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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.

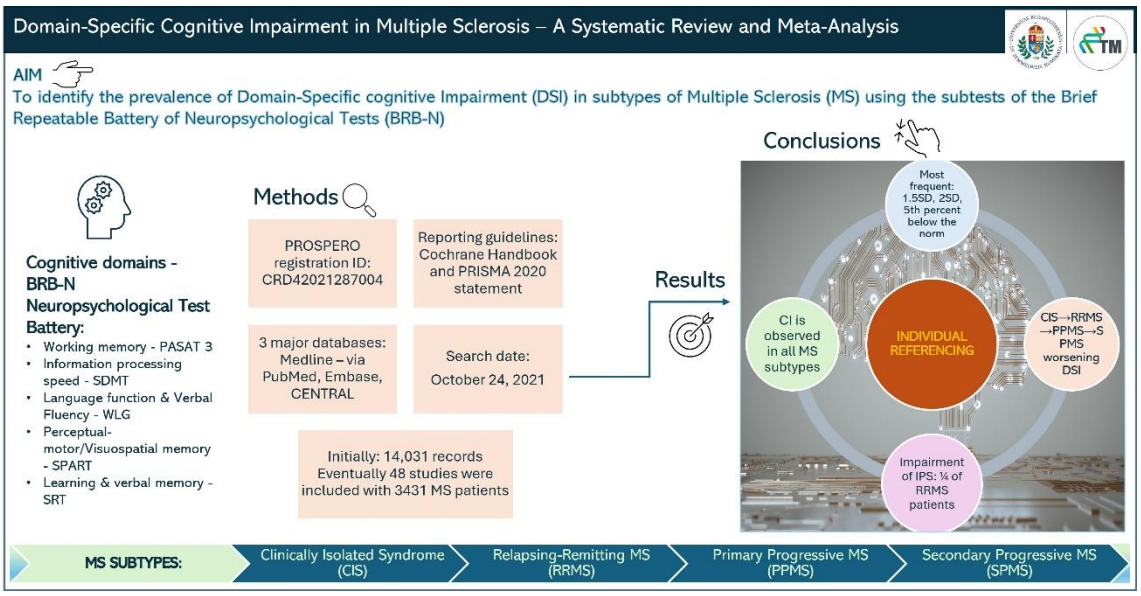
3 SUMMARY OF THE THESIS

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.

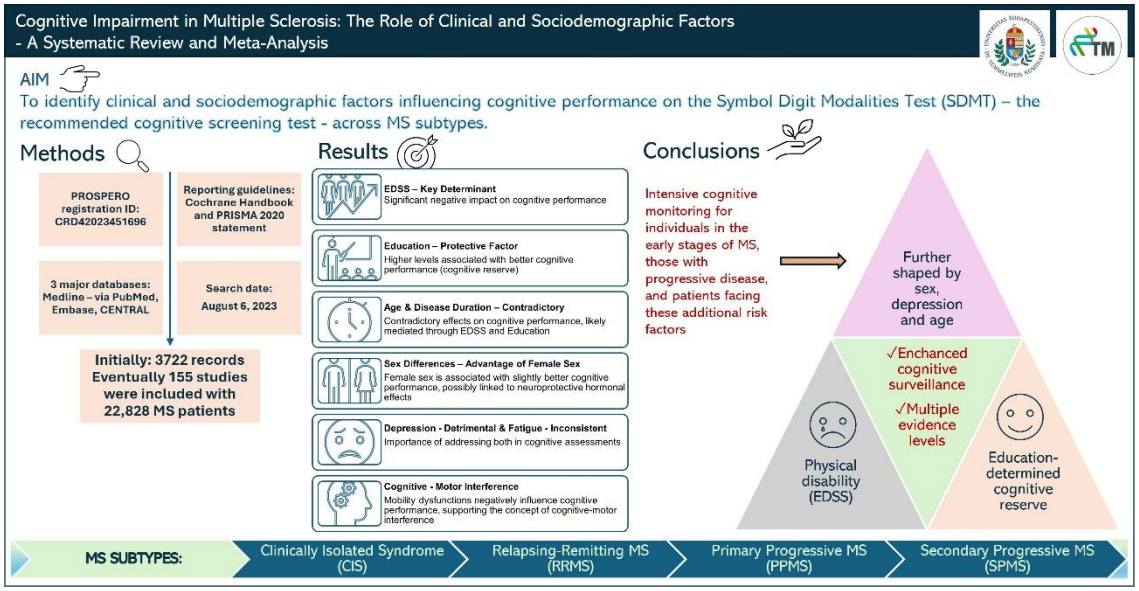
CI is common across all MS subtypes, worsens with progression, and is most likely in patients with higher EDSS and lower education, especially with other risk factors. Intensive cognitive monitoring and personalized care are essential, particularly for early-stage and progressive MS patients, and our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

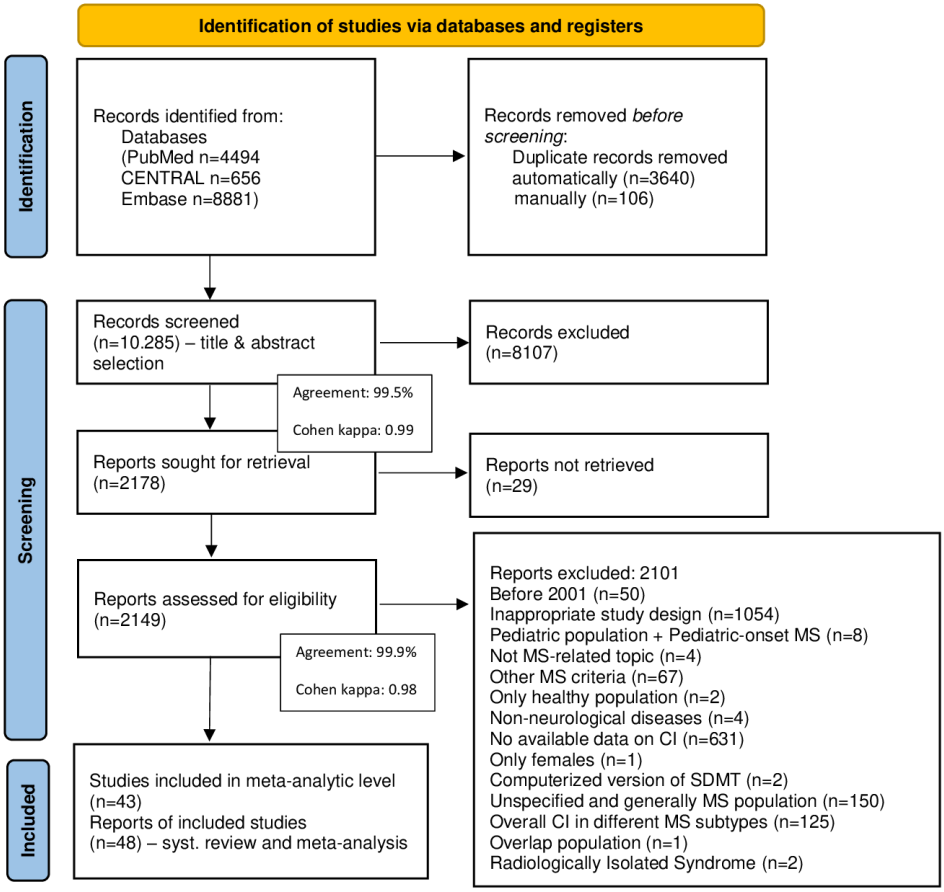


Figure 1. Flow diagram of study identification and selection by PRISMA 2020 with details of the reasons for exclusion [44].

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).

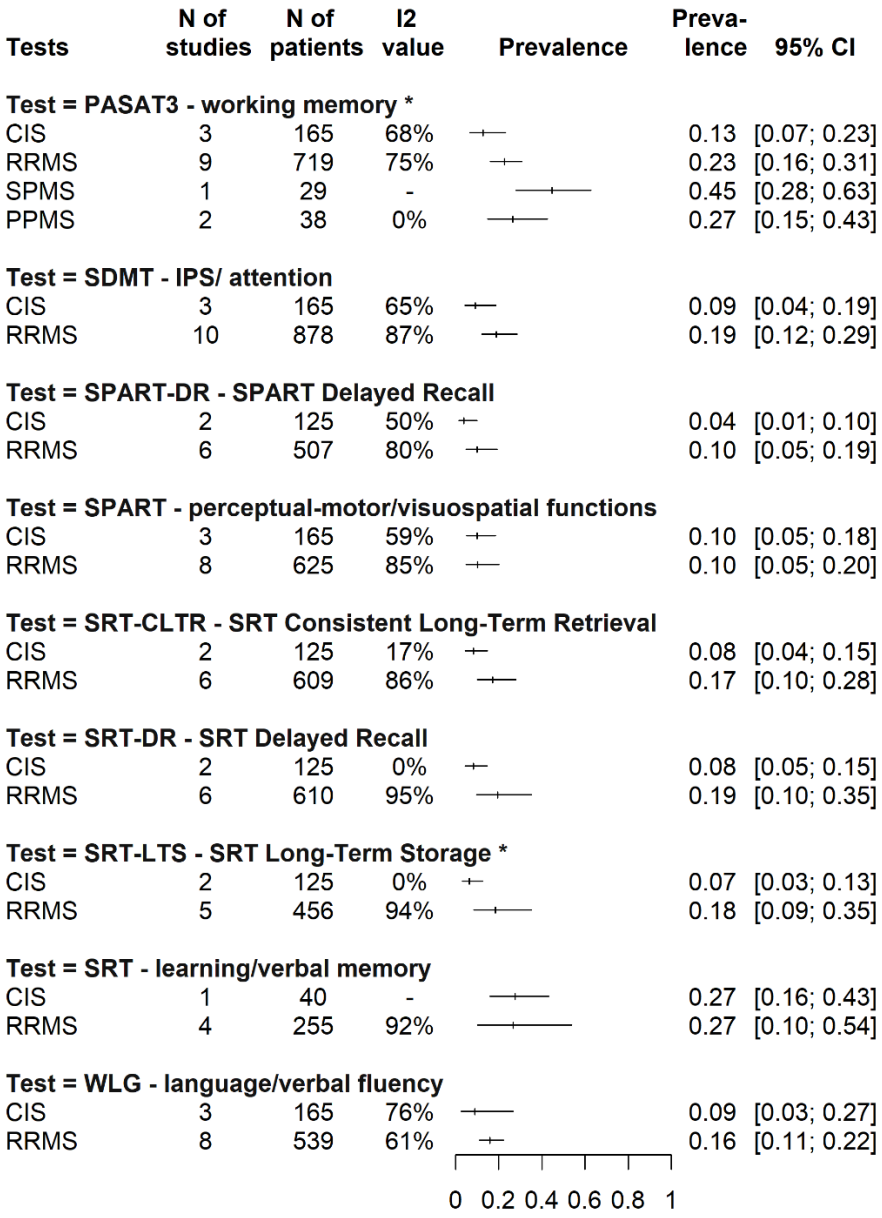


Figure 2. Summary panel of DSI prevalence rates across the subtests of the BRB-N battery at the ”**2.0 SD below the normative values**” cut-off [44].

*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).

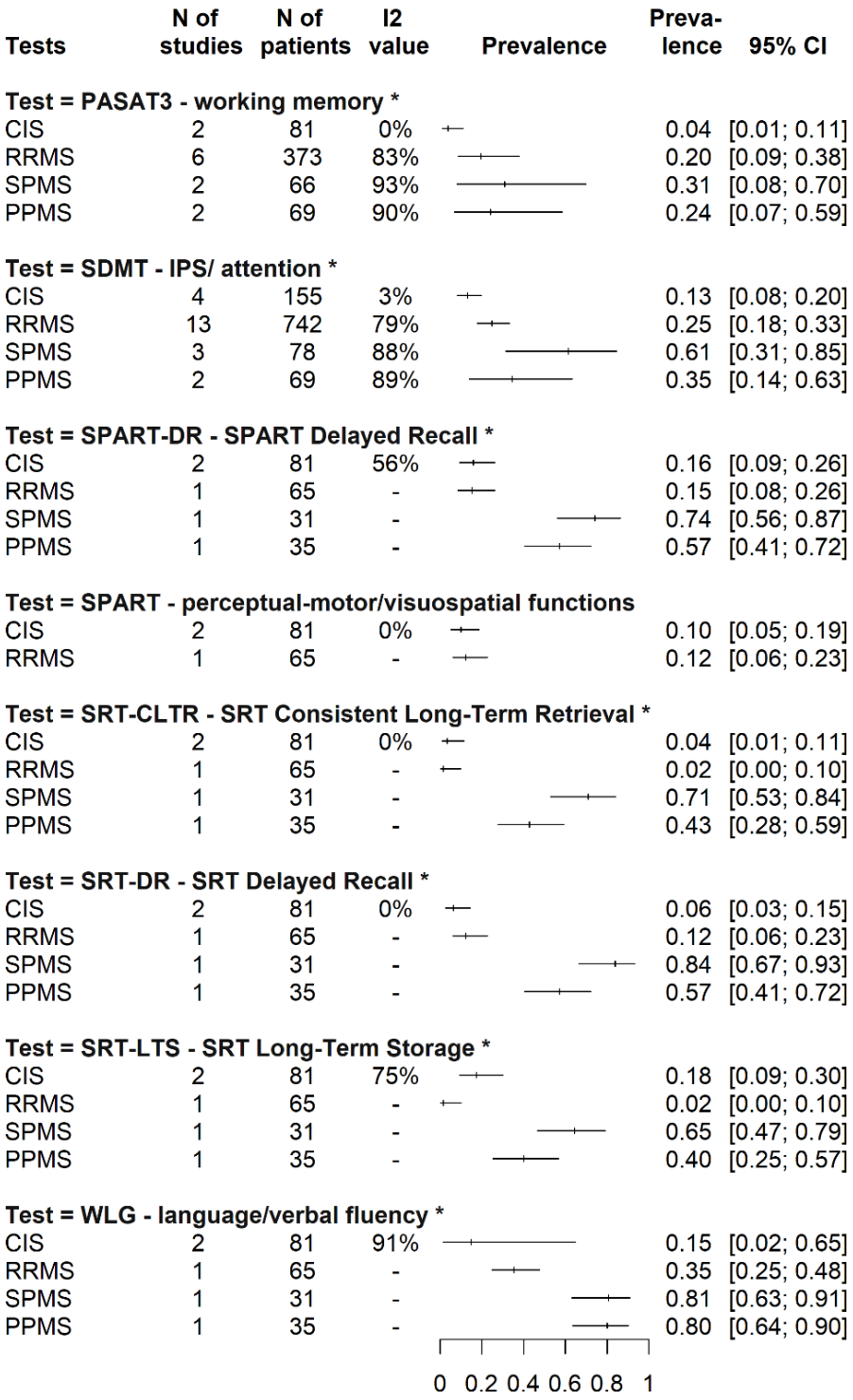


Figure 3. Summary panel of DSI prevalence rates across the subtests of the BRB-N battery at the "**1.5 SD below the normative values**" cut-off [44].

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).

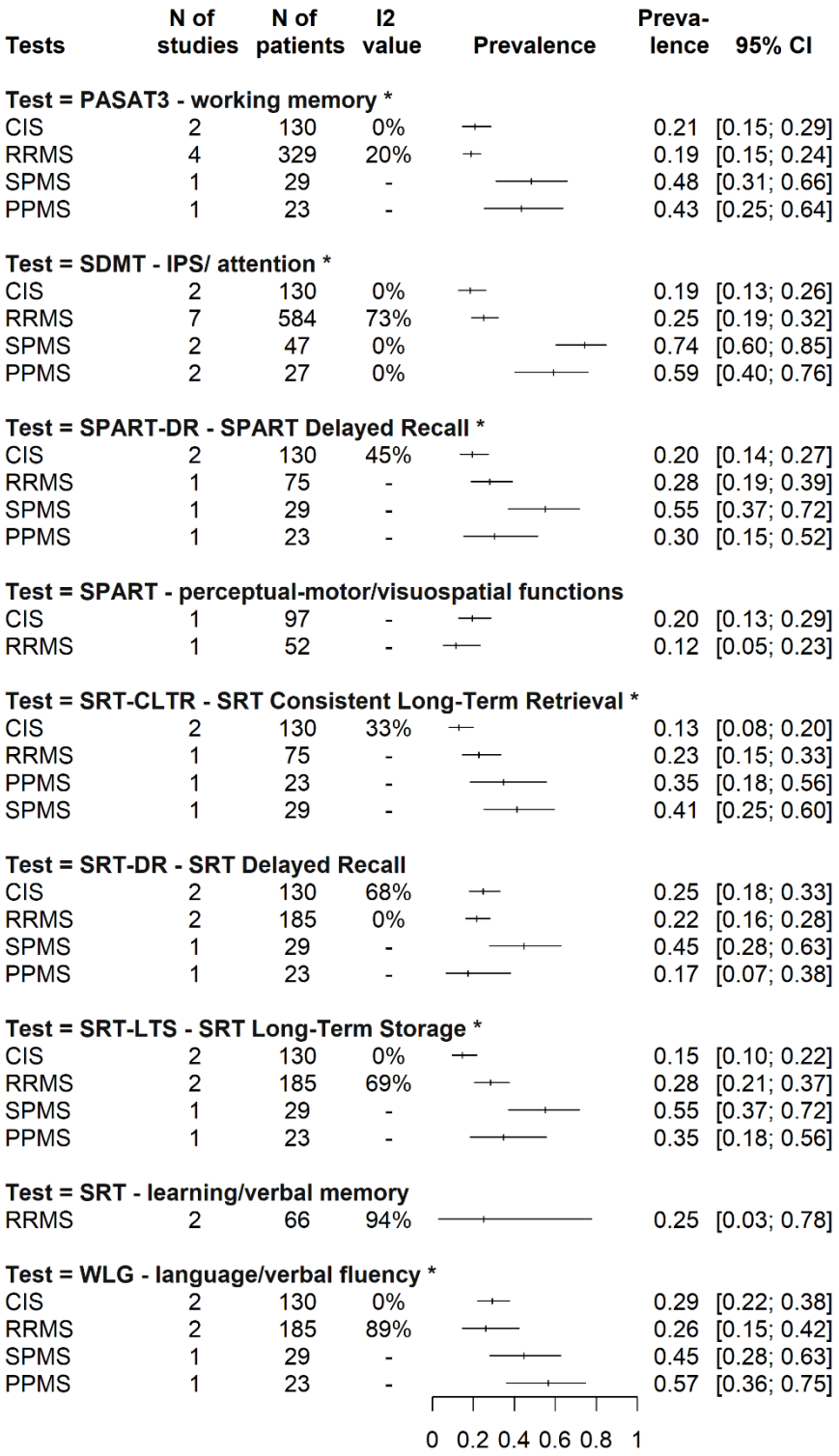


Figure 4. Summary panel of DSI prevalence rates across the subtests of the BRB-N battery at the „**score below the 5th percentile of the normative values**" cut-off [44].

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).

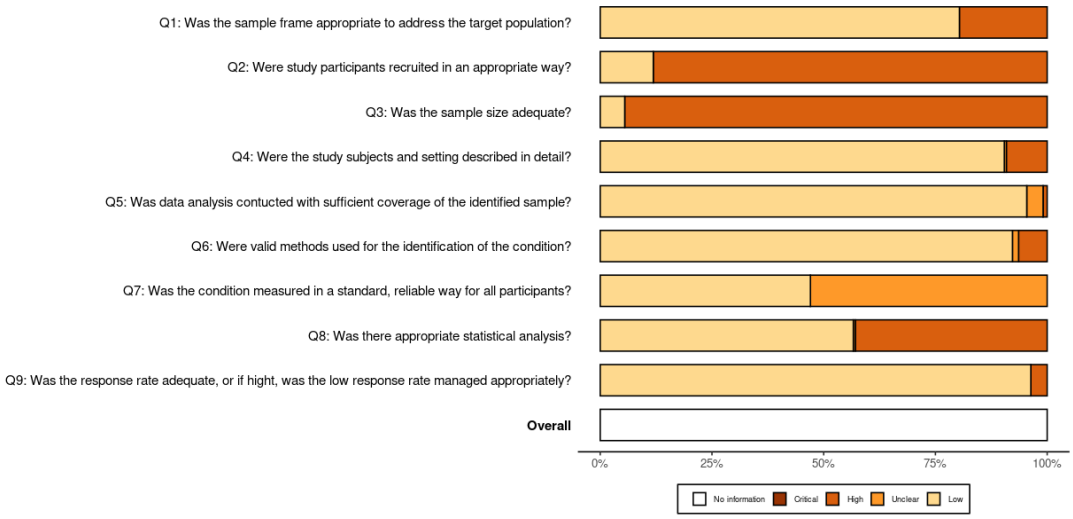


Figure 5. Assessment of risk of bias for each included study (Summary plot) [44].

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.

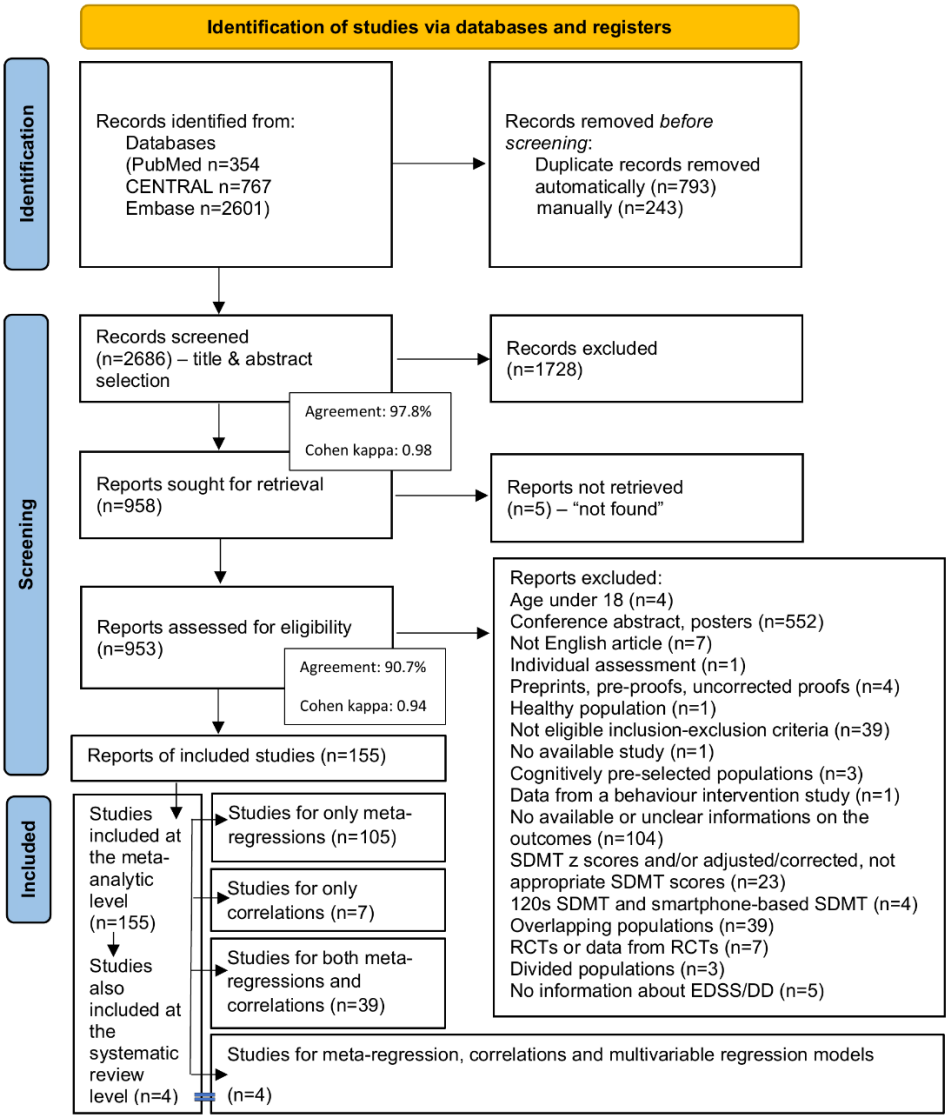


Figure 7. Flow diagram of study identification and selection by PRISMA 2020 with details of the reasons for exclusion [45].

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.

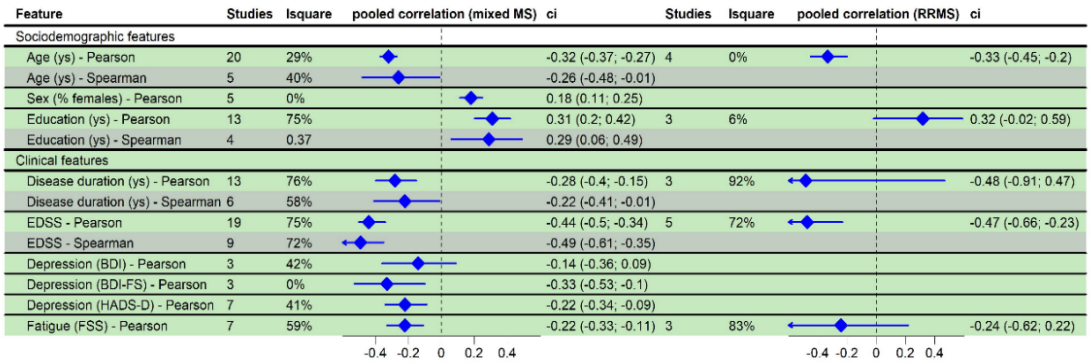


Figure 8. Summary plot of the meta-analyzed study-level correlation results [45].

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**

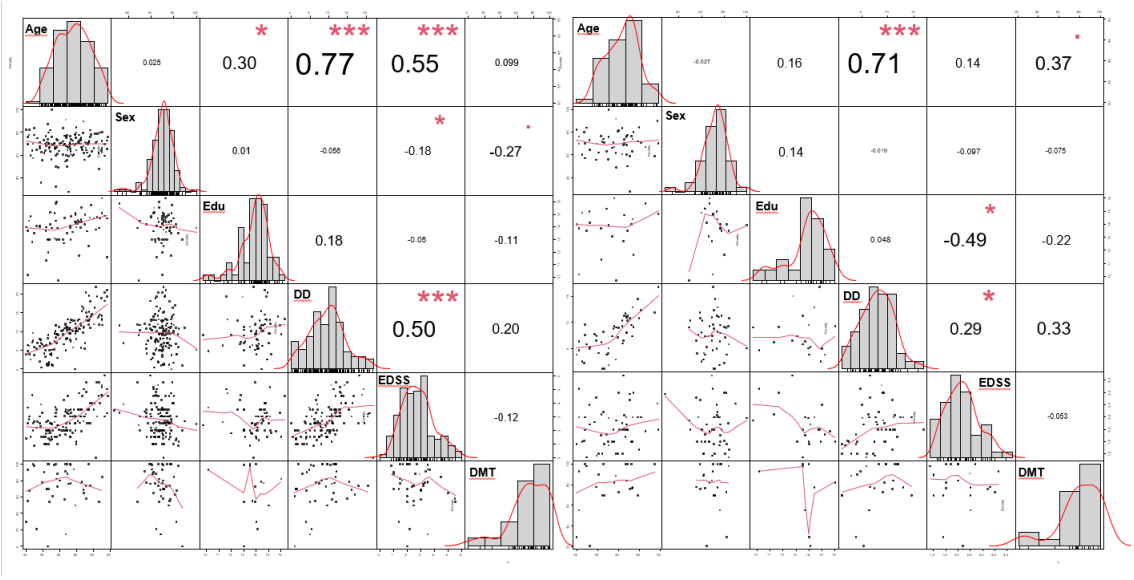


Figure 9a-b. Pairwise dependency matrix of the covariates in mixed (Figure 9a) and in RRMS populations (Figure 9b). [45]

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.

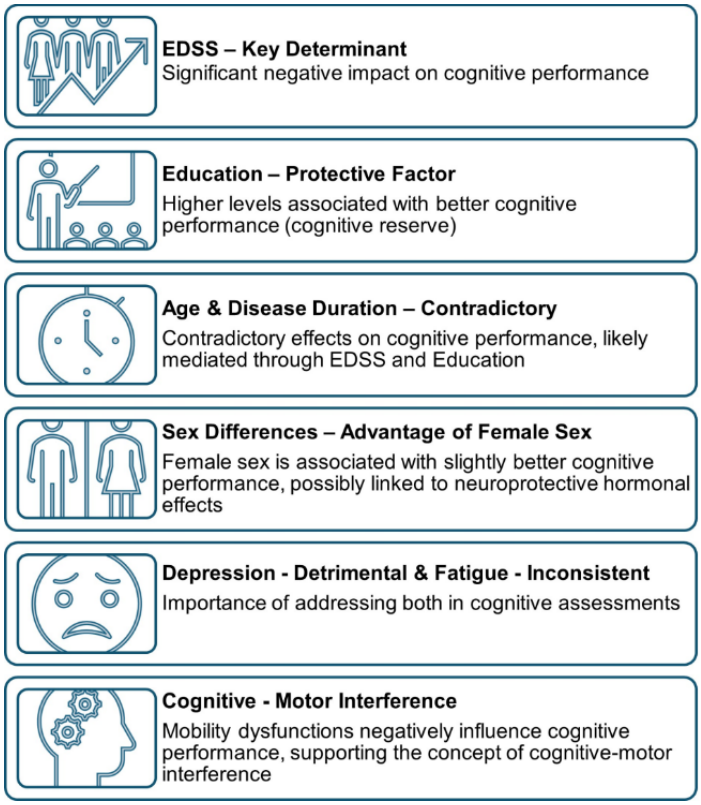


Figure 10. Key findings of our study reveal the multifactorial nature of the relationship between disease-related and sociodemographic factors and SDMT performance as a key sentinel test for cognitive impairment [45].

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.

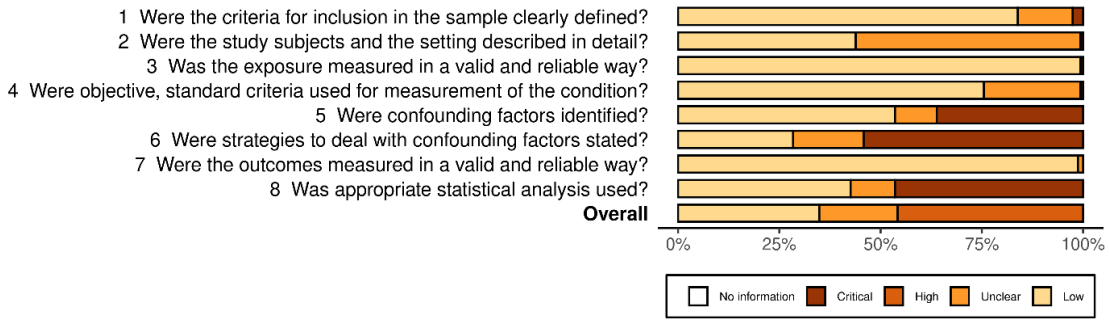


Figure 11. Summary plot of the assessment of risk of bias for each included study using Risk-of-bias VISualization (robvis) visualization tool [45].

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.

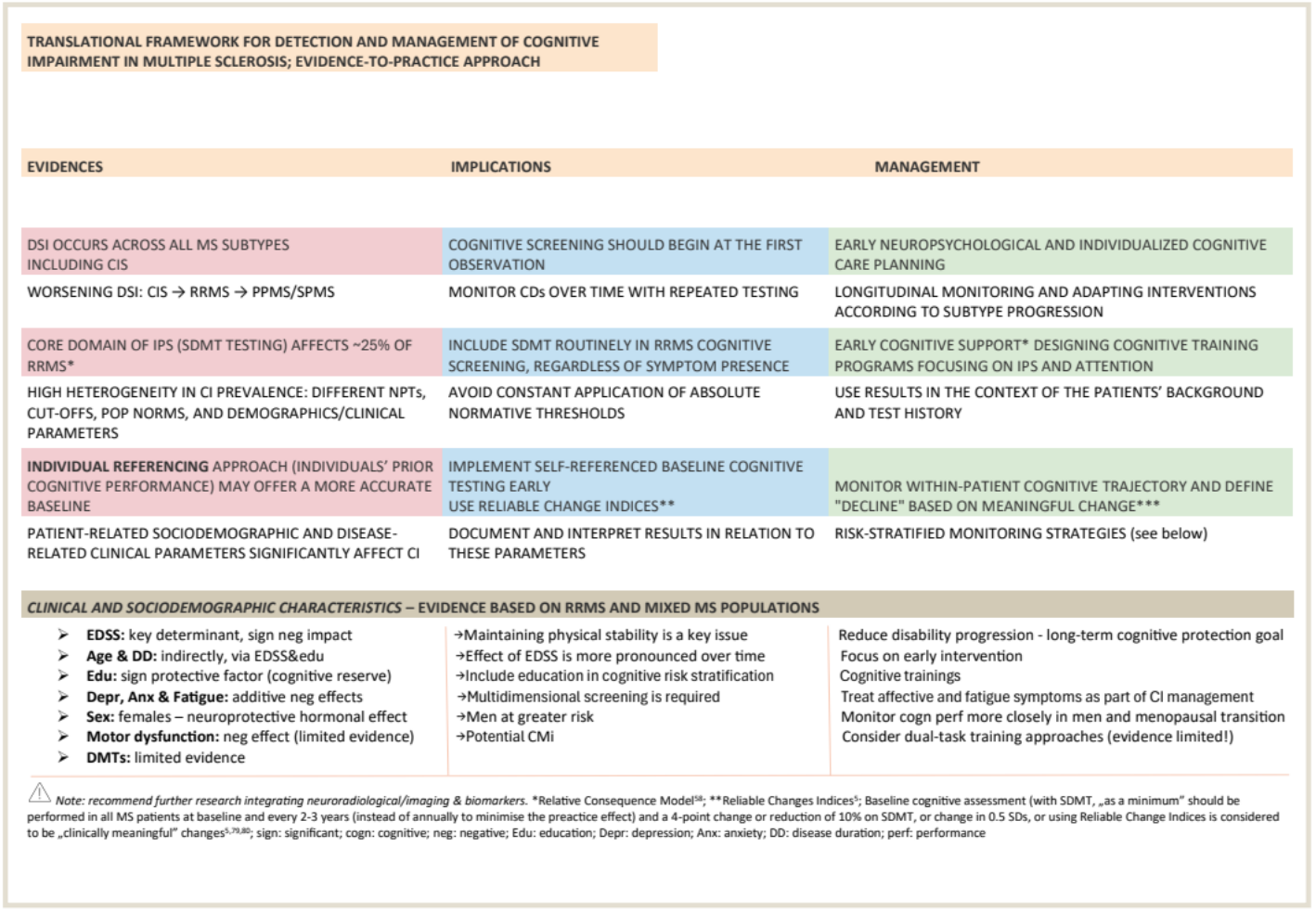


Figure 12. Translational framework for detection and management of cognitive impairment in multiple sclerosis [81,82].

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

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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

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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

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

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RESEARCH ARTICLE

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

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Abstract

Objective: Methods of cognitive measurements in multiple sclerosis (MS) are not standardized. We aimed to identify the prevalence of cognitive domain-specific impairment (DSI) in MS by using subtests of the Brief Repeatable Battery of Neuropsychological Tests (BRB-N) with analyzing different cutoff values. **Methods**: The systematic review and meta-analysis were registered on PROSPERO (ID: CRD42021287004). The systematic literature search was performed via PubMed, Embase, and CENTRAL on 24 October 2021. Inclusion criteria were adults of different MS subtypes (CIS, RRMS, PPMS, and SPMS) with the condition of distinct DSI measured by BRB-N. Pediatric MS, computerized versions of BRB-N, and patients receiving steroids were excluded. Primary outcome was pooled prevalence rates of impaired patients within each cutoff and MS subtype, with 95% confidence interval, I-squared statistics for heterogeneity, and chi-squared test for subgroup differences. Risk of bias was assessed using the "JBI Quality Assessment Tool for Prevalence Studies." **Results**: In 48 eligible observational studies (n = 3431 patients), the three most prevalent thresholds were the 2.0 SD and 1.5 SD below the mean of normative values, and the score below the fifth percentile of the normative values. A progressively increasing worsening of the overall DSI was observed from CIS, moving toward RRMS, PPMS, and SPMS. **Interpretation**: Cognitive impairment is observed in all MS phenotypes, with varying degrees. Due to several potential influencing factors, our comprehensive literature review has not revealed consistent findings, and we, therefore, recommend considering a more sophisticated, "*individual referencing*" approach, acknowledging the diverse clinical and sociodemographic characteristics among populations and disparities in cognitive testing.

Introduction

Cognitive impairment (CI) is one of the most common, life-altering consequences of multiple sclerosis (MS), and it can occur independently of physical disability. The prevalence of CI in MS is estimated to range from 43% to 70%.[1]

The fifth revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; published by the American Psychiatric Association)[2] assesses the symptomatology of cognitive disorders along the six main cognitive domains (complex attention/information processing speed, memory/learning functions, language abilities, executive functions, perceptual-motor/visuospatial abilities, and social cognition) by examining CI of various etiologies and grading them into "major" and "mild" severity. CI in MS is discussed in a subsection of "mild neurocognitive disorders."

However, in "mild neurocognitive disorders," a neuropsychological test (NPT) performance should be 1–2 SD below the normative values or between the 3rd and 16th percentile for tests, where appropriate norms are available,[3] neither the currently available international literature nor the DSM-5 manual provides recommended, standardized, internationally accepted neuropsychological tests and cutoff values for measuring cognitive domain-specific impairment (DSI), which would presumably be essential for the exact, consistent definition of CI in MS.[4]

Nevertheless, beyond the scope of DSM-V, there is a particular perception of CI in MS. Due to the various main clinical manifestations of the disease (relapsing–remitting or progressive) and the additional subclassifications of progressive forms ("active" or "not active", "with," or "without progression"),[5] the assessment of cognitive function in MS requires a "continuous reflection strategy" that resonates with the changing clinical characteristics of the disease. This means that reassessments are needed to detect the influence of disease activity, clinical/radiological progression, relapses/recovery of relapses, treatment response, and patients' self-reported cognitive complaints.[6,7]

Although some evidence suggests that as "hallmark"[6] or "core deficits," IPS/attention and working memory are probably the most affected CDs early in the course of the disease[1,8] and accordingly, "as a minimum," the Symbol Digit Modalities Test (SDMT) measuring IPS should be performed at baseline and every 2–3 years,[6,7] the exploration of domain-specific impairments with a series of neuropsychological tests aligns best with the abovementioned reflective assessment strategy.

Three batteries of validated NPTs are widely accepted for the assessment of DSI: the Rao's Brief Repeatable Battery of Neuropsychological Tests (BRB-N),[9] the Minimal Assessment of Cognitive Functioning in Multiple Sclerosis (MACFIMS),[10] and the Brief International Cognitive Assessment for MS (BICAMS).[11]

BRB-N is one of the most sensitive, specific (71% sensitivity and 94% specificity),[9] and widely used validated testing tools detecting five measurable parts of six main cognitive domains (CD). The Paced Auditory Serial Addition Test 3 (PASAT3)[12] measures working memory; the Symbol Digit Modalities Test (SDMT)[13] measures information processing speed (IPS) and complex attention; the Word List Generation Test (WLG)[14] measures language function and verbal fluency; the 10/36 Spatial Recall Test (SPART)[15] measures perceptual-motor/visuospatial memory and refers to some aspects of executive functions; and the Selective Reminding Test (SRT)[16] measures learning and verbal memory.

However, it is essential to recognize that an ongoing and perpetual debate surrounds the precise domain(s) assessed by these specific tests, moreover, the individual CDs overlap and mutually influence each other.[17]

For all these reasons, only a few studies have conducted comprehensive population-level or meta-analysis studies of cognitive domain-specific impairment using sophisticated neuropsychological batteries. The results are also heterogeneous, despite the fact that this approach would provide the clearest picture of this aspect of MS.[18]

Planche et al., in their population-based study, found that regardless of disease course, the IPS was the most frequently impaired cognitive domain, followed by verbal episodic memory, executive functions, visuospatial construction, verbal fluency, working memory, and language. However, they did not use a predefined and elaborate test battery, but a customized one. Patients with SPMS were more frequently affected than patients with LRRMS (late relapsing–remitting MS with a disease duration of more than 10 years) in all CDs except language.[18]

Potagas et al. provide a comprehensive picture of the cognitive DSI (exploring possible "pattern of cognitive impairment") observed in different clinical subtypes of MS (RRMS, PPMS, and SPMS), including CIS patients. A further advantage is that it presents this through evaluating a standardized neuropsychological battery (BRB-N). They found that except for the relatively spared (not significantly different from healthy controls) cognitive domain of verbal learning/memory (as measured by SRT) in CIS patients, a progressively worse cognitive impairment was observed for all cognitive domains along the CIS-RRMS-PPMS-SPMS axis. Still, the study failed to detect different patterns of impairment between MS subtypes.[19]

Johnen et al. conducted a comparative analysis to assess the extent and characteristics of cognitive impairment (CI) as determined by standardized neuropsychological tests in patients with primary progressive multiple sclerosis (PPMS) as compared to relapsing–remitting multiple sclerosis (RRMS). A comprehensive non-predefined neuropsychological battery was employed to evaluate 12 domains of dysfunction, including cognitive, manual dexterity, anxiety and depression, and fatigue. The study revealed that individuals with PPMS exhibited significantly more pronounced CI across all assessed CDs compared to those with RRMS. Notably, distinctions in verbal learning and memory were particularly prominent, establishing a clear demarcation between PPMS and RRMS irrespective of demographic variances.[20]

Accordingly, in order to clarify and organize the issues discussed above, our aim was to determine the prevalence of DSI in subtypes of MS, based on specific standardized NPTs, taking into account different cutoff values. We chose the subtests of BRB-N battery, because it had been widely validated in several countries and it had relatively high sensitivity and specificity. Using this approach, our study is expected to contribute to unveiling research gaps or contradictions within the existing international literature, which

could inspire further investigations and the development of international guidelines. Moreover, expanding our understanding in this field can facilitate interdisciplinary collaboration among related scientific areas, including neurology, clinical neuropsychology, psychiatry, and rehabilitation.

Methods

Study registration

Our analysis protocol was registered in PROSPERO (international database of prospectively registered systematic reviews; registration ID: CRD42021287004) which we followed without any deviations during the process. We followed the recommendations of the Cochrane Handbook[21] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement[22] (Supplementary Material, Appendix 1).

Search strategy

The systematic search was performed within three major databases (Medline—via PubMed, Embase, and CENTRAL—The Cochrane Central Register of Controlled Trials) without restrictions on 24 October 2021 (Supplementary Material, Appendix 2). We searched the databases from the inception.

Selection process

The selection was performed using Endnote 20 (Clarivate Analytics, Philadelphia, PA, USA) software. After automatic and manual removal of duplicates, a selection process was conducted by two independent review authors (KL and ZH) in two steps (by title and abstract, then by full-text), with any disagreements resolved by a third author (ZMe). The degree of agreement was quantified by Cohen's kappa statistics.

The "CoCoPop" framework (i.e., condition – context – population)[23] was used to define our selection criteria: the population included adult patients of both sexes (age ≥ 18 years) diagnosed with MS in the context of MS subtypes (i.e., CIS: clinically isolated syndrome, RRMS: relapsing–remitting MS, PPMS: primary progressive MS and SPMS: secondary progressive MS) according to the Lublin classifications[5] with the condition of distinct DSI measured by subtests of the BRB-N battery (Supplementary Material, Appendix 3).

We excluded studies that examined pediatric or pediatric-onset MS (POMS) populations, computerized versions of BRB-N subtests, and tested patients during relapse/steroid administration, as it could significantly alter cognitive test results.[24]

Diagnosis of MS was based on the McDonald criteria,[25] and as this was first established in 2001, studies published before 2001 were eventually excluded (Supplementary Material, Appendix 4).

As no language restrictions were set, two eligible articles in languages other than English were included and translated using a translation tool (DeepL Translator),[26] Only observational studies were eligible for analysis. The primary outcome was the prevalence (%) of DSI in clinical MS subtypes based on BRB-N subtests.

As different cutoff values had been mentioned in the literature to define abnormal results in BRB-N subtests, each cutoff value was analyzed individually.

Data collection

Data extraction was performed by two reviewers independently (KL and ZH) and compared by a third author (ZMe). Baseline data, outcomes, and their definitions for studies and populations were extracted into a predesigned Excel (Microsoft Corporation, Redmond, Washington, USA) spreadsheet.

SRT also provides the short-term and long-term components of memory by the consistency of retrieval from long-term memory (SRT LTS: SRT – long-term storage and SRT CLTR: SRT – consistent long-term retrieval) and delayed recall (SRT DR: SRT – delayed recall), which is the total number of words recalled after the delayed period.

The 10/36 SPART test has immediate (SPART) and delayed recall (SPART DR) subtests.

Where a study provided information on these subtests, these were also collected and analyzed.

Statistical analysis

The statistical analysis of the data was conducted using the R programming language.[27] We used the *meta*[28] package for calculations and plots.

For each MS subtype, test, and cutoff 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 chose the three most commonly used cutoff values: a cutoff 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 whose scores fell below these cutoff values were declared as impaired in the given CD. Raw prevalences from the selected studies were transformed to logit scale, then pooled using a random-effects model and then transformed back to the original scale for data presentation.[29] T^2 was estimated using the restricted maximum likelihood method.[30] Statistical heterogeneity across trials was assessed using the Cochrane Q test, and the

I^2 values.[31] Forest plots were used to summarize results graphically. Where applicable, we reported the 95% prediction interval (i.e., the estimated range that contains 95% of true prevalence) following the recommendations.[32]

Risk of bias assessment

Risk of bias was assessed using the Joanna Briggs Institute (JBI) Quality Assessment Tool for Prevalence Studies[33] framework by two independent reviewers (KL and DM) with disagreements resolved by a third reviewer (ZMe).

Results

Selection and study characteristics

Our search key initially identified 14,031 articles, and eventually 48 studies were included in the synthesis (both in the systematic review and in the meta-analysis).

Details of the complete selection process are shown in the PRISMA flowchart (Fig. 1).

The abovementioned three most commonly used NPT cutoff values were included in our meta-analysis, as they were suitable for quantitative analysis, and five additional studies were also reviewed systematically that did not qualify for our meta-analysis as they did not adhere to our predefined cutoff values. No distinction was made between cutoff values in the score or calculated z score if they contained the same SD value, or between the prespecified "normative" or self-reported "healthy controls" reference populations.

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

Finally, the results of 3131 MS patients (450 CIS, 2393 RRMS, 134 PPMS and 154 SPMS) were included in the meta-analysis, and a further 300 were included in the qualitative assessment only (18 CIS, 197 RRMS, 12 PPMS and 73 SPMS).

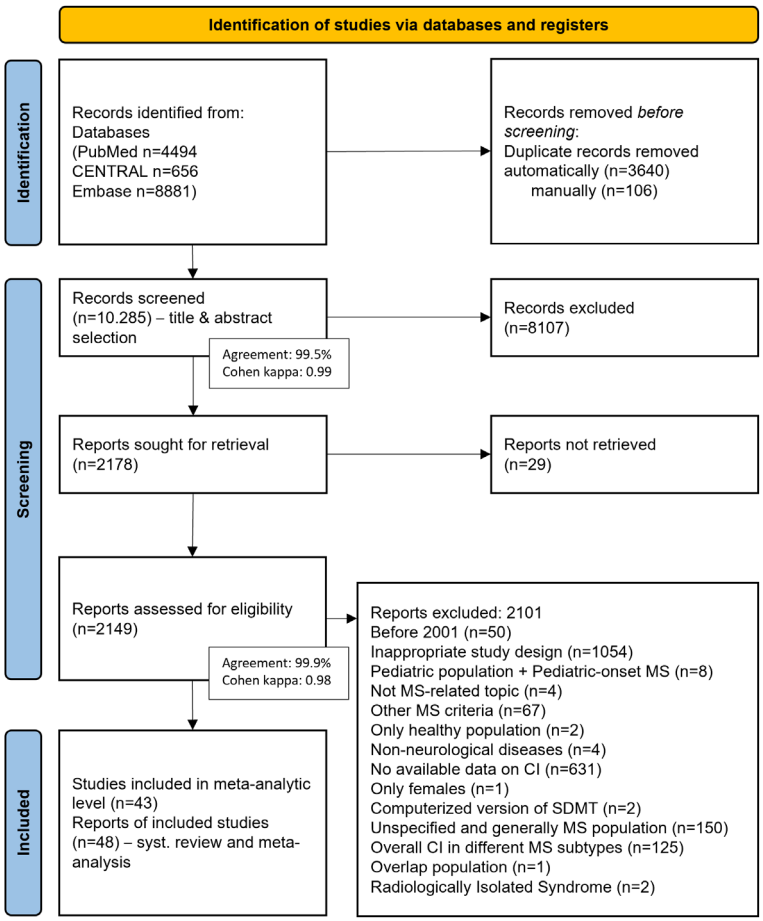

Figure 1. Flow diagram of study identification and selection by PRISMA 2020 with details of the reasons for exclusion (See also Supplementary Material, Appendix 4).

A list of the references for all included studies are available in the Supplementary Material, Appendix 5. Baseline characteristics of the included studies are detailed (Supplementary Material, Appendix 6, eTable 1).

Evaluation of individual DSI across different MS subtypes based on separate cutoffs used to define impairment

A cutoff of 2.0 SD below the normative value

Due to a lack of data, at this cutoff 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. All these prevalence values can be found visually in the summary of Fig 2.

A cutoff of 1.5 SD below the normative value

At this cutoff value, working memory impairment (PASAT3) is present 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) affects **13%** CI: [0.08; 0.20] of CIS patients and **25%** CI: [0.18; 0.33] of RRMS patients, with PPMS and SPMS being affected by **35%** CI: [0.14; 0.63] and **61%** CI: [0.31; 0.85], respectively. 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. For visuospatial skills, there are sufficient data only for the impairment of delayed recall (SPART DR): almost equal in CIS and RRMS (**16%** CI: [0.09; 0.26] and **15%** CI: [0.08; 0.26] respectively), **57%** CI: [0.41; 0.72] in PPMS, and a very high proportion of patients in SPMS (**74%** CI: [0.56; 0.87]).

Impairment of delayed recall of learning/verbal memory (SRT) is present only in **6%** CI: [0.03; 0.15] of CIS patients, **12%** CI: [0.06; 0.23] of RRMS patients, **57%** CI: [0.41; 0.72] of PPMS and **84%** CI: [0.67; 0.93] of SPMS group. All these prevalence values can be found visually in the summary of Figure 3.

A cutoff of the score below the fifth percentile of the normative values

At this cutoff value, IPS impairment (SDMT) affects **74%** CI: [0.60; 0.85] of SPMS patients, it is present in **59%** CI: [0.40; 0.76] of PPMS, it is the lowest in CIS (**19%** CI: [0.13; 0.26]) and the RRMS subtype is intermediate between the early form (CIS) and progressive forms, affecting **25%** (CI: [0.19; 0.32]) of patients.

In terms of working memory impairment (PASAT3), the CIS group shows a slightly higher rate compared to the RRMS group (**21%** CI: [0.15; 0.29] vs. **19%** CI: [0.15; 0.24]), followed by PPMS (**43%** CI: [0.25; 0.64]) and then the SPMS (**48%** CI: [0.31; 0.66]) subtype. For visuospatial memory impairment, only the delayed recall test (SPART DR) has sufficient information for all subtypes, with **20%** (CI: [0.14; 0.27]) of CIS patients, **28%** (CI: [0.19; 0.39]) of RRMS, **30%** (CI: [0.15; 0.52]) of PPMS and slightly more than half (**55%** CI: [0.37; 0.72]) of SPMS patients impaired. In terms of learning and verbal memory impairment, depending on the type of memory retrieval, **13%–25%** (CI: [0.18; 0.33] at SRT DR, CI: [0.10; 0.22] at SRT LTS, CI: [0.08; 0.20] at SRT CLTR) of CIS patients, **22%–28%** (CI: [0.16; 0.28] at SRT DR, CI: [0.21; 0.37] at SRT LTS, CI: [0.15; 0.33] at SRT CLTR) of RRMS patients, **17–35%** (CI: [0.70; 0.38] at SRT DR, CI: [0.18; 0.56] at SRT LTS, CI: [0.18; 0.56] at SRT CLTR) of PPMS patients, and **41%–55%** (CI: [0.28; 0.63] at SRT DR, CI: [0.37; 0.72] at SRT LTS, CI: [0.25; 0.60] at SRT CLTR) of SPMS patients are affected. An interesting observation is the impairment of verbal fluency (WLG): in this domain, **57%** CI: [0.36; 0.75] of PPMS patients were affected compared 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 groups. All these prevalence values can be found visually in the summary of Fig 4.

Individual results of each study for each subtype and CDs are detailed in the Supplementary Material, Appendix 7.

Further systematic analysis with other cutoff values

Five of the eligible studies could not be included at the meta-analytic level, because they all used a cutoff value other than the cutoffs of 1.5 SD, 2.0 SD below the normative value or fifth percentile of the normative

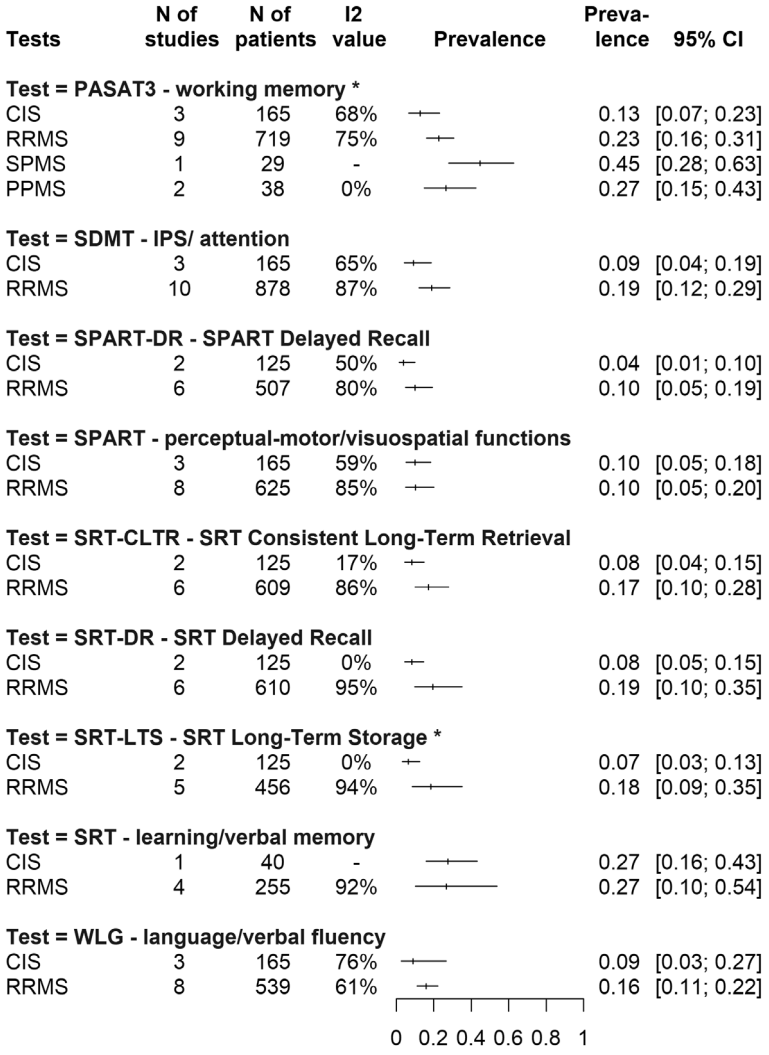

Figure 2. Summary graph of DSI (domain-specific impairment) prevalence rates across the subtests of the BRB-N (Brief Repeatable Battery of Neuropsychological Tests) battery at the "2.0 SD below the normative values" cutoff. On the left side of the figure are the subtests of the BRB-N battery. Below each test, MS subtypes are shown. At this cutoff value, only the PASAT3 (Paced Auditory Serial Addition Test 3) subtest had sufficient data in the literature for all MS subtypes; for the other BRB-N subtests only the CIS and RRMS subtypes were available. On the right side of the figure are the prevalence rates (with confidence intervals) of impaired patients grouped by MS subtype, for the given BRB-N subtest, using the "2.0 SD below the normative values" cutoff.

population to define the DSI, and their modest data were not suitable for statistical analysis of all subtypes; therefore, we conducted only a systematic review of these.

Cutoff values were as follows: at PASAT3 test 1 SD below the mean of healthy controls and a score of 32 correct or less, for the SDMT test a score equal or less than 35 T score and equal or below 55 points, at WLG, SRT-DR, SRT-CLTR z score <-1.68.

These studies were largely focused on the RRMS group and were also in line with the previous findings: disregarding the differences in cutoff values, it can be concluded, that IPS impairment affects at least one-third of RRMS patients.

Risk of bias assessment and quality of evidence

As most of the included studies were found to be high risk according to at least one, but in most cases two or three aspects of the JBI criteria, in the overall assessment we considered our study as "moderate risk," which mainly refers to the potential for "selection bias" and "performance bias."

The assessment of the risk of bias for each included study (listed according to the criteria of the "JBI Quality Assessment Tool for Prevalence Studies") and ratings of

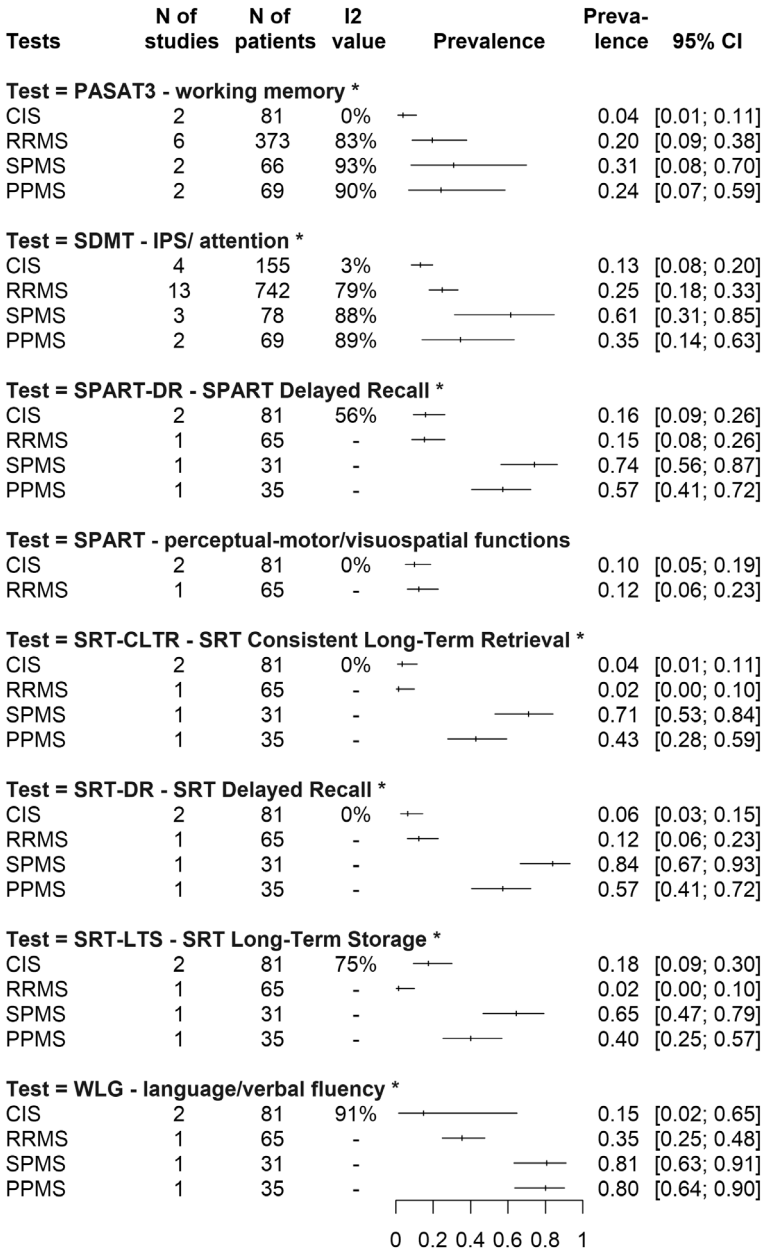

Figure 3. Summary graph of DSI (domain-specific impairment) prevalence rates across the subtests of the BRB-N (Brief Repeatable Battery of Neuropsychological Tests) battery at the "1.5 SD below the normative values" cutoff. On the left side of the figure are the subtests of the BRB-N battery. Below each test, MS subtypes are shown. On the right side of the figure are the prevalence rates (with confidence intervals) of impaired patients grouped by MS subtype, for the given BRB-N subtest, using the "1.5 SD below the normative values" cutoff.

the quality of the evidence are detailed in Supplementary Material, Appendices 8 and 9.

Discussion

Long overlooked since Jean-Martin Charcot's first description,[34] the importance of cognitive symptoms in multiple sclerosis has been brought back into the spotlight over the past 25 years thanks to the explosion of neuropsychological testing, advanced brain imaging techniques and new therapeutic options.

Consequently, the questioning is currently structured around the following aspects: (1) what are the characteristics and patterns, (2) early detection, (3) influencing and predictive factors, and (4) targeted treatment options in MS with CI?[35]

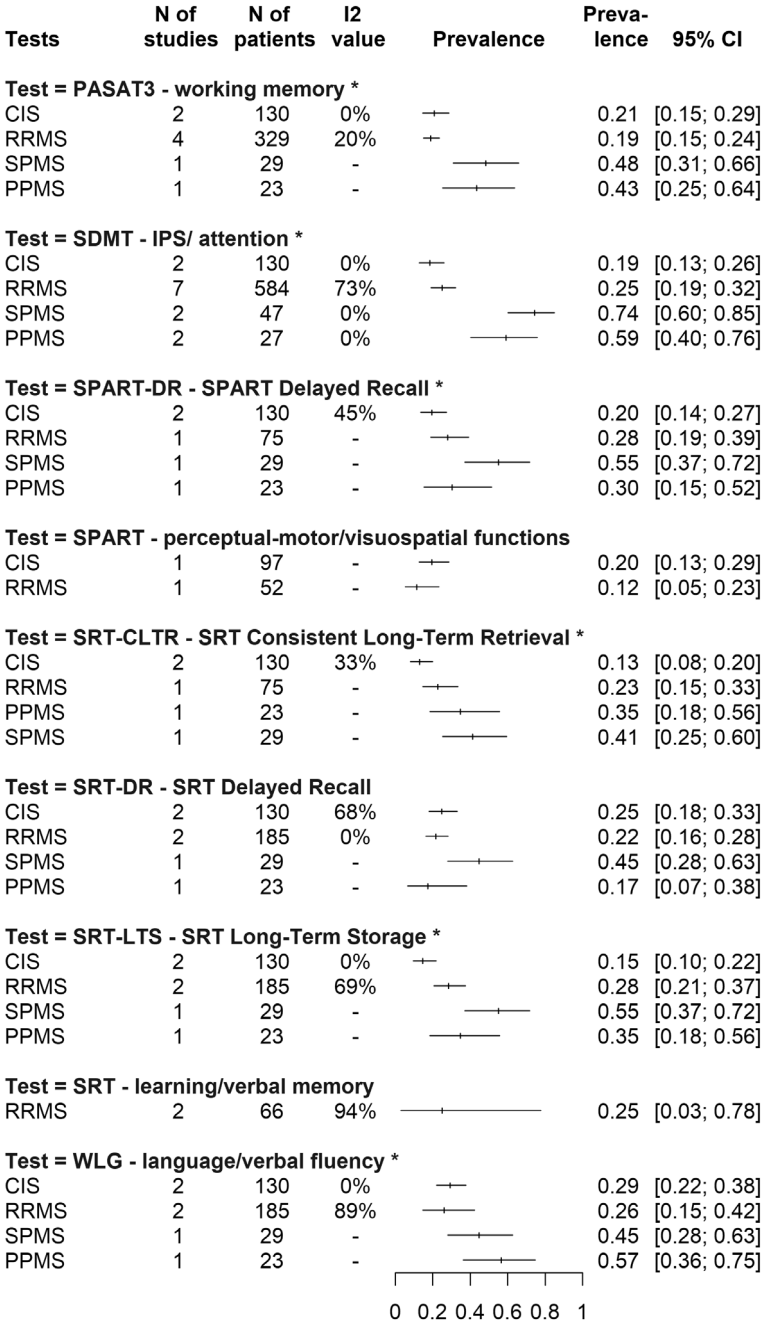

Figure 4. Summary graph of DSI (domain-specific impairment) prevalence rates across the subtests of the BRB-N (Brief Repeatable Battery of Neuropsychological Tests) battery at the "score below the fifth percentile of the normative values" cutoff. On the left side of the figure are the subtests of the BRB-N battery. Below each test, MS subtypes are shown. On the right side of the figure are the prevalence rates (with confidence intervals) of impaired patients grouped by MS subtype, for the given BRB-N subtest, using the "score below the fifth percentile of the normative values" cutoff.

The complexity of this issue and the logical sequence would first require the development of a common professional language at international level: the same definitions, the same NPTs and the same cutoff values should be used to define CI characteristics and prevalence levels, in order to identify predictive factors and to design and implement comparable, targeted therapeutic options. That is, the first step seems to define

the characteristics and patterns of CI in MS, along the same assessment criteria.

However, based on the currently available literature, the definition of CI, in particular DSI in MS is not uniform, contradictory and sometimes confusing, both in terms of the tests used and the thresholds for impairment.

For the reasons detailed above, in our meta-analysis, we selected a prespecified neuropsychological test battery with high specificity and sensitivity, which relatively selectively assesses CDs, and analyzed impairment thresholds to investigate the characteristics and prevalence of cognitive DSI in different clinical subtypes of MS.

In our study, the following general considerations were observed in relation to the results obtained, regardless of the cutoff value used:

CI is observed in all MS phenotypes, with varying degrees, including early forms as well.

Starting from CIS, a broadly tending toward RRMS, PPMS, and finally SPMS, a worsening overall DSI is observed, which basically correlates with the results of previous studies,[19] although some studies, such as Rosti-Otajärvi et al. in their analysis found the overall CI was more pronounced in the PPMS group than in SPMS.[36]

Using the BRB-N test, it was found that the most common cutoffs were 1.5 SD and 2.0 SD below the normal mean and the score below the fifth percentile of the normative values.

Impairment in IPS, referred to in the literature as the "core" symptom, was found to be present in about a quarter of RRMS patients. This is a particularly important finding because, based on the results of EEG, PET, and the most sophisticated functional MRI studies, often used in cognitive psychology, it is now well established that the integrity of cognitive functions is linked to the organization of neuronal networks underlying the ability to process information and attention, that is, impairment to this CD is somehow responsible for the impairment of all other domains (related to DeLuca et al.'s *Relative Consequence Model*, 2004.[37]).[38]

The studies we have included span 20 years and during this period, the therapy of MS has undergone enormous changes. The advent of disease-modifying therapies (DMT), other new therapeutic approaches (neurorehabilitation, cognitive therapy, dietary approaches, etc.) and multimodal interventions have allowed a demonstrable slowing of disease progression, a significant reduction in relapse rate and long-term preservation of patients' neuroradiological and physical status (AFFIRM, OPERA I-II, ASCLEPIOS I-II, CARE MS I-II, CLARITY, and CLARITY EXTENSION studies).[39–43] This primarily begs the question of whether changes in the use of DMTs have had any impact on the prevalence of CI in MS?

Although our study does not directly help to answer this question, given that DMTs have been shown to delay the time of conversion to SPMS (EXPAND, ONTARIO trials)[40,44] and our study suggests that the SPMS subtype has the highest rates of total DSI, it is conceivable that DMTs may also play a role in rewriting the prevalence rates of DSI. However, more precise analyses are needed to clarify this issue.

Nevertheless, based on the prevalence data obtained in our meta-analysis, we must see that our results have not provided a consistent clarity to understand the pattern of DSI in MS, which is due to several reasons and gives rise to very important considerations and conclusion.

One of the most important is that the results obtained are obviously influenced by various clinical (physical status-EDSS score, disease duration, comorbidities, additive affective disorders/mood disorders/depression, sleep disturbances, presence of fatigue, etc.) and sociodemographic (age, gender, race, education, occupational status, marital status, etc.) parameters. For example, a previous cross-sectional study[19] examining the prevalence and profile of cognitive dysfunction in different MS subtypes showed that differences in cognitive performance between MS subtypes largely disappeared after controlling for physical disability (EDSS), suggesting that clinical parameters have a crucial impact on cognitive dysfunction in MS.

In our present study, there were insufficient data available for statistical analyses in the included studies in this regard. However, the analyzed patient populations all tend to represent a unique pattern in terms of overall clinical and sociodemographic characteristics, which raises the question of *whether it is even possible to define domain-specific impairment in a consistent manner, generalized across MS subtypes*. It is also worth mentioning the role of the cognitive reserve as a purely individual characteristic influencing the results, acting as a kind of neuroprotection or compensatory mechanism against the progression of CI and its detectability. The extent and the time of depletion of the cognitive reserve show a high individual variability, although this is occasionally considered in the assessment of cognitive tests (as the "Cognitive Reserve Index").[35,45,46]

A further reason for the diversity of our results is apparent in the variations on detection of DSI. As mentioned previously, there is and will continue to be a very intense international debate about exactly which CD is being measured by the NPTs that are becoming more widely available. A classic example is the seminal 1991 study by Rao and colleagues describing CI in MS,[9] which cited verbal fluency as a prominent deficit, but the test measuring this (COWAT) is listed under memory in the article, which probably contributed to the decades-long disregard of the significance of deficits in verbal fluency in MS.

Furthermore, the cutoff values used to define impairment dichotomously (impaired–not impaired) are also completely inconsistent in the literature. As the definitions of "impairment" and "impaired" vary from study to study—depending on where the cutoff is placed—and this can lead to confusion about nomenclature, it would be preferable to use the term "falling below this cutoff" in scientific comparisons. However, it must be recognized that there is also a sociological and social theoretical dimension to this question, as the perception of what is considered "normal" varies from continent to continent, from country to country, even from region to region. This difference in the definition of reference also implies cultural, subcultural characteristics, making it highly questionable whether *a uniform consensus on the definition of "normative" values can ever be feasibly attained*.

This statement leads us back to the individual evaluation system, in which the reference is the person under examination.

For summary, we should consider whether it is at all possible or desirable to push for a uniform definition of CI in MS, and within that DSI. Instead of a mechanical, definition-like understanding of DSI, the term *interindividual heterogeneity of cognitive impairment* should be considered in MS, adding, that further studies may be needed in the future to discover trend patterns by comparing very large numbers of individual patterns and extrapolating individual characteristics to the population level (as in the 2021 study by DeMeo et al. in which cognitive phenotype patterns appeared to emerge from comparing individual clinical and neuroradiological parameters[47]).

Additionally, there has been growing recognition that individual variability, including a person's own previous cognitive performance, can be more relevant in assessing cognitive changes in MS. This approach is often referred to as "Reliable Change Indices."[6,48,49]

Several reasons support the use of *individual referencing* in assessing cognitive achievement in MS:

1 *Baseline variability*: Cognitive function can be influenced by various factors, such as the above-mentioned clinical és sociodemographic characteritics. Using normative data that does not account for these parameters can lead to misinterpretation. *Individual referencing* allows for a better understanding of how these factors affect a specific patient.
2 *Individual disease course*: MS is a highly variable disease, and cognitive function can change over time. Comparing a patient's cognitive performance to their own previous results allows for a more accurate assessment of disease-related changes.
3 *Clinical versus lifestyle significance*: What matters most for a patient is whether their cognitive function has changed in a way that is meaningful to their daily life. *Individual referencing* can capture significant clinical and lifestyle changes that are not necessarily reflected in population norms.
4 *Personalized treatment*: Although the 2020 Canadian recommendation[7] clearly states that optimizing DMTs on the basis of cognitive function is not currently recommended, by monitoring a patient's own cognitive status, clinicians can more effectively adjust neuropsychological interventions and supports to improve quality of life.

In accordance with recommendations from the Consortium of Multiple Sclerosis Centers and the International Multiple Sclerosis Cognition Society,[6] the Canadian Multiple Sclerosis Working Group (CMSWG)[7] recommends that a baseline cognitive assessment (with SDMT, „as a minimum"[6]) should be performed in all MS patients at baseline and every 2–3 years (instead of annually[6] in order to minimize the practice effect) and a 4-point change or reduction of 10% on SDMT, or change in 0.5 standard deviations, or using Reliable Change Indices is considered to be "clinically meaningful" changes[6,50] which is equally applicable to *individual referencing* as well.

Conclusion

Based on our extensive literature review and synthesis of the aggregated evidence, we conclude that, rather than a mechanistic, definition-bound understanding of cognitive DSI in different subtypes of MS, it is recommended that individuals' own past performance, experiences, and self-report should be used as a benchmark for cognitive assessment from the moment of the diagnosis. As a key concept, *individual referencing* allows taking into account the individual's unique characteristics and evaluating the results by comparing them to one's own performance. Thus, *individual referencing* means not using a predefined normative population, but using individual data to interpret test results and determine impairment, which obviously requires longitudinal follow-ups. This would introduce a new approach to cognitive testing that is flexible, personalized, and reflective.

Strengths and limitations

The strength of our study is that we used the same NPTs and cutoffs to assess different CDIs, which was not the case in previous meta-analyses on similar topics,[20,51,52] and we were the first to include CIS patients in the calculations.

Furthermore, it provides a new approach to the topic (*individual referencing*) by evaluating its results.

However, in the absence of sufficient data for further analysis, we have ignored variations in the clinical and sociodemographic parameters underlying the results, which may represent a significant source of bias and limitation in the reporting of results.

In addition, measures of executive function are underrepresented in the BRB-N battery, meaning that we were unable to perform analyses on this measure.

Implications for research and clinical practice

By introducing the concept of *individual referencing*, we are pointing in a new direction that may facilitate the assessment of patients' cognitive abilities in clinical work and provide further opportunities for research to make meaningful advances in our knowledge of CI in MS.

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Author Contributions

KL: Conceptualization, acquisition, project administration, formal analysis, and writing—original draft; **MAE:** Conceptualization, project administration, formal analysis, methodology, data curation, and writing—review and editing; **ZH, KH, and DM**: Conceptualization, formal analysis, visualization, and writing—review and editing; **PH**: Conceptualization, funding acquisition, methodology, and writing—review and editing; **PM and GCs**: Conceptualization, data curation, statistics, formal analysis, and writing—review and editing; **ZMo**: Conceptualization and writing—review and editing; **ZMe**: Conceptualization, project administration, formal analysis, data curation, supervision, writing—original draft, and visualization. All authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript.

Conflict of Interest

KL received speaker fees and conference/travel grants from Biogen, Merck, and Novartis. MAE, ZH, PH, GCs, KH, DM: Nothing to declare. PM received payment as a senior full time biostatistician from the Institute for Translational Medicine, Medical School, University of Pécs. ZMo received payment as a senior medical director from CytoSorbents Europe, Berlin, Germany. ZMe: Received speaker fees and conference/travel grants from: Biogen, Merck, Novartis, Roche, and Sanofi Genzyme.

Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1.
Text S1.

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RESEARCH ARTICLE OPEN ACCESS

Cognitive Impairment in Multiple Sclerosis: The Role of Clinical and Sociodemographic Factors - A Systematic Review and Meta-Analysis

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ABSTRACT

Objective: Cognitive impairment (CI) affects the quality of life in multiple sclerosis (MS). Identifying influencing factors is key to improving CI monitoring. This systematic review and meta-analysis examines 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.

Methods: Registered on PROSPERO (CRD42023451696), a literature search was conducted on August 6, 2023, using PubMed, Embase, and CENTRAL. Following the PRISMA 2020 guideline, a random-effects meta-analysis addressed heterogeneity in correlation and meta-regression analyses. Multivariable regression model results were qualitatively synthesized (systematic review). The JBI Critical Appraisal Tool assessed bias risk. Primary outcome was SDMT raw scores, with EDSS and disease duration as primary exposures, extended with age, sex, education, depression, fatigue, mobility scores, and treatment as secondary exposures, according to our protocol. Associations were evaluated via univariate study-level correlations, univariate meta-regressions, study-level multivariable regression models, and multivariate meta-regressions, assessing covariate interdependence. Heterogeneity was quantified with I^2. Only observational cross-sectional data (or baseline data from longitudinal studies) were included.

Results: A total of 155 studies with 22,828 patients were analyzed. In mixed and relapsing–remitting MS (RRMS), EDSS was the strongest negative correlate of SDMT (mixed MS: −0.44 CI:[−0.50; −0.36]; RRMS: −0.47 [−0.66; −0.23]). Education showed a moderate positive correlation (mixed MS: 0.31 [0.20; 0.42]; RRMS: 0.32 [−0.02; 0.59]). Due to cross-sectional design, heterogeneity, and potential aggregation/ecological bias, findings are exploratory.

Interpretation: Poor SDMT performance is mainly driven by physical disability and cognitive reserve (education), modulated by sex, depression, and age, highlighting the need to integrate clinical and sociodemographic data in MS cognitive monitoring.

1 | Introduction

Multiple sclerosis (MS) is one of the leading causes of disability in young adults [1]. Traditionally, clinical perspectives have emphasized that the degree of *physical impairment*—given the dual main mechanism of "relapse-associated worsening (RAW)" and "progression independent of relapse activity (PIRA)"—predominantly determines the daily functioning of patients, their ability to work, and consequently, their quality of life [2].

However, seminal studies over the past 20 years have established that *cognitive impairment* is also highly prevalent in MS and can serve not only as a contributing factor but also as a primary cause of overall disability in people with MS (PwMS) [3–5].

Due to its ease of administration and characteristics such as reliability, validity, predictive validity, sensitivity, and specificity, the Symbol Digit Modalities Test (SDMT) [6] has emerged as the leading neuropsychological assessment tool for MS [3, 7]. As a minimum, the SDMT test is recommended for baseline cognitive screening, as it measures information processing speed—a core feature of overall cognitive impairment—while also assessing connected domains such as attention, working memory, visuomotor coordination, and executive functions [5]. Current recommendations suggest that SDMT-based cognitive screening is advised at baseline and subsequently annually for patients deemed "clinically stable". If a "clinically meaningful" change—a 4-point change or a reduction of 10% on SDMT, or a change with a 0.5 standard deviation, or using Reliable Change Indices change—is detected, a more comprehensive neuropsychological evaluation (including mood assessment) is warranted [5, 7].

Several previous studies have investigated the influence of different patient- and disease-related characteristics on cognitive performance frequently assessed in everyday clinical practice as well (e.g., age, sex, race, education, disease duration, EDSS score). The results suggest that increased EDSS score, older age, lower educational level, and longer disease duration mostly led to a trend toward cognitive dysfunction in the populations studied; although the results are sometimes inconsistent, and the small number of studies, as well as the lack of analysis of the interdependencies between these parameters, often limit the validity of these findings [8–11].

By identifying key patient and disease characteristics associated with poorer performance on cognitive tests—which may also serve as risk factors for cognitive impairment—we could emphasize intensive neuropsychological monitoring from the outset. This would enable the early detection of subtle, latent signs that may not yet be apparent in the everyday activities of patients, allowing for timely intervention before significant impairment occurs.

Our current comprehensive meta-analysis seeks to address these considerations. First, we aim to identify the sociodemographic and clinical factors that significantly influence SDMT scores, a test widely recognized as an indicator of overall cognitive function. Following this, we aim to establish a hierarchy of these factors to highlight their relative importance.

2 | Methods

2.1 | Study Registration

Our analysis protocol was registered in PROSPERO (international database of prospectively registered systematic reviews; registration ID: CRD42023451696), which we followed without any deviations during the process. We applied the recommendations of the Cochrane Handbook [12] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [13] (Appendix S1).

2.2 | Information Sources and Search Strategy

A systematic search was performed in three major databases (Medline—via PubMed, Embase, CENTRAL—The Cochrane Central Register of Controlled Trials) on August 6, 2023 (Appendix S2).

2.3 | Selection Process

The selection was performed using Endnote 20 (Clarivate Analytics, Philadelphia, PA, USA) software. After automatic and manual removal of duplicates, a selection process was conducted by two independent review authors (Katalin Lugosi and Klaudia Horváth) in two steps (by title and abstract, then by full text), with any disagreements resolved by a third author (Zsolt Mezei). The degree of agreement was quantified by Cohen's kappa statistic.

The "CoCoPop" framework (i.e., condition—context—population) [14] was used to define our selection criteria: the population included adult patients of both sexes (age $\geq$ 18 years) diagnosed with MS, in the context of their clinical-sociodemographic features (Expanded Disability Status Scale/EDSS score [15] and disease duration as a minimum), with the condition of SDMT raw score test results (Appendix S3). The initial context of EDSS and disease duration parameters, as a minimum inclusion criterion, was justified by the preliminary literature search, based on feasibility considerations. However, as stated in the PROSPERO protocol, since sufficient data were available, we analyzed other relevant characteristics of the population, such as age, sex, education, depression, fatigue, mobility scores, and treatment. We excluded studies that examined pediatric or pediatric-onset MS (POMS) populations, smartphone-based, digital/computerized, or modified/adapted versions of SDMT, and excluded patients who were tested during a relapse, recovery from relapse, or steroid treatment, as these factors could significantly impact cognitive test outcomes [16].

We included only articles that applied the SDMT raw score results—that is, the number of insertions under 90 s—and excluded those that only provided an adjusted "z" or "t" score, as these are already derived values and may distort biased results when examining associations. There was no restriction on the criteria for setting up MS diagnosis, and all MS subtypes [17] were included, except for radiologically isolated syndrome (RIS) patients and "benign MS". RIS was excluded

because not all cases convert to MS, whereas "benign MS" was excluded due to the lack of a universally accepted standardized definition.

A detailed description of all inclusion and exclusion criteria recorded during the selection process can be found in Appendix S4.

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

2.4 | Data Collection Process and Data Items

Data extraction was performed by three reviewers independently (Katalin Lugosi, Klaudia Horváth, and Emma Hargitai) and compared by a fourth author (Zsolt Mezei). 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.

2.5 | 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. [18]. For all statistical analyses, a p-value of <0.05 was considered significant. All meta-analyses performed included random effect terms.

When only observational data are available, drawing the right conclusions may be challenging. Confounding can lead to spurious results in univariate analyses. In multivariate analyses, interdependence between predictors makes it difficult to draw the right conclusion. When the meta-regression is based on aggregated variables, then the results should be interpreted with caution because of the possibility of aggregation bias, as described in section 7.6.2. by Schmid et al. [19]. To obtain the most accurate picture possible, we used four types of analysis separately for mixed MS (including various phenotypes) and RRMS, PPMS, 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.

- We separately meta-analyzed the *Pearson and Spearman correlations*. They can be interpreted as *univariate study-level correlation* measures. We pooled Fisher's z-transformed correlations using the classical inverse variance approach with REML τ 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.
- We extracted mean SDMT values along with standard deviation from the studies involved. When only the median and ordered statistics (quartiles, min, max) were available, we used the default method of the metamean () R function to estimate the mean and standard deviation. We performed univariate regression of the SDMT means using the mean or median of the clinical and sociodemographic covariates (*univariate meta-regressions*). We visualized meta-regression results in bubble/scatter plots.
- The *study-level multivariable regression* approaches differed substantially across the studies involved. Several studies selected the covariates involved based on clinical judgment, whereas several studies applied some kind of variable selection. Some of the studies applied methods to detect multicollinearity, while others did not. The type of regression tool also differed between studies. For these reasons, a meta-analysis of the resulting adjusted regression coefficients was not possible. Instead, we created a summary regression table that provided a complete picture of the study-level multivariable regression results (systematic review part).
- We also performed *meta-level multivariate regression analyses* of the examined clinical and sociodemographic parameters. We collected covariates that were frequently presented in the studies involved. Then, following the advice of Harrer et al. [18], we used the PerformanceAnalytics R package to assess the pairwise dependency among these covariates. 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; that is, 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 runnings served as sensitivity analyses of each other.

For univariate study-level correlations, meta-analysis was performed when at least three appropriate studies were available. In cases with fewer studies, or where the correlation method was not Pearson or Spearman, the data were still displayed in the forest plot but were not included in the meta-analysis. We performed univariate meta-regression when the number of studies involved was at least eight. However, the Cochrane Handbook [12] does not recommend performing meta-regression when the number of studies is <10. For this reason, results based on eight and nine studies should be interpreted with caution.

2.6 | Risk of Bias Assessment

The risk of bias was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Tool for Analytical Cross-Sectional Studies [20, 21] framework by two independent reviewers (KL, EH), with

disagreements resolved by a third reviewer (ZMe). Level of evidence rated by The Oxford 2011 Levels of Evidence [22].

3 | Results

3.1 | 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).

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.

A comprehensive overview of the included studies is provided in Appendix S6, Table S1. Details of the complete selection process are shown in the PRISMA flowchart (Figure 1).

A sufficient amount of aggregate data was available for the following sociodemographic and clinical parameters: age in years, sex: percentage of females, education in years, disease duration in years ("not specified," "time since diagnosis," and "time since first symptoms"), EDSS score, depression scores (BDI: Beck Depression Inventory [23], BDI-II: Beck Depression Inventory-II [24], BDI-FS: Beck Depression Inventory-Fast Screen [25], HADS-D: Hospital Anxiety and Depression Scale-Depression score [26]), fatigue scores (FSS: Fatigue Severity Scale [27], MFIS: Modified Fatigue Impact Scale, total scores [28]), Nine-Hole Peg Test (T9HP) [29] and Timed 25-Foot Walk Test (T25FW) [30]. The role of "disease-modifying therapy" (DMT) in influencing cognitive functions was assessed based on the aggregate data from the studied population. Specifically, we evaluated the percentage of patients receiving DMT, distinguishing between "platform" and "highly effective (HET)" treatments. This involved determining what proportion of the population was on DMT (hereafter referred to as "percentage on DMT") and the respective percentages of those on "platform" versus "high-efficacy therapy" (hereafter referred to as "percentage on platform" vs. "percentage on HET"). A detailed list of the medications considered "platform" and "highly effective" therapies is provided in the Appendix S1.

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

In line with our CoCoPop framework, we report the mean SDMT raw scores as the main cognitive outcome to be interpreted within the context of the relevant and statistically applicable clinical and sociodemographic parameters (EDSS and disease duration as the primary exposures and age, sex, education, depression, fatigue, mobility scores, and treatment as secondary exposures) described above.

A list of references for all included studies is available in the Appendix S5. Baseline characteristics of the studies included are detailed (Appendix S6; Table S1).

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.

3.2 | Meta-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 provided in Figure 2.

3.2.1 | 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 are associated with lower SDMT scores.

3.2.2 | 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:

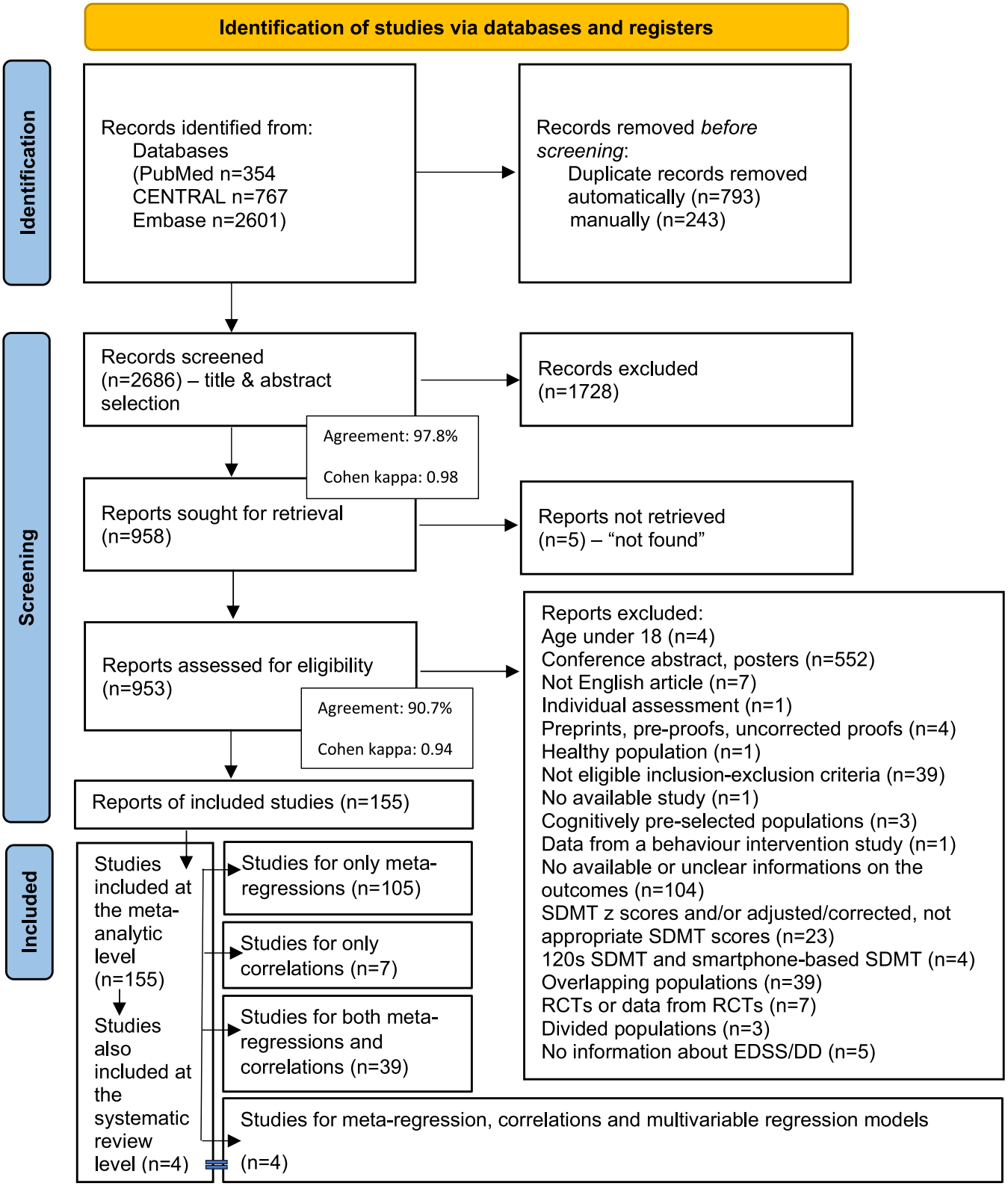

FIGURE 1 | Legend on next page.

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.

A summary panel plot of all the meta-analyzed direct correlation results is shown in Figure 2. The individual forest plots of

FIGURE 1 | Flow diagram of study identification and selection by PRISMA 2020 with details of the reasons for exclusion (see also Appendix S4 and Appendix S6, Table S1). 155 studies were included at the meta-analytic level, of which 4 studies were also included at the systematic review level (with statistically non-analyzable multivariable regression models). From the 155 studies, 105 studies 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 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. *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 (Katalin Lugosi and Klaudia Horváth) during study selection. *Agreement*: The degree to which independent review authors made the same inclusion or exclusion decisions during the screening process.

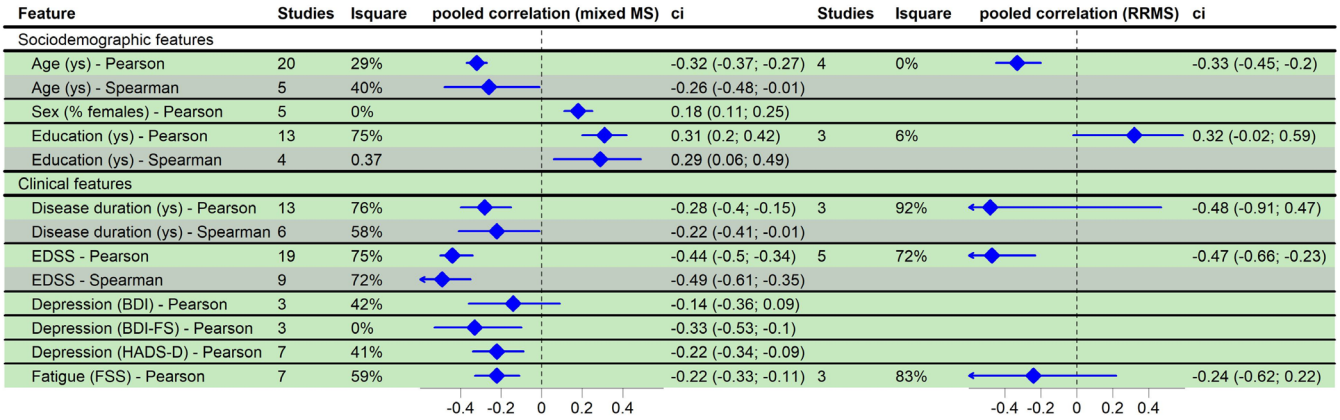

FIGURE 2 | Meta-analysis results of study-level correlations. Out of the total 155 included articles, 50 addressed *univariate study-level correlations*. Among these 50 studies, 1 investigated both Mixed and RRMS populations, 36 focused solely on Mixed populations, and 13 exclusively on RRMS populations. The number of studies presented in Figure 2 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. BDI, beck depression inventory; BDI-FS, beck depression inventory-fast screen; CI, confidence interval; EDSS, Expanded Disability Status Scale; FSS, Fatigue Severity Scale; HADS-D, Hospital Anxiety and Depression Scale-Depression score; I^2, level of heterogeneity; *N*, number of the included studies.

the pooled univariate study-level correlation analyses examined are detailed in Appendix S7.

3.3 | Results of Univariate Meta-Regressions Stratified by Different MS Subtypes

Univariate meta-regression analyses were conducted for the mixed MS and 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 1.

3.3.1 | 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).

3.3.2 | RRMS Populations

In RRMS populations, similar to mixed MS, the EDSS score showed the most pronounced and significant negative association; that is, 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

TABLE 1 | Tabular summary of univariate meta-regression results stratified by different MS subtypes.

	Covariates	Mixed MS	RRMS	PPMS	SPMS
Socio-demographic features	Age (years)	−0.096 *p*: 0.285 *n*: 164 *N*: 22,211	0.209 *p*: 0.311 *n*: 57 *N*: 4217	−0.408 *p*: 0.777 *n*: 8 *N*: 224	0.11 *p*: 0.679 *n*: 13 *N*: 426
	Sex (% female)	**0.185 *p*: 0.001 *n*: 155 *N*: 21,320**	0.132 *p*: 0.108 *n*: 52 *N*: 3587	nd	0.13 *p*: 0.496 *n*: 12 *N*: 418
	Education (years)	**2.443 *p* < 0.001 *n*: 67 *N*: 7722**	**3.636 *p*: < 0.001 *n*: 22 *N*: 1833**	nd	nd
Clinical features	DD (years)	***−0.278 p: 0.064 n:121 N: 18,324*** −0.474 *p*: 0.246 *n*: 15[a] **N**: 1218 −0.305 *p*: 0.379 *n*: 9[b] *N*: 1041	0.044 *p*: 0.913 *n*: 41 *N*: 3085	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*: 4217**	0.264 *p*: 0.947 *n*: 8 *N*: 224	−2.367 *p*: 0.555 *n*: 13 *N*: 426
	Depression	**−2.031 *p*: 0.003 *n*: 9[c] *N*: 1157 −4.926 *p*: 0.006 *n*: 12[d] *N*: 1256 −2.337 *p*: 0.007 *n*: 20[e] *N*: 3086**	**−3.607 *p*: 0.01 *n*: 8[e] *N*: 746**	nd	nd
	Fatigue	1.817 *p*: 0.397 *n*: 22[f] *N*: 2078 −0.168 *p*: 0.297 *n*: 10[g] *N*: 1097	−0.04 *p*: 0.992 *n*: 10[f] *N*: 853	nd	nd
	T25FW	**−0.492 *p*: 0.028 *n*: 22 *N*: 2573**	**−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*: 9392 −0.011 *p*: 0.86 *n*: 25[i] *N*: 7139 0.026 *p*: 0.673 *n*: 24[j] *N*: 7097	0.011 *p*: 0.858 *n*: 24[h] *N*: 1662 −0.059 *p*: 0.414 *n*: 15[i] *N*: 896 0.107 *p*: 0.174 *n*: 14[j] *N*: 854	nd	nd

Note: Significant results are highlighted in bold, results close to significance are highlighted in bold and italics.
Abbreviations: DD, disease duration; EDSS, Expanded Disability Status Scale; Edu, education; MS, multiple sclerosis; *N*, number of the included patients; *n*, number of the included studies; nd, no data; *p*, significance level; PPMS, primary progressive multiple sclerosis; RRMS, relapsing–remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; T25FW, timed 25-ft walk test; T9HP, nine-hole peg test.
[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).

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 negative association parameter with SDMT scores in the RRMS subgroup (b: 3.636, $p < 0.001$), with a relatively moderate number of studies included.

A tabular summary of all the univariate meta-regression results is shown in Table 1. The individual scatter plots for the examined meta-regressions are detailed in Appendix S8.

3.4 | Results of the Systematic Review of Study-Level Multivariable Regression Models

Given the heterogeneity of variables included in the regression models of the studies and regression model types, we provide *a systematic review* of study-level multivariable regression analyses.

Four studies conducted multivariate regressions on mixed MS populations. These analyses included linear, stepwise, or logistic regressions with sociodemographic, clinical variables, and other parameters.

Adjustment for age and education was performed in all regression models, with one showing a significant negative coefficient for both parameters. EDSS was the most impactful, with three studies showing significant negative effects, including one with a pronounced impact. Disease duration, sex, and depression showed no significant effects alongside other parameters.

A tabular summary of all the adjusted variables, which were included in the multivariable regression models and adjusted for SDMT as a target parameter, is detailed in Appendix S9, Table S2.

3.5 | Meta-Level Multivariate Regression Analyses of the Investigated Clinical and Sociodemographic Factors (Covariates) – Interdependence Analyses

For mixed MS populations, pairwise dependency analysis of the covariates (Appendix S10, Figure S8a) revealed strong positive pairwise linear associations between covariates *age*, *disease duration*, and *EDSS*. For this reason, we fitted three multivariate meta-regression models. Each model contained the variables *sex* and *education* and one of the three strongly correlated variables.

Sex and *education* are always significant, with *education* showing a stronger effect (lower *p*-value). Age and disease duration are not significant alongside sex and education. EDSS keeps its strong significance in the multivariate regression model, even with the sex and education variables, although education has the strongest effect (for details, see Appendix S11, Table S3).

For RRMS (Appendix S10, Figure S8b), the pairwise correlation analysis revealed that most of the pairwise correlations between the variables *age*, *disease duration*, *EDSS*, and *education* are quite large. We only fitted models containing covariates with not too high pairwise correlations. *Education* and *EDSS* remained consistently strong predictors, while *sex* and *age* had non-significant or borderline effects. For details, see again Appendix S10, Figure S8, and Appendix S11, Table S3.

3.6 | Risk of Bias Assessment and Quality of Evidence

On the basis of the JBI Quality Assessment Tool for Analytical Cross-Sectional Studies, the first four questions indicate a low risk of selection and performance bias, suggesting that the populations in the meta-analysis were representative. However, the remaining questions highlight a high risk of detection bias, and to a lesser extent, reporting bias, mainly due to variability in how associations were analyzed across studies. This is likely to reflect the heterogeneous reporting of factors influencing cognitive impairment and adjustments in the analyses.

The summary of the assessment of the risk of bias for each included study (listed according to the criteria of the "JBI Quality Assessment Tool for Prevalence Studies") is detailed in Appendix S12

Rating of the quality of evidence is provided in Appendix S13.

4 | Discussion

Our study aimed to evaluate the relationship between disease-related and sociodemographic factors and SDMT performance as a key sentinel test for cognitive impairment. Using robust methods across two levels of evidence, our findings revealed the multifactorial nature of cognitive dysfunction as a significant determinant of overall disability in MS. In the absence of complete evidence for PPMS and SPMS, our conclusions primarily focused on RRMS and mixed MS populations. In this section, our aim is to interpret the hierarchy of all primary and secondary exposure parameters examined in terms of their impact on SDMT performance and to highlight their relative importance based on our findings. Given the inclusion of observational studies (cross-sectional data), population heterogeneity, and the potentially distorting effects of aggregation/ecological bias, the conclusions should be regarded as primarily exploratory and directional. The key findings supporting this perspective are summarized in Figure 3.

The most significant finding—at all levels of evidence—, was a clear negative impact of *EDSS* on SDMT in the mixed population, a trend also evident in RRMS. In these populations, increased EDSS scores correlated with poorer SDMT performance, supporting its role as a key risk factor of cognitive impairment. In parallel, pairwise dependency analyses in mixed MS populations revealed that age and disease duration had strong positive linear interference, while age positively correlated with EDSS. Educational attainment consistently emerged as a significant predictor for all these parameters in multivariate regression models, indicating that *the negative association between clinical status and cognition becomes more pronounced over time* (*referring to the role of age and disease duration*), *further shaped by the cognitive reserve, which is mainly determined by educational attainment* [31]. This is partially supported by the literature, but the EDSS-cognition relationship remains debated [4, 32–34]. Lynch et al. [35] found a definite association between cognitive impairment and EDSS score, but—contrary to the assumption above—it was significant in both the early stage of MS and in those with over 10 years of disease duration. They noted that studies showing strong EDSS-cognition correlations often used "speeded information processing" tests (e.g., Hohol et al. [36], Sonneville et al. [37])—such as the SDMT—, highlighting that "*patients' sensory and motor deficits simply suppress their performance on these tests, leading to poorer scores than their cognitive powers would otherwise yield*", which also points to the effect of EDSS as a possible explanation. However, Lynch used a battery

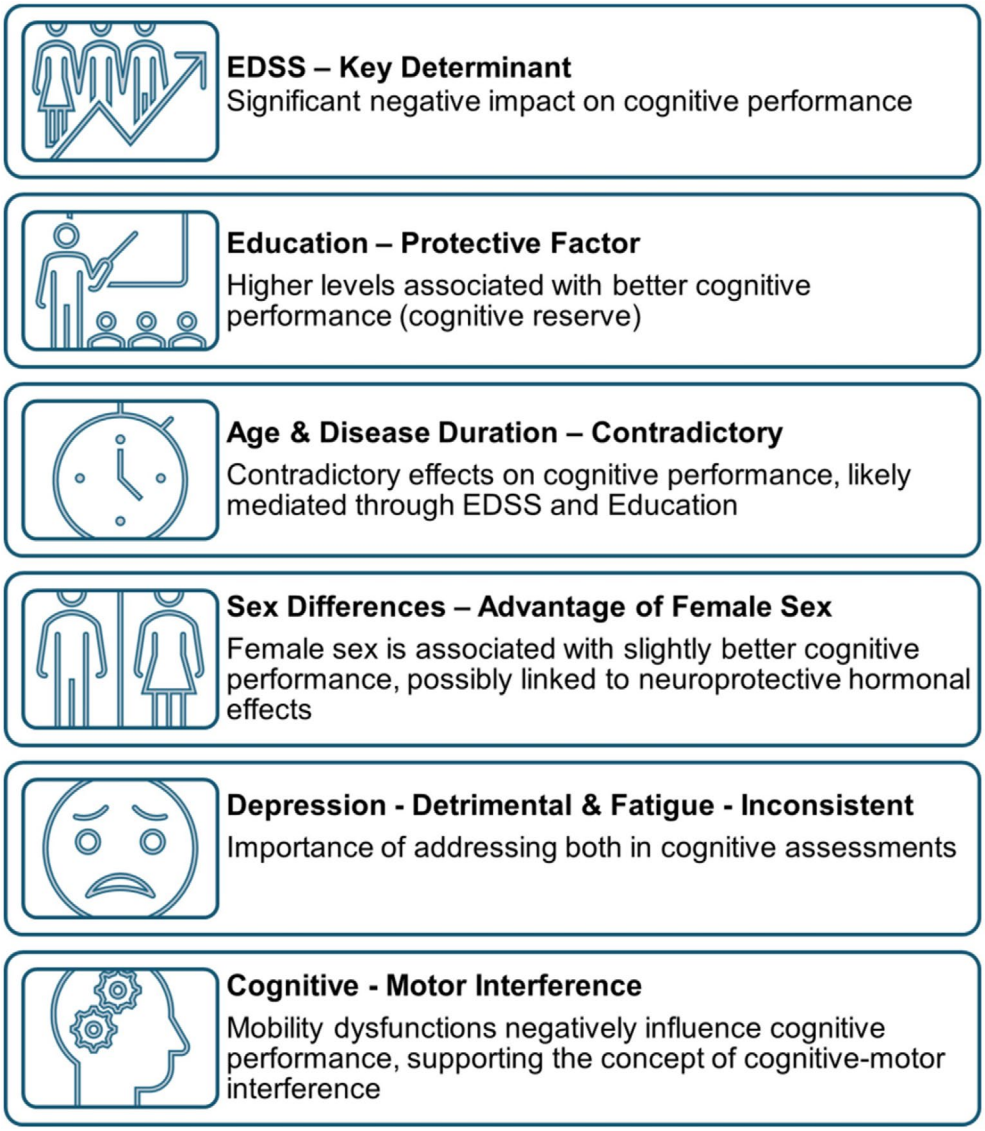

FIGURE 3 | Key findings of our study reveal the multifactorial nature of the relationship between disease-related and sociodemographic factors and SDMT performance as a key sentinel test for cognitive impairment.

of more comprehensive tests and identified a correlation of similar magnitude, consistent with our findings.

Our results showed that *age* and *disease duration* had contradictory effects among mixed and RRMS populations. At the meta-regression level, age was negatively correlated with SDMT scores in mixed MS and positively correlated in RRMS, whereas study-level correlations and regression models suggested a negative trend in both populations. This discrepancy may be due to the fact that meta-regression is based on average age in years, which raises the question of whether the observed association reflects different population age averages. Data from countries with higher life expectancy (i.e., higher income, better healthcare, better treatment access)—and thus higher average age—might reverse the association between increased age and improved cognitive performance. However, further investigation is needed to explore this. Disease duration showed a negative trend, but only in study-level correlations, and was contradictory at the univariate meta-regression level in RRMS. This complexity of the role of age and disease duration—considering their interdependency and multivariable regression analyses—suggests that *age and disease duration are likely to affect cognitive performance through other parameters* (such as EDSS and education). Lynch et al. [35] found no evidence between cognitive impairment and disease duration. They also questioned the interpretation of the relationship between cognitive impairment and physical disability, as measured by EDSS, as the former is not correlated with disease duration, whereas the latter is. They suggest that in MS, the "inevitable" progression of physical disability—in relation to disease duration and temporal deterioration—allows the association with cognitive decline to persist, despite different dynamics. Our cross-evidence-level and multivariable regression analysis appears to support this. Amato et al. [38] also concluded that the negative correlation between clinical status (EDSS) and cognition strengthens over time. This suggests a possible link between disease duration and EDSS, implying that EDSS *might, in fact, operate through the length of time with MS*. A meta-analysis by Prakash et al. [39] also confirms this interdependence.

Education undoubtedly had a positive effect. In RRMS, it showed a significant impact at the meta-regression level and study-level multivariable regression models, and marginally significant at the study-level correlations. In the mixed populations, it was significant at the meta-regressions and the study-level correlations, consistent with study-level multivariable regression models. Overall, *higher educational attainment*—although it appears to be less important compared to EDSS changes—*is associated with higher SDMT scores*. Although there is a lack of detailed studies on years of education and SDMT, the existing literature suggests that education—as one of the main determinants of 'cognitive reserve'—tends to positively influence cognitive functions in MS [40].

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 study was based on cross-sectional data; however, a recent longitudinal observational study by Longinetti et al. [41], conducted on a large population-based sample, showed similar results. They aimed to identify trajectories of SDMT and EDSS and their connections and explore patient characteristics associated with trajectory groups over an 11-year follow-up (from DMT initiation) of 1645 RRMS patients, including analyses of conditional probabilities. They found that there is a strong association between processing speed (SDMT) and physical disability (EDSS) trajectories. Based on their results, older age was associated with cognitive impairment 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. [42], based on a large longitudinal study of RRMS patients, which identified that higher EDSS, older age, male sex, and depression predicted poorer processing speed (measured by Processing Speed Test/PST—an iPad version of SDMT) over time, while higher educational attainment was protective. Importantly, patients with low baseline cognitive performance and no practice effect were at significantly greater risk of sustained decline. These findings support our cross-sectional results and highlