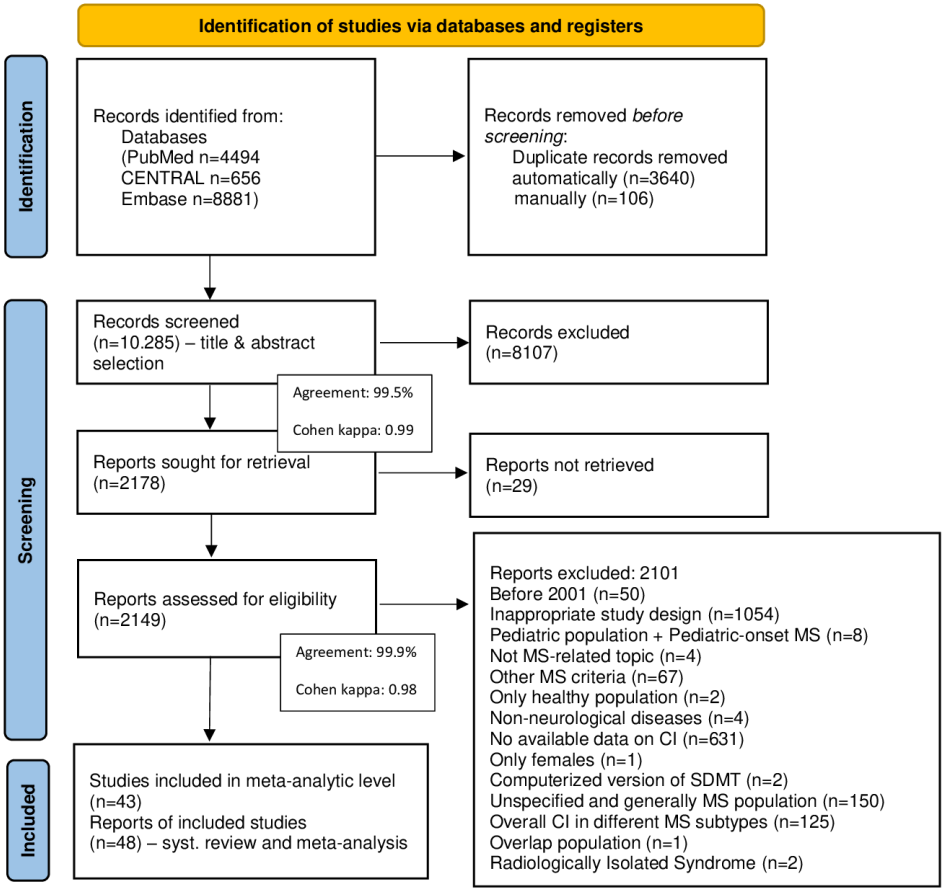


Figure 1. Flow diagram of study identification and selection by PRISMA 2020 with details of the reasons for exclusion [44].

Cohen kappa: A statistical measure of inter-rater agreement that accounts for agreement occurring by chance. It quantifies the consistency between the two independent review authors (KL, KH) during study selection.

Agreement: The degree to which independent review authors made the same inclusion or exclusion decisions during the screening process.

We included the three most frequently applied neuropsychological test cut-off values in our meta-analysis, as these allowed for quantitative synthesis. Additionally, five other studies that did not meet our predefined cut-off criteria were included in a systematic review but excluded from the meta-analysis. No distinction was made between raw score cut-offs and z-score thresholds when they represented the same standard deviation values, nor between reference groups described as "normative" or self-reported „healthy controls."

All studies included were observational in design. Where a longitudinal study was considered eligible, baseline results were used as cross-sectional data.

In total, data from 3,131 patients with MS (450 with CIS, 2,393 with RRMS, 134 with PPMS, and 154 with SPMS) were pooled in the meta-analysis. Furthermore, a systematic review was conducted on an additional 300 patients (18 CIS, 197 RRMS, 12 PPMS, and 73 SPMS).

Baseline characteristics of the included studies are detailed further in eTable 1 of the published study's Supplementary Material Appendix 6 [44].

8.1.2 Quantitative and qualitative analysis

Evaluation of individual DSI across different MS subtypes based on separate cut-offs used to define impairment – quantitative analysis/meta-analysis

8.1.2.1 A cut-off of 2.0 SD below the normative value

Due to a lack of data, at this cut-off value, we were only able to perform a detailed analysis for all subtypes at PASAT-3, while at all other tests, we only had data for CIS and RRMS.

Impaired working memory (**PASAT3**) affects **13%** CI:[0.07%; 0.23%] of **CIS**, **23%** CI:[0.16%; 0.31%] of **RRMS**, **27%** CI:[0.15%; 0.43%] of **PPMS** and **45%** CI:[0.28%; 0.63%] of **SPMS** patients, whereas impairment of delayed recall in visuospatial abilities (**SPART DR**) is present in only in **4%** CI:[0.01%; 0.10%] of CIS patients and **10%** CI:[0.05%; 0.19%] of **RRMS** patients. Impairment of IPS (**SDMT**) and decline in verbal fluency (**WLG**) also affect **9%** CI:[0.04%; 0.19%] - **9%** CI:[0.03%; 0.27%] of **CIS** patients and are present in **19%** CI:[0.12%; 0.29%] and **16%** CI:[0.11%; 0.22%] of **RRMS** patients, respectively. Impairment of learning and verbal memory domains affects **7-8%** (CI:[0.05%; 0.15%] at **SRT DR**, CI:[0.03%; 0.13%] at **SRT LTS**, CI:[0.04%; 0.15%] at **SRT CLTR**) of CIS patients and **17-19%** (CI:[0.10%; 0.35%] at **SRT DR**, CI:[0.09%; 0.35%] at **SRT LTS**, CI:[0.10%; 0.28%] at **SRT CLTR**) of **RRMS** patients, depending on the SRT test recall (see Figure 2).

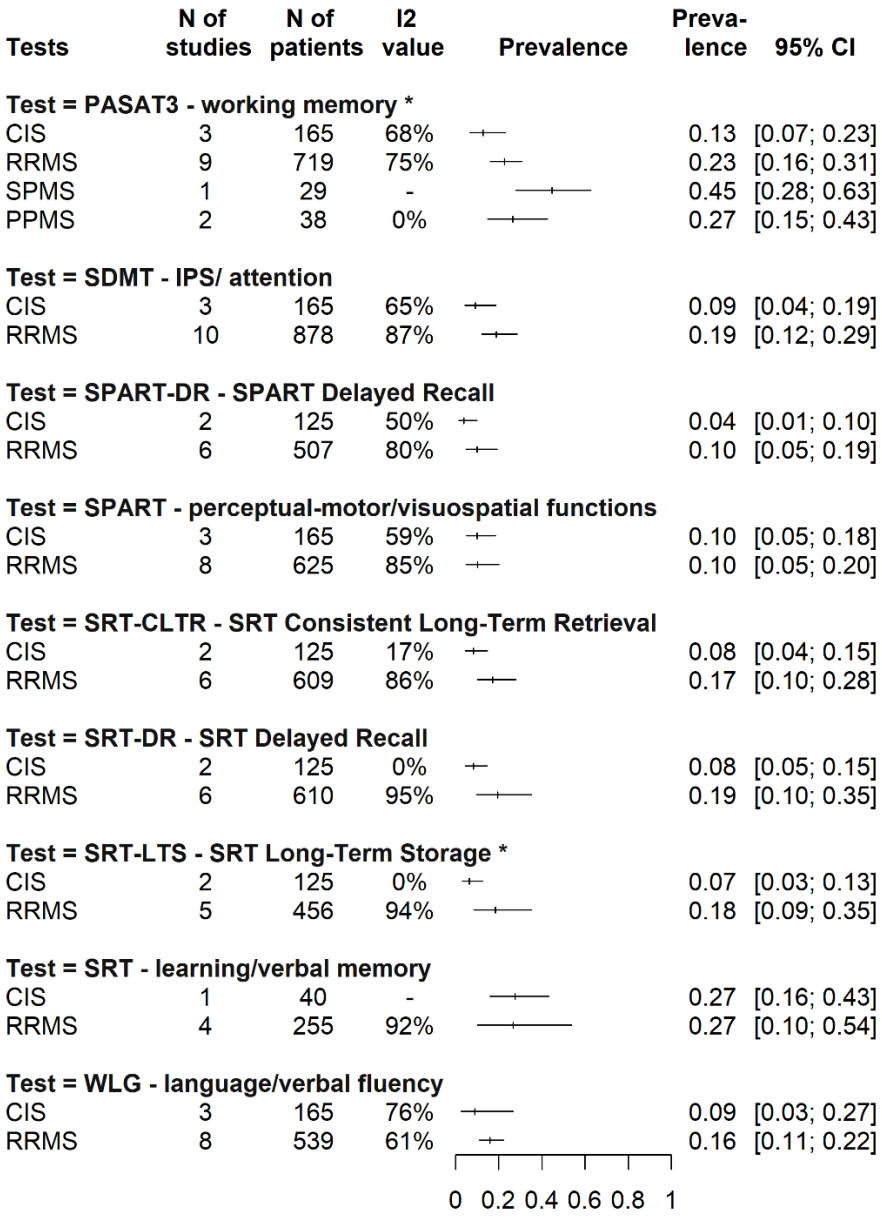


Figure 2. Summary panel of DSI prevalence rates across the subtests of the BRB-N battery at the ”**2.0 SD below the normative values**” cut-off [44].

*The subtests of the BRB-N battery are displayed on the left side of the figure. Below each test, MS subtypes are shown. At this cut-off value, sufficient data across all MS subtypes were available only for the PASAT3 subtest. For the remaining BRB-N subtests, data were limited to the CIS and RRMS subtypes. On the right side of the figure, the prevalence rates (along with confidence intervals) of patients showing impairment, categorized by MS subtype, are shown for each BRB-N subtest, based on the "**2.0 SD below the normative values**" cut-off.*

8.1.2.2 A cut-off of 1.5 SD below the normative value

Using this cut-off value, working memory impairment (**PASAT3**) was found in only **4%** CI: [0.01%; 0.11%] of **CIS** patients, **20%** CI: [0.09%; 0.38%] of **RRMS** patients, **24%** CI: [0.07%; 0.59%] of **PPMS**, and **31%** CI: [0.08%; 0.70%] of **SPMS** groups. IPS impairment (**SDMT**) was observed in **13%** CI: [0.08%; 0.20%] of **CIS** patients and **25%** CI: [0.18%; 0.33%] of **RRMS** patients, while the prevalence was higher in **PPMS** (**35%**, CI: [0.14%; 0.63%]) and **SPMS** (**61%**, CI: [0.31%; 0.85%]) groups. Impairment of verbal fluency (**WLG**) affects almost the same proportion of **PPMS** and **SPMS** patients (**80%** CI:[0.64%; 0.90%] and **81%** CI:[0.63%; 0.91%], respectively), compared to **15%** CI:[0.02%; 0.65%] in **CIS** and **35%** CI:[0.25%; 0.48%] in **RRMS**. Regarding visuospatial abilities, data were available only for delayed recall (**SPART DR**), with similar impairment levels in **CIS** (**16%**, CI: [0.09%; 0.26%]) and **RRMS** (**15%**, CI: [0.08%; 0.26%]), while higher rates were noted in **PPMS** (**57%**, CI: [0.41%; 0.72%]) and **SPMS** (**74%**, CI: [0.56%; 0.87%]). Deficits in delayed recall of learning/verbal memory (**SRT**) were present in **6%** CI: [0.03%; 0.15%] of **CIS** patients, **12%** CI: [0.06%; 0.23%] in **RRMS**, **57%** CI: [0.41%; 0.72%] in **PPMS**, and reached **84%** CI: [0.67%; 0.93%] in **SPMS** group (see Figure 3).

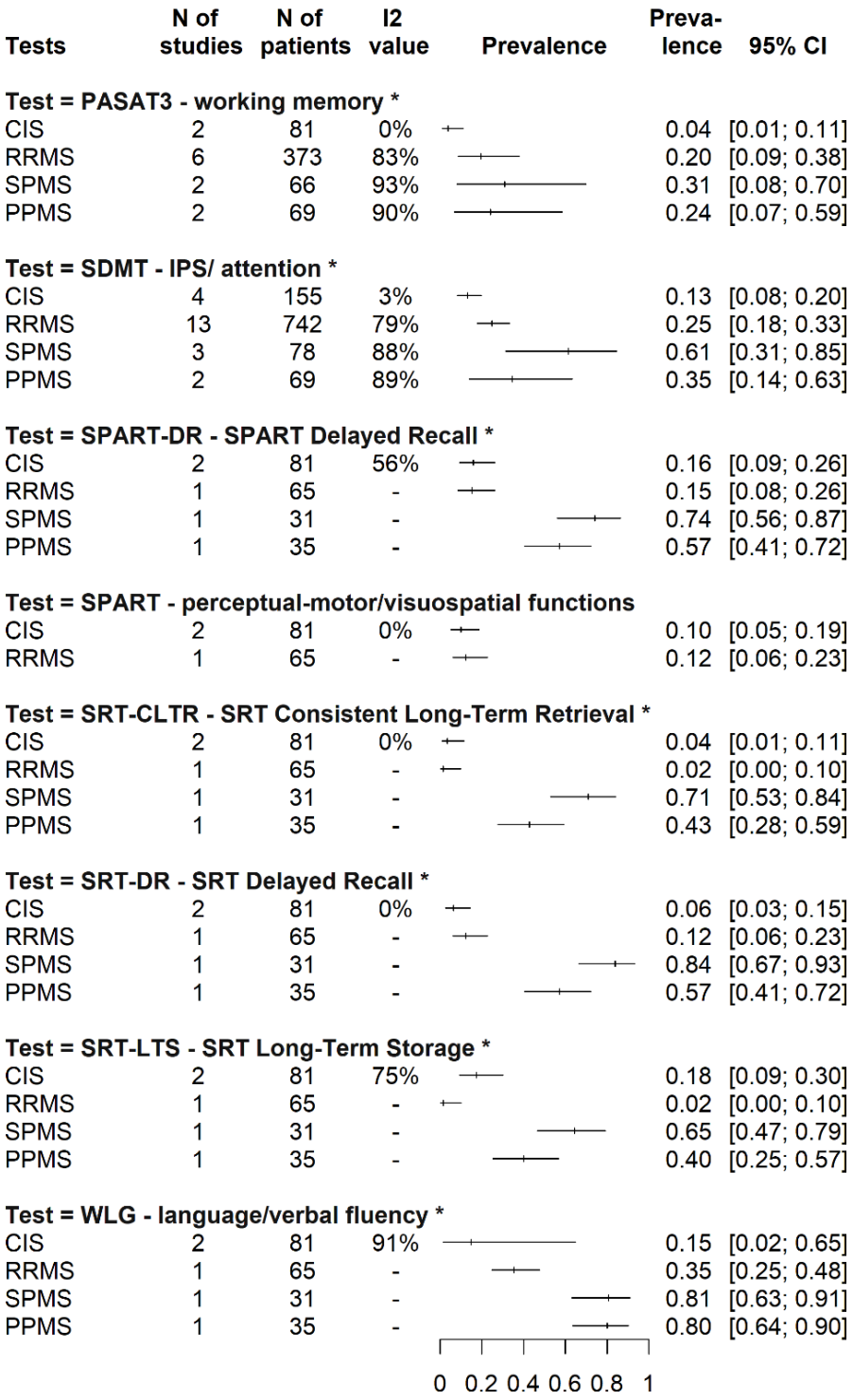


Figure 3. Summary panel of DSI prevalence rates across the subtests of the BRB-N battery at the "**1.5 SD below the normative values**" cut-off [44].

The subtests of the BRB-N battery are displayed on the left side of the figure. Below each test, MS subtypes are shown. On the right side of the figure, the prevalence rates (along with confidence intervals) of patients showing impairment, categorized by MS subtype, are shown for each BRB-N subtest, based on the ***"1.5 SD below the normative values"*** *cut-off.*

8.1.2.3 A cut-off of the score below the 5th percentile of the normative values

At this cut-off value, IPS impairment (**SDMT**) is observed in **74%** CI: [0.60%; 0.85%] of patients with **SPMS**. In comparison, **59%** CI: [0.40%; 0.76%] of **PPMS** patients are affected. The lowest rate is found in the **CIS** group, where only **19%** CI: [0.13%; 0.26%] show impairment, while **RRMS** patients fall between these extremes with a prevalence of **25%** CI: [0.19%; 0.32%].

Regarding working memory deficits (**PASAT3**), the **CIS** group shows a slightly higher frequency (**21%**, CI: [0.15%; 0.29%]) than the **RRMS** group (**19%**, CI: [0.15%; 0.24%]). These are followed by higher rates in **PPMS** (**43%**, CI: [0.25%; 0.64%]) and **SPMS** (**48%**, CI: [0.31%; 0.66%]).

For visuospatial memory, sufficient data are available only for delayed recall (**SPART DR**). In this domain, impairment is seen in **20%** CI: [0.14%; 0.27%] of **CIS** patients, **28%** CI: [0.19%; 0.39%] of those with **RRMS**, **30%** CI: [0.15%; 0.52%] in the **PPMS** group, and **55%** CI: [0.37%; 0.72%] of **SPMS** patients.

Concerning learning and verbal memory, depending on the retrieval measure, the following proportions are affected: in the **CIS** group, **13–25%** (CI: [0.18%; 0.33%] for **SRT DR**, CI: [0.10%; 0.22%] for **SRT LTS**, CI: [0.08%; 0.20%] for **SRT CLTR**); among **RRMS** patients, **22–28%** (CI: [0.16%; 0.28%] for **SRT DR**, CI: [0.21%; 0.37%] for **SRT LTS**, CI: [0.15%; 0.33%] for SRT CLTR); in **PPMS**, **17–35%** (CI: [0.07%; 0.38%] for SRT DR, CI: [0.18%; 0.56%] for both **SRT LTS** and **CLTR**); and in **SPMS**, **41–55%** (CI: [0.28%; 0.63%] for **SRT DR**, CI: [0.37%; 0.72%] for **SRT LTS**, CI: [0.25%; 0.60%] for **SRT CLTR**).

A notable finding emerges in the area of verbal fluency (**WLG**), where **57%** CI: [0.36%; 0.75%] of **PPMS** patients show impairment. This compares to **45%** CI: [0.28%; 0.63%] of **SPMS**, **29%** CI: [0.22%; 0.38%] of **CIS**, and **26%** CI: [0.15%; 0.42%] of **RRMS** patients (see Figure 4).

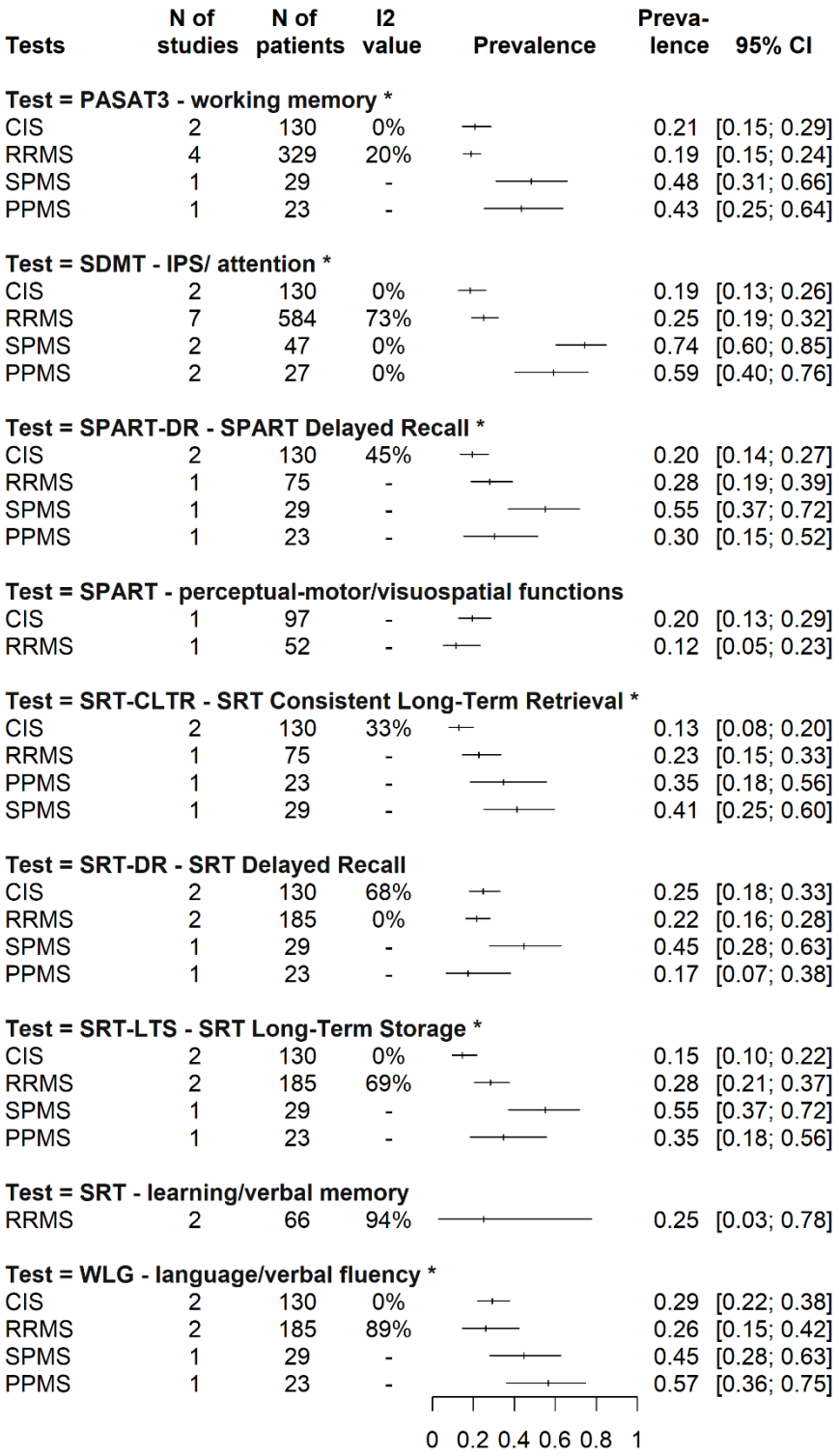


Figure 4. Summary panel of DSI prevalence rates across the subtests of the BRB-N battery at the „**score below the 5th percentile of the normative values**" cut-off [44].

The subtests of the BRB-N battery are displayed on the left side of the figure. Below each test, MS subtypes are shown. On the right side of the figure, the prevalence rates (along with confidence intervals) of patients showing impairment, categorized by MS subtype, are shown for each BRB-N subtest, based on the ***"score below the 5th percentile of the normative values"*** *cut-off.*

Further systematic analysis with other cut-off values – qualitative analysis/systematic review

Five otherwise eligible studies were excluded from the meta-analysis because they used alternative cut-off values to define DSI, different from the commonly applied thresholds of 1.5 or 2.0 SD below the normative value, or the 5th percentile of the normative population. These studies were included only in the systematic review, as they provided insufficient data and were not suitable for statistical (quantitative) analysis across subtypes.

The specific cut-offs were as follows: for the PASAT3, either 1 SD below the mean of healthy controls or a raw score of 32 or less; for the SDMT, a T score of 35 or lower, or a raw score of 55 or below; and for the WLG, SRT-DR, and SRT-CLTR tests, a z score less than -1.68.

Most of these studies focused on RRMS patients, and despite the heterogeneity in cut-off values, their findings aligned with previous results, indicating that information processing speed impairment affects at least one-third of individuals with RRMS.

8.1.3 Assessment of the Risk of Bias and Level of Evidence Certainty

Quality evaluation based on the "JBI Quality Assessment Tool for Prevalence Studies" criteria examines the transparency of evidence synthesis results and findings along 9 aspects. The first three items address selection and performance bias. Given that 67% of primary outcomes were rated high risk, there is a notable possibility of selection bias. Q4, related to reporting bias, showed only 8.8% high-risk outcomes, indicating a low error rate in this respect. Q5–Q7 assess detection bias. With just 2.5% of outcomes rated high risk, this suggests minimal error and reflects one of the strengths of our meta-analysis: consistent but distinct detection criteria. For Q8 (statistical clarity), a study was considered low risk if it reported both the exact number and percentage of impaired individuals, along with a clearly defined cut-off. In this respect, our study is considered

low risk. Q9, which concerns attrition bias, showed a low error rate as well, with only 3.7% of outcomes at high risk.

In summary, while many studies showed high risk in at least one (often two or three) JBI domains, the overall quality of our meta-analysis was rated as moderate risk, primarily due to potential selection and performance bias (see Figure 5).

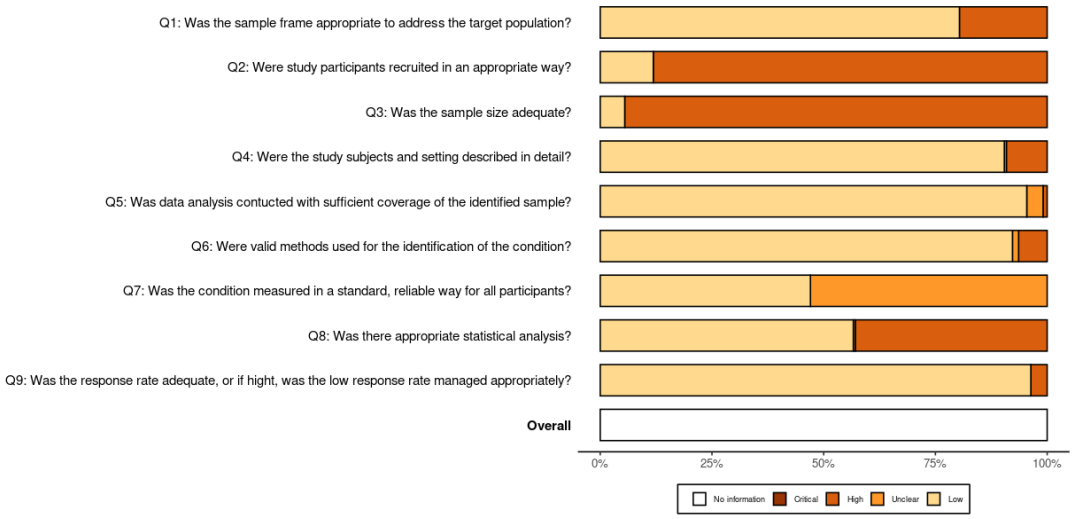


Figure 5. Assessment of risk of bias for each included study (Summary plot) [44].

Based on the modified Oxford Centre for Evidence-Based Medicine Levels of Evidence, our study is classified as *Level 2* (see Figure 6).

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table
OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".
Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653
** OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson*

Figure 6. Modified Oxford Centre for Evidence-Based Medicine Levels of Evidence (2011) [44].

8.2 Study 2 – Cognitive impairment in multiple sclerosis: the role of clinical and sociodemographic factors

8.2.1 Systematic Literature Search, Selection, and Study Characteristics

Our search key initially identified 3722 records, and eventually, 155 studies were included in the synthesis (both in the systematic review and in the meta-analysis).

The detailed record of the complete selection process is presented in Figure 7.

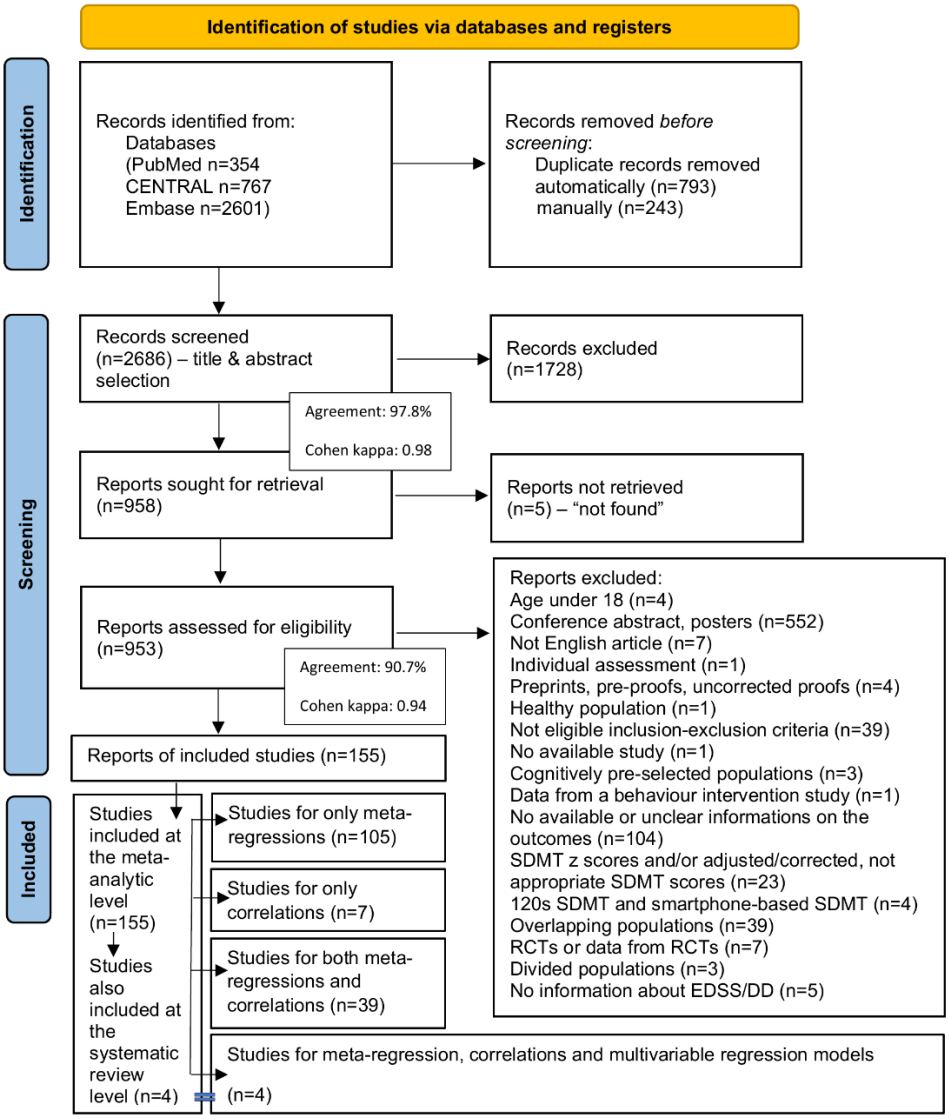


Figure 7. Flow diagram of study identification and selection by PRISMA 2020 with details of the reasons for exclusion [45].

Although a total of 155 studies were included in the overall analysis,105 were fit only for univariate meta-regression analyses, 7 studies examined only univariate study-level correlations, and 39 studies were suitable for both. Additionally, 4 studies were fit for univariate meta-regression analyses, univariate study-level correlations, and multivariable regression models (the multivariable regression models of these 4 articles were also included at the systematic review level). From the 155 included studies, 21 articles examined multiple MS subtypes (i.e., Mixed MS, RRMS, PPMS, SPMS) simultaneously.

Sufficient aggregate data were available for several sociodemographic and clinical variables, including: age in years, sex (percentage of females), education in years, and disease duration in years ("not specified", "time since diagnosis", or "time since first symptoms"), EDSS scores, depression assessments (such as BDI: Beck Depression Inventory [46], BDI-II: Beck Depression Inventory-II [47], BDI-FS: Beck Depression Inventory-Fast Screen [48], and HADS-D: Hospital Anxiety and Depression Scale-Depression score [49]), and fatigue scores (FSS: Fatigue Severity Scale [50] and the total score of MFIS: Modified Fatigue Impact Scale[51]). Additionally, motor performance was assessed using the Nine-Hole Peg Test (T9HP) [52] and the Timed 25-Foot Walk Test (T25FW) [53].

The role of „disease-modifying therapies" (DMTs) in influencing cognitive performance was assessed using aggregated treatment data from the included studies. We specifically examined the overall percentage of patients receiving DMT (referred to as "percentage on DMT"), further distinguishing between those on "platform therapies" (interferons, teriflunomide, dimethyl-fumarate, glatiramer-acetate) and those receiving "high-efficacy therapies", such as fingolimod, natalizumab, ocrelizumab, alemtuzumab, cladribin, siponimod, ponesimod, ofatumumab, ozanimod, mitoxantron, daclizumab, rituximab, and other immunomodulatory therapies used in rheumatology that are not approved for the treatment of MS: mycophenolate-mofetil, azathioprin, methotrexate. Hereafter, we will refer to the above as "percentage on platform" and "percentage on HET", respectively.

Finally, data from 22,828 individuals with MS were included in the meta-analysis. Simultaneously, a systematic review of 505 patients was also performed.

Following the CoCoPop framework, the primary cognitive outcome - mean raw scores on the SDMT - was interpreted in the context of relevant and statistically applicable clinical and demographic variables. EDSS and disease duration served as primary exposures, while age, sex, education, depression, fatigue, mobility scores, and treatment served as secondary exposures.

Baseline characteristics of the included studies are detailed further in Supplemental table 1 of the published study's Supplementary Material Appendix 6 [45].

8.2.2 Quantitative and qualitative analysis

In the following, we present our results across four types of analyses at two levels of evidence (first level: univariate study-level correlations and multivariable study-level regression models, and second level: univariate meta-regressions) with multivariate regressions based on the pairwise dependency (interdependence) analysis of the examined clinical and sociodemographic covariates.

Meta-analysis (quantitative analysis) of *univariate study-level correlations* stratified by different MS subtypes

For direct intra-study pooled correlation analyses, based on the available literature, a meta-analysis could only be performed for the ”mixed MS” and RRMS populations. The main findings – taking into account the primary exposures (EDSS and disease duration), the number of the included articles, and the congruence between the levels of evidence - are discussed below, with further details of meta-analyzed direct correlation results provided in Figure 8.

Mixed MS populations:

For our primary exposures, ***EDSS***, and ***disease duration***, both Pearson and Spearman correlations show a highly significant and clearly negative association: higher EDSS score is strongly associated with lower SDMT scores (*Pearson*: **-0.44** CI:[-0.50; -0.36], *Spearman*: **-0.49** CI:[-0.61; -0.35]) and longer disease duration is correlated with poorer SDMT performance (*Pearson*: **-0.28** CI:[-0.40; -0.15], *Spearman*: **-0.22** CI:[-0.41; -0.01]).

The female ***sex*** has a significantly positive impact on SDMT performance (*Pearson*: **0.18** [0.11; 0.25]), indicating that a higher proportion of females in the population is associated with better SDMT scores.

Pearson correlation analyses for the variable of ***education*** yielded highly significant positive correlations (*Pearson*: **0.31** CI:[0.20; 0.42], *Spearman*: **0.29** CI:[0.06; 0.49]), indicating that higher years of education were associated with higher SDMT scores.

For the ***depression*** scales - however, with only a few studies were available - a consistent, negative correlation with SDMT scores was observed (**BDI**: *Pearson*: **-0.14**

CI:[-0.36; 0.09], **BDI-FS**: *Pearson*: **-0.33** CI:[-0.53; -0.10], **HADS-D**: *Pearson*: **-0.22** CI:[-0.34; -0.09]), indicating that a negative trend can be inferred: higher depression scores associated with lower SDMT scores.

RRMS populations:

Regarding our primary exposures, ***EDSS*** showed a significant negative correlation: higher EDSS scores are associated with lower SDMT scores (*Pearson*: **-0.47** CI:[-0.66; -0.23]), and ***disease duration*** showed a non-significant negative association: longer disease duration is correlated with poorer SDMT performance (*Pearson*: **-0.48** CI:[-0.91; 0.47]).

Education (in years) also demonstrated a nearly significant positive correlation with SDMT scores in the RRMS population (**0.32** CI:[-0.02; 0.59]), indicating that higher education is associated with higher SDMT scores. However, this significance level is marginal, based on *Pearson* correlations, and is derived from only three eligible studies.

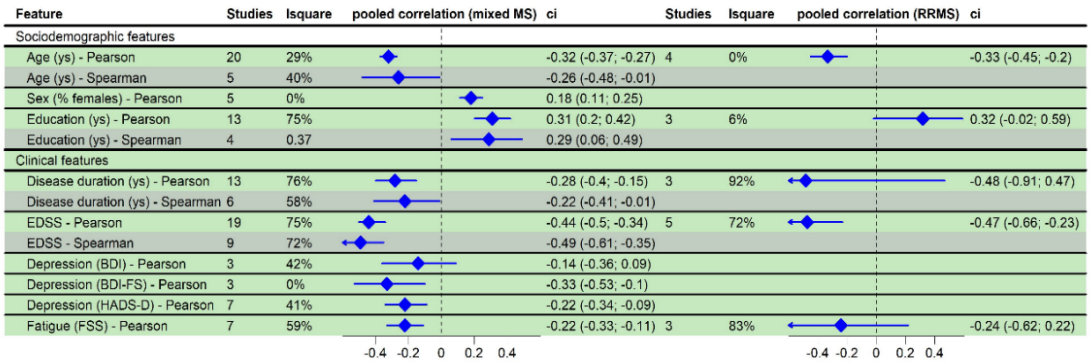


Figure 8. Summary plot of the meta-analyzed study-level correlation results [45].

Out of the total 155 included articles, 50 addressed univariate study-level correlations. Among these 50 studies, 1 investigated both Mixed and RRMS populations, 36 focused solely on Mixed populations, and 13 exclusively on RRMS populations. The number of studies presented in Figure 8 reflects the number of studies examining a given parameter within each MS subtype (the subtypes are indicated at the top of the figure). The total count in the figure exceeds 50 because most studies analyzed the ***study-level correlation*** *between SDMT raw scores and more than one clinical and/or sociodemographic parameter.*

I^2: level of heterogeneity; N: number of the included studies; ci: Confidence Interval; EDSS: Expanded Disability Status Scale; BDI: Beck Depression Inventory; BDI-FS: Beck Depression Inventory-Fast Screen; HADS-D: Hospital Anxiety and Depression Scale-Depression score; FSS: Fatigue Severity Scale

Meta-analysis (quantitative analysis) of *univariate meta-regressions* stratified by different MS subtypes:

Univariate meta-regression analyses were conducted for the mixed MS, RRMS, PPMS, and SPMS populations. However, for the PPMS and SPMS subgroups, only limited data were available for some parameters, as this was based on a very small number of studies. Therefore, considering the number of included studies, our primary exposures (EDSS and disease duration), the other available parameters, and the congruence across the two levels of evidence, we focus our main findings only on the mixed and RRMS populations, with further details for other MS subgroups and variables provided in Table 3.

Mixed MS populations:

In mixed MS populations, one of our primary exposures, ***EDSS***, showed the most pronounced and significant negative association with SDMT performance (b: **-2.772** p<0.001). Our other primary exposure, ***disease duration***, showed a marginally significant negative association with SDMT scores (b: **-0.278** p: 0.064).

Of the additional parameters examined, the severity of ***depression*** showed an effect of similar strength to EDSS (as assessed by **BDI**: b: **-2.031** p:0.003, **BDI-FS** scores: b: **-4.926** p:0.006; and **HADS** depression scores: b: **-2.337** p:0.007). For ***education*** (in years), a strong, significant positive association was observed with SDMT scores (b: **2.443** p<0.01).

A strong association was observed for ***sex*** (percentage of females), with a significance similar to that of EDSS: the higher the percentage of females in the ”mixed MS” populations studied, the higher the SDMT score (b: **0.185** p:0.001).

RRMS populations:

In RRMS populations, similar to mixed MS, the ***EDSS*** score showed the most pronounced and significant negative association, i.e., the more severe the physical impairment, the lower the raw SDMT scores (b: **-3.731** p:0.001). The ***disease duration***,

primary exposure parameter, showed a positive, non-significant association with SDMT scores (b: **0.044** p:0.913), in the opposite direction compared to the mixed MS group.

Among the other parameters studied, also notable is that ***education*** emerged as a very strong, significantly positive association parameter with SDMT scores in the RRMS subgroup (b: **3.636** p<0.001), with a relatively moderate number of studies included.

Table 1. Tabular summary of univariate meta-regression results stratified by different MS subtypes. [45]

	Covariates	Mixed MS	RRMS	PPMS	SPMS
Sociodemographic features	**Age (ys)**	-0.096 *p:*0.285 n:164 N: 22,211	0.209 *p:*0.311 n:57 N: 4,217	-0.408 *p:*0.777 n:8 N: 224	0.11 *p:*0.679 n:13 N: 426
	Sex (% fem)	**0.185 *p:*0.001 n:155 N: 21,320**	0.132 *p:*0.108 n:52 N: 3,587	nd	0.13 *p:*0.496 n:12 N: 418
	Edu (ys)	**2.443 *p*<0.001 n:67 N: 7,722**	**3.636 *p:*<0.001 n:22 N: 1,833**	nd	nd
Clinical features	**DD (ys)**	***-0.278 p:0.064 n:121 N: 18,324*** -0.474 *p:*0.246 n:15[a] N: 1,218 -0.305 *p:*0.379 n:9[b] N: 1,041	0.044 *p:*0.913 n:41 N: 3,085	nd	-0.018 *p:*0.959 n:10 N: 400
	EDSS	**-2.772 *p:*<0.001 n:151 N: 15,028**	**-3.731 *p:*0.001 n:57 N: 4,217**	0.264 *p:*0.947 n:8 N: 224	-2.367 *p:*0.555 n:13 N: 426
	Depr	**-2.031 *p:*0.003 n:9[c] N: 1,157 -4.926 *p:*0.006 n:12[d] N: 1,256 -2.337 *p:*0.007 n:20[e] N: 3,086**	**-3.607 *p:*0.01 n:8[e] N: 746**	nd	nd
	Fatigue	1.817 *p:*0.397 n:22[f] N: 2,078 -0.168 *p:*0.297 n:10[g] N: 1,097	-0.04 *p:*0.992 n:10[f] N: 853	nd	nd
	T25FW	**-0.492 *p:*0.028 n:22 N: 2,573**	**-0.818 *p:*0.016 n:13 N: 911**	nd	nd
	T9HP	-0.669 *p:*0.218 n:10 N: 965	nd	nd	nd
	Treatment	-0.017 *p:*0.674 n:45[h] N: 9,392 -0.011 *p:*0.86 n:25[i] N: 7,139 0.026 *p:*0.673 n:24[j] N: 7,097	0.011 *p:*0.858 n:24[h] N: 1,662 -0.059 *p:*0.414 n:15[i] N: 896 0.107 *p:*0.174 n:14[j] N: 854	nd	nd

Significant results are highlighted in bold and burgundy, results close to significance are highlighted in bold and italics.

MS: multiple sclerosis, RRMS: relapsing-remitting multiple sclerosis, PPMS: primary progressive multiple sclerosis, SPMS: secondary progressive multiple sclerosis; ys: years; fem: females; Edu: education; DD: disease duration; n: number of the included studies, N: number of the included patients, EDSS: Expanded Disability Status Scale, T25FW: Timed 25-foot Walk test, T9HP: Nine-Hole Peg Test; nd: no data. *p:* significance level; [a]: time since diagnosis; [b]: time since first symptom; [c]: BDI: Beck Depression Inventory; [d]: BDI-FS: Beck Depression Inventory Fast Screen; [e]: HADS-D: Hospital Anxiety and Depression Scale-depression score; [f]: FSS: Fatigue Severity Scale; [g]: MFIS: Modified Fatigue Impact Scale, total scores; [h]: % on DMT (Disease-Modifying Therapy); [i]: % on platform therapy; [j]: % on HET (Highly Effective Therapy)

Results of the systematic review (qualitative analysis) of study-level multivariable regression models

Due to the variability in both the variables included and the types of regression models applied across studies, we conducted a systematic review of study-level multivariable regression analyses.

Four studies conducted multivariable regression techniques on mixed MS populations, utilizing linear, stepwise, or logistic regression models incorporating sociodemographic, clinical, and other relevant factors.

All models accounted for age and education as covariates, with one study reporting significant negative associations for both. EDSS emerged as the most impactful variable, with significant negative effects observed in three studies, one of which reported a particularly strong association. In contrast, variables such as disease duration, sex, and depression showed no significant effects, alongside other parameters.

8.2.3 Meta-level multivariate regression analyses of the investigated clinical and sociodemographic factors (covariates) – interdependence analyses

For mixed MS populations, pairwise dependency analyses among covariates indicated strong positive pairwise linear associations between covariates *age, disease duration*, and *EDSS*. For this reason, we fitted three multivariate meta-regression models; each including the variables *sex* and *education*, and one of the three strongly correlated variables. In all models, *sex* and *education* emerged as significant predictors, with *education* showing a more pronounced effect (lower *p*-values). While *age* and *disease duration* were not significant when analyzed alongside sex and education, *EDSS*

remained a robust and significant predictor, even when controlling for the other two variables, though education retained the strongest overall effect.

For RRMS, pairwise correlations among *age, disease duration, EDSS*, and *education* were generally high. Therefore, we limited model inclusion to covariates with moderate correlations to avoid multicollinearity. Across these models, *education* and *EDSS* consistently remained strong predictors, while *sex* and *age* were either non-significant or showed borderline effects.

Further details are available in Figure 9a–b and Table 2.

a **b**

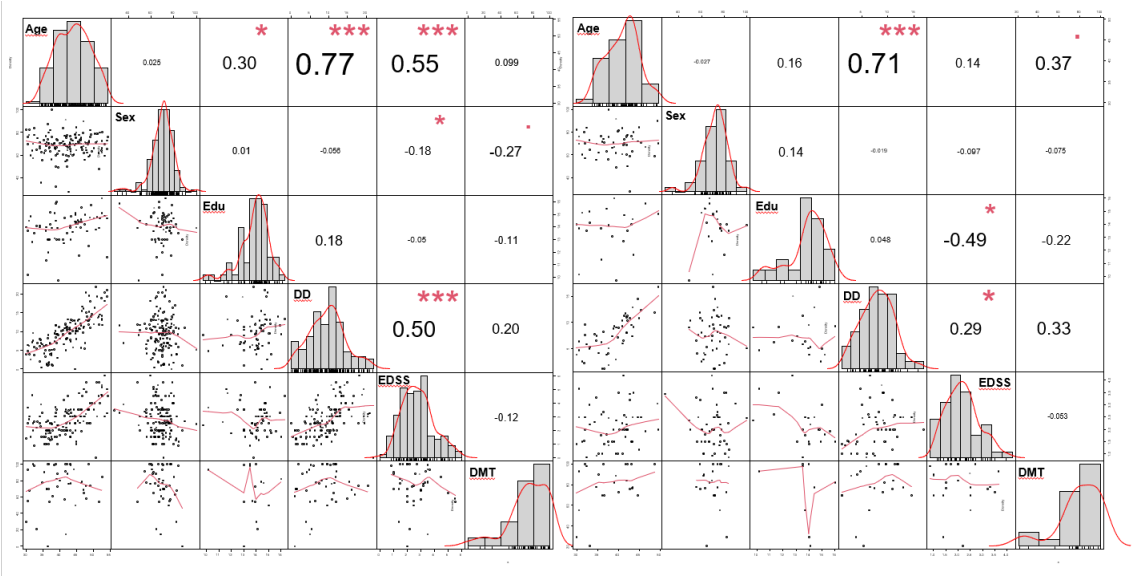


Figure 9a-b. Pairwise dependency matrix of the covariates in mixed (Figure 9a) and in RRMS populations (Figure 9b). [45]

The results of the pairwise dependency analyses. The main diagonal elements contain the histograms of the covariates. Below the main diagonal pairwise scatter plot, visualizations are present while upper the main diagonal Pearson correlations are printed. The absolute value of the correlations represents the strength of the linear relationship between the variables while the sign indicates the direction of the relationship. One, two and three stars indicate p-values less than 0.001, 0.1 and 0.05, respectively. A small rectangle is used to indicate a p-value between 0.05 and 0.1.

DD: disease duration (ys), Edu: education (ys), EDSS: Expanded Disability Status Scale

Table 2. Multivariable regression models, based on the results of the pairwise analysis of the covariates. [45]

MS subtypes	Multivariable regression models	Variables	n	estimate	p-value	CI
Mixed MS	Sex+Edu+Age	**Sex**	68	**0.2011**	**0.0132**	[0.0421; 0,3601]
		Edu		**2.4129**	**0.0003**	[1.1173; 3.7084]
		Age		0.0111	0.9270	[-0.2262; 0.2483]
	Sex+Edu+DD	**Sex**	64	**0.1799**	**0.0269**	[0.0206; 0.3392]
		Edu		**2.7090**	**<0.0001**	[1.4338; 3.9842]
		DD		-0.1305	0.4574	[-0.4748; 0.2137]
	Sex+Edu+EDSS	**Sex**	63	**0.1680**	**0.0459**	[0.0030; 0.3330]
		Edu		**2.4995**	**0.0001**	[1.2360; 3.7630]
		EDSS		**-1.5403**	**0.0395**	[-3.0066; -0.0739]
RRMS	Sex+Age	Sex	52	0.1406	0.0876	[-0.0207; 0.3019]
		Age		0.1390	0.4535	[-0.2244; 0.5023]
	Sex+DD	Sex	47	0.1552	0.1272	[-0.0443; 0.3547]
		DD		-0.0856	0.7603	[-0.6356; 0.4644]
	Sex+% on DMT	Sex	22	0.1224	0.4734	[-0.2122; 0.4570]
		% on DMT		0.0296	0.6432	[-0,0958; 0.1551]
	Sex+EDSS	Sex	51	0.1057	0.1614	[-0.0422; 0.2535]
		EDSS		**-3.8686**	**0.0003**	[-5.9580; -1.7791]
	Sex+Edu+Age	Sex	21	0.1679	0.2532	[-0.1201; 0.4558]
		Edu		**3.1657**	**0.0005**	[1.3956; 4.9357]
		Age		0.0236	0.9263	[-0.4757; 0.5229]
	Sex+Edu	Sex	21	0.1650	0.2447	[-0.1130; 0.4431]
		Edu		**3.1807**	**0.0002**	[1.4879; 4.8734]
	Sex+% on DMT+Age	Sex	22	0.1762	0.3132	[-0.1662; 0.5186]
		% on DMT		0.0026	0.9689	[-0.1290; 0.1343]
		Age		0.3356	0.2261	[-0.2078; 0.8790]
	Sex+EDSS+Age	Sex	51	0.1041	0.1625	[-0.0420; 0.2501]
		EDSS		**-4.1249**	**0.0001**	[-6.2115; -2.0383]
		Age		0.2640	0.1253	[-0.0736; 0.6016]

Significant results are highlighted in bold and burgundy, results close to significance are highlighted in bold and italics. n: number of the included studies; CI: confidence interval; Edu: education; DD: disease duration; EDSS: Expanded Disability Status Scale; DMT: Disease-Modifying Therapies

Based on all of the above, our main findings are summarized in Figure 10.

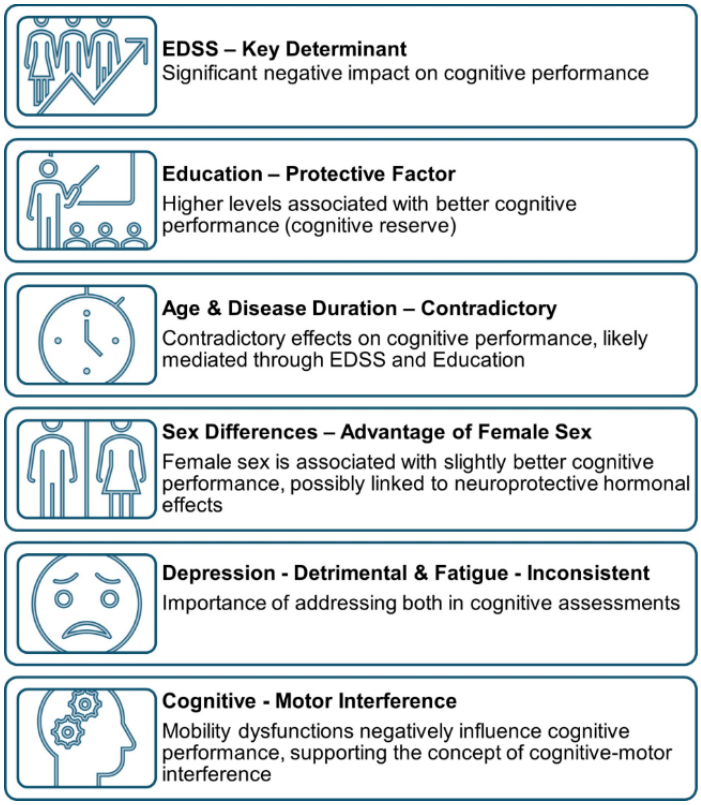


Figure 10. Key findings of our study reveal the multifactorial nature of the relationship between disease-related and sociodemographic factors and SDMT performance as a key sentinel test for cognitive impairment [45].

8.2.4 Assessment of the Risk of Bias and Level of Evidence Certainty

Based on the JBI Quality Assessment Tool for Analytical Cross-Sectional Studies, the first four items indicate a low risk of selection and performance bias, implying that the study populations included in the meta-analysis were generally representative. In contrast, the remaining items suggest a higher risk of detection bias, and to a lesser extent, reporting bias. This elevated risk is primarily due to inconsistencies in how associations were assessed across studies, likely reflecting the heterogeneity in reporting of factors related to cognitive impairment and the differences in statistical adjustments applied in the analyses.

The summary of the assessment of the risk of bias for each included study is detailed in Figure 11.

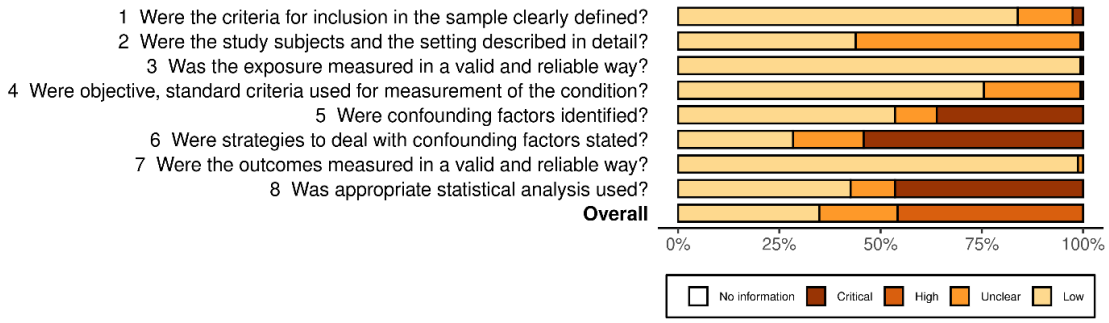


Figure 11. Summary plot of the assessment of risk of bias for each included study using Risk-of-bias VISualization (robvis) visualization tool [45].

9 DISCUSSION

9.1 Summary of findings and their comparisons with other international publications

Although cognitive impairment (CI) in multiple sclerosis (MS) was long neglected since Jean-Martin Charcot's impressively accurate initial observations *("marked enfeeblement of the memory, conceptions formed slowly, and intellectual and emotional faculties blunted in their totality"*) [54], the past few decades have seen a substantial revival in research attention of CI in MS, largely due to the development of refined neuropsychological tests, advanced brain imaging techniques, and evolving therapeutic strategies. As a result, current scientific discourses are structured around the following four key questions: 1) *What are the characteristics and patterns of CI in MS?* 2) *How can it be detected early?* 3) *What are the influencing and predictive factors?* 4) *What targeted therapeutic interventions can be designed accordingly?*

In our first meta-analysis, we sought to address the first question by examining the characteristics and prevalence of domain-specific impairment (DSI) in MS. Recognizing the inconsistencies and contradictions in the literature regarding both the definitions (i.e., the different cut-off values used to define impairment) and assessment NPTs of CI, we used a pre-specified NPT battery (BRB-N) with high specificity and sensitivity to identify CDs across different MS subtypes, focusing on the most commonly used cut-off values (1.5 SD, 2.0 SD below the normative values, and the score below the 5th percentile of the normative values). Our findings confirmed that CI is prevalent across all MS phenotypes, including early forms such as CIS, with a progressive worsening observed from CIS through RRMS and PPMS to SPMS, in line with the results of previous studies [55-58]. Impairment in information processing speed (IPS) - the "core" domain of CI in MS - was present even in early RRMS, underscoring its role as a potential primary deficit influencing other cognitive domains, consistent with DeLuca et al.'s *Relative Consequence Model* [59,60]. However, the broad variation in CI prevalence across studies pointed to unresolved heterogeneity in clinical and sociodemographic characteristics of study populations, the definition of impairment thresholds, and the nature of the tests used - issues that limit the comparability and generalizability of findings. This was also confirmed by a previous cross-sectional study that examined the

prevalence and profile of cognitive dysfunction in different MS subtypes, and showed that the differences in cognitive performance observed between MS subtypes largely disappeared after controlling for physical disability (EDSS), suggesting that clinical parameters have a crucial influence on cognitive dysfunction in MS [55].

Therefore, to investigate these sources of heterogeneity further and to understand the complex interactions between disease-related and sociodemographic parameters and CI, we conducted a second meta-analysis focusing specifically on Symbol Digit Modalities Test (SDMT) performance as a sentinel marker for CI. With this, we sought to answer the third key debating question above, namely, "*What are the influencing and predictive factors of CI in MS?*". This analysis incorporated two levels of evidence and included interdependency analysis among the investigated covariates, allowing for the identification of independent predictors of SDMT outcomes. Based on comprehensive data availability, our results mainly focused on mixed and RRMS populations and showed that EDSS, reflecting overall physical status, consistently had the strongest negative effect on SDMT scores at all levels of evidence. Importantly, the interplay between EDSS, age, and disease duration revealed that age and disease duration likely influence cognition indirectly, via their association with physical disability, i.e. *the negative association between clinical status and cognition likely becomes more pronounced over time (referring to the role of age and disease duration), or EDSS might operate through the length of time with MS.* Amato et al. [61] and Prakash et al. [9] also confimed this interdependence. This association is further shaped by the cognitive reserve, which is mainly determined by educational attainment [62], which emerged as a significant protective factor on CI performance in our study. This is partially supported by the literature; however, the relationship between EDSS and cognition remains controversial [2,63-65]. Lynch et al. [66] reported a clear association between EDSS score and cognitive impairment, observed also in early stages of MS. They emphasized that strong EDSS-cognition correlations often appear in studies [67,68] using speeded information processing tasks, such as the SDMT, which may be confounded by motor or sensory deficits.

In summary, the highly comprehensive and delicately balanced interplay between EDSS, education, age, and disease duration highlights the complexity of factors influencing SDMT performance. Our studies were based on cross-sectional data;

however, a recent longitudinal observational study by Longinetti et al. [69], conducted on a large population-based sample, showed similar results. Based on their results, older age was associated with CI at baseline, while female sex and having more than 12 years of education were initially linked to better cognitive trajectories, although these associations weakened after adjusting for MS severity, reinforcing the dominant influence of physical disability on cognitive performance. This is consistent with findings from Foong et al. [70], based on a large longitudinal study of RRMS patients, which identified that higher EDSS, older age, male sex, and depression predicted poorer processing speed over time, while higher educational attainment was protective. These also raise questions about the reliability of general adjustments solely for age and education when calculating derived SDMT values (such as z-scores or t-scores), which calls for further research to develop more precise models in this regard.

Among the other variables examined, *depression* had a significant adverse impact on SDMT performance, though the link is likely complex, and based on the previous findings in the literature, parallel testing for cognition, anxiety, depression, and *fatigue* is essential [71,72]. *Female sex* appears protective, possibly due to estrogen's neuroprotective effects [73,74], though menopause may reverse this association [75]. Motor performance (*T25FW, T9HP scores*) shows weak but notable negative associations with SDMT, supporting theories like "cognitive-motor interference" (CMi) or, alternatively, "dual-task interference" (DTi) [76] or "cognitive-postural interference" (CPI) [77], commonly referred to in the literature. They are associated with special neural correlates and the interactions of complex neural networks [78]. Regarding *DMTs*, current evidence is limited and inconsistent based on our findings, highlighting the need for trials targeting well-defined neurocognitive endpoints directly.

Due to all of the above, the heterogeneity observed in the MS populations studied, the influencing role of clinical and sociodemographic characteristics, and the differences in the tests and cut-off values used to define CI, raise doubts about *whether it is even feasible to define domain-specific impairment in a consistent manner, generalised across MS subtypes*. Moreover, it should also be acknowledged that this issue has a sociological and socio-theoretical dimension, as the concept of what is deemed '*normal*' varies significantly across continents, from country to country, even from region to region. These variations in defining reference norms reflect underlying cultural and subcultural

influences, making it highly questionable whether *a uniform consensus on the definition of 'normative' values can ever be feasibly attained*. Rather than a rigid, definition-based approach to domain-specific impairment (DSI), the concept of *inter-individual heterogeneity* in CI should be emphasized in MS, i.e., *patients' own previous cognitive performance can be more relevant in assessing cognitive changes in MS*. This ***„individual referencing"*** approach accounts for baseline variability, individual disease courses, clinical vs. everyday significance of CI, and enables personalized supports for our patients. This approach is often referred to as "Reliable Change Indices" [5,79,80] in the literature.

Based on our findings, Figure 12, as a translational framework, can serve as a conceptual basis and algorithm for the future development of advanced cognitive recognition and intervention strategies, as well as for more refined recommendations and clinical guidelines developed in this field.

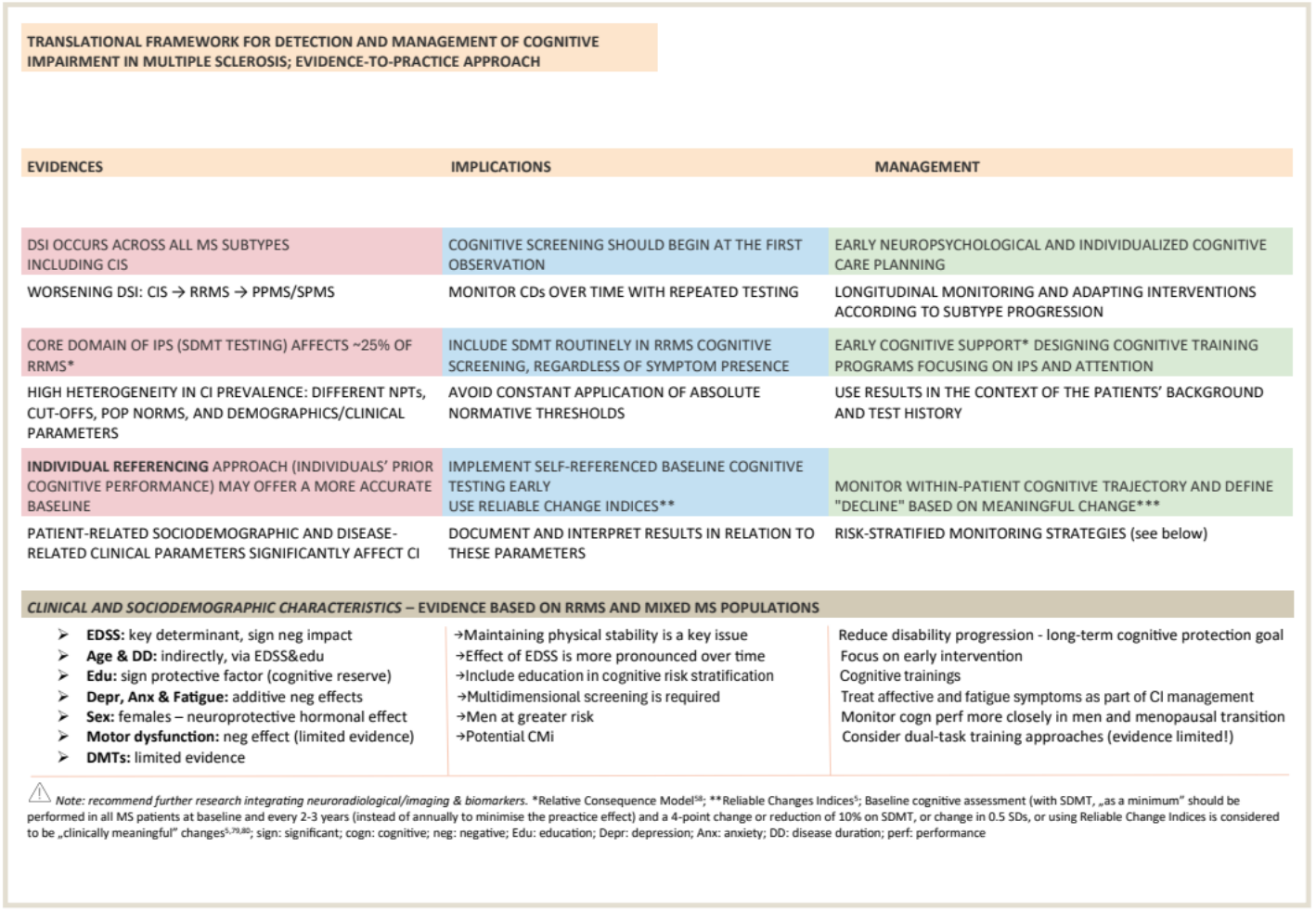


Figure 12. Translational framework for detection and management of cognitive impairment in multiple sclerosis [81,82].

9.2 Strengths

Study 1

One of the main strengths of our study lies in the consistent use of the same NPTs and cut-off values across various CDIs, which distinguishes it from previous meta-analyses on related topics [7-9]. Additionally, we were the first to include CIS patients in the analysis. The study also introduces a novel perspective by applying *individual referencing* and assessing its impact on the results.

Study 2

A major strength of our study is the use of an extensive dataset along with a consistent and comprehensive methodological approach, in line with the established recommendations, which is crucial for evaluating future association studies.

However, the cross-sectional design limits our ability to draw causal conclusions, and working with aggregated data can sometimes distort relationships due to ecological and aggregation bias. Additionally, the interdependence among predictors makes it difficult to identify the contribution of each parameter to the dependent variable (SDMT scores). Nevertheless, instead of ignoring these issues, according to Harrer's guidelines [5], we addressed them by analysing results across different evidence levels and conducting interdependence and multivariable regressions, as well. This approach helped reduce bias and made our findings more reliable, especially when ranking which predictors impact cognitive outcomes the most. This is an undeniable strength of our study.

9.3 Limitations

Study 1

Due to limited data availability, we were unable to account for differences in clinical and sociodemographic variables that may have influenced the outcomes, potentially introducing bias and limiting the interpretability of our findings. However, this limitation is among the issues our second meta-analysis aims to address.

Furthermore, the BRB-N battery includes only a limited assessment of executive functions, which prevented us from conducting specific analyses related to this cognitive domain.

Study 2

The main limitations of our study, in accordance with the above, are the use of cross-sectional data, which prevents causal inferences and assessment of changes over time. Additionally, using aggregated data to draw individual conclusions introduces the "fallacy of the wrong level," leading to ecological and aggregation biases that can distort relationships. The interdependence among predictors complicates regression analyses, making it difficult to isolate the effect of each parameter on SDMT scores.

Another possible limitation is that although the SDMT is a highly sensitive and specific cognitive screening test, it cannot be said to provide the most complete picture of overall CI. Furthermore, in the absence of available, comparable data, we were unable to take into account the role of other potentially meaningful influencing factors (e.g., radiological characteristics of the patients).

10 CONCLUSIONS

Through our two meta-analyses, we have reached a meaningful conclusion where we provide a valuable translational framework to address the above-mentioned two remaining comprehensive, multidimensional, and challenging key questions, namely: „*How can CI in MS be detected early?*" and „*What targeted therapeutic interventions can be designed accordingly?*".

In response to the first question, our results support the routine, standardized use of sensitive cognitive screening tools at the beginning of the MS disease course, such as the SDMT, implemented with an „*individual referencing*" model, enabling longitudinal monitoring and detection of significant cognitive changes across all phenotypes of MS.

In response to the second question, the translational framework highlights the importance of personalized cognitive rehabilitation, which focuses on core cognitive areas such as IPS and is supported by multidisciplinary care, adaptive intervention plans, and the integration of cognitive health into national and international MS treatment guidelines.

Together, these findings highlight a more accurate and effective cognitive care approach and direction for the care of MS patients.

11 IMPLICATIONS FOR PRACTICE

Study 1

With the introduction of the concept *of individual referencing*, we are setting a new direction that may facilitate the assessment of patients' cognitive abilities in clinical practice. This approach allows for a more personalized assessment by comparing current cognitive performance to the patient's own baseline or estimated premorbid functioning, rather than relying solely on normative group data. This method may improve the accuracy of detecting subtle cognitive decline, provide better information for clinical decision-making, and further support personalized interventions for the treatment of CI in MS.

Study 2

Our study supports a previously debated claim in the international scientific community: the physical condition of patients with MS - as reflected in EDSS scores - is a strong, independent predictor of CI and plays a critical role in the progression of overall disability. This finding underscores the importance of physical stabilization in clinical care. Long-term stability of EDSS scores is not only a neurological goal but also a key strategy for preserving patients' cognitive function, independence, social roles, family relationships, and overall QoL.

From a practical perspective, incorporating regular physical and cognitive assessments into routine care can help identify patients at higher risk of cognitive decline and provide guidance for early, holistic interventions.

12 IMPLICATIONS FOR RESEARCH

Study 1

Identifying the prevalence of DSI in MS provides further opportunities for research to make significant advances in understanding CI in MS and, thereby, in developing targeted cognitive study designs. This could lead to the development of more sensitive research tools, refinement of diagnostic criteria, and a deeper understanding of the mechanisms underlying cognitive dysfunction in MS, thus enabling the development of more precise endpoints in studies investigating therapeutic options.

The concept of *individual referencing* also provides a framework for examining cognitive changes over time within individuals, allowing researchers to better distinguish between disease-related decline and variability due to other factors, such as aging or education.

Study 2

A clear implication of our study for research is the multi-level, integrated analysis and methodological approach described above, which may also serve as a model for future association studies.

With a comprehensive understanding of the impact of disease- and patient-related factors on CI in MS, it is also possible to design more sophisticated research protocols in the future, in which population and individual differences can be taken into account in an exact manner.

13 IMPLEMENTATION FOR POLICYMAKERS

With the development of the translational framework for the detection and management of CI in MS, the scientific and clinical community should develop further recommendations and guidelines. Additionally, the importance and significance of the influencing role of patient-related sociodemographic and disease-related clinical parameters enable the development of further prognostic scoring systems in the future.

These could eventually provide the scientific basis for the establishment of international guidelines on the management of CI in MS.

Policymakers in the field of neurology should prioritize the development of precise recommendations for early and routine cognitive screening for all MS subtypes, starting from the first clinical observation, to enable timely intervention and monitoring of cognitive decline.

Local and international guidelines should include standardized, validated tools such as the SDMT as a cognitive screening test; and standardized cognitive test batteries for more complex neuropsychological analysis, and should emphasize longitudinal follow-ups using individual baseline values ("*individual referencing*") rather than population norms. Resource allocation should support multidisciplinary neuropsychological assessment, individualized care planning, and cognitive rehabilitation programs, especially those that enable individual reintegration opportunities.

Recommendations and guidelines should emphasize cognitive training for healthcare professionals and enable equal access to resources among sociodemographic and clinical subgroups of MS patients.

14 FUTURE PERSPECTIVES

On the basis of the current translational framework, my future perspectives will focus on refining individualized cognitive assessment protocols for MS, integrating both clinical and digital monitoring tools.

I plan to conduct longitudinal studies to validate "*individual referencing*" baseline approaches and adapt intervention programs to different MS subtypes. In addition, I aim to collaborate with national and international neurological policymakers to translate these findings into practical guidelines, ensuring equal access to cognitive screening and rehabilitation. Through multidisciplinary partnerships, I will work to make cognitive health a central component of MS care.

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16 BIBLIOGRAPHY OF THE CANDIDATE'S PUBLICATIONS

16.1 Publications related to the thesis

Domain-specific cognitive impairment in multiple sclerosis: A systematic review and meta-analysis

Katalin Lugosi, Marie A Engh, Zsolt Huszár, Péter Hegyi, Péter Mátrai, Gábor Csukly, Zsolt Molnár, Klaudia Horváth, Dóra Mátis, Zsolt Mezei

Ann Clin Transl Neurol. 2024 Mar;11(3):564-576

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IF: 3,9

Cognitive Impairment in Multiple Sclerosis: The Role of Clinical and Sociodemographic Factors: A systematic review and meta-analysis

Katalin Lugosi, Marie A Engh, Tamás Kói, Zsolt Molnár, Gábor Csukly, Klaudia Horváth, Emma Hargitai, Péter Hegyi, Zsolt Mezei

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16.2 Publications not related to the thesis

Plasma Exchange versus Intravenous Immunoglobulin in Worsening Myasthenia Gravis: A Systematic Review and Meta-Analysis with Special Attention to Faster Relapse Control

Mark Pavlekovics, Marie Anne Engh, **Katalin Lugosi**, Laszlo Szabo, Peter Hegyi, Tamas Terebessy, Gabor Csukly, Zsolt Molnar, Zsolt Illes, Gabor Lovas

Biomedicines. 2023 Nov 29;11(12):3180.

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Nabiximols is Efficient as Add-On Treatment for Patients with Multiple Sclerosis Spasticity Refractory to Standard Treatment: A Systematic Review and Meta-Analysis of Randomised Clinical Trials

Dénes Kleiner, István László Horváth, Stefania Bunduc, Dorottya Gergő, **Katalin Lugosi**, Péter Fehérvári, Péter Hegyi, Dezső Csupor

Curr Neuropharmacol. 2023;21(12):2505-2515.

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Szklerózis multiplex és várandósság - klinikai kihívások és gyakorlati megfontolások

Dr.Lugosi Katalin, Dr.Horváth Klaudia, Dr.Szabó Tímea, Dr.Hargitai Emma, Dr.Györök Gyöngyike Katalin

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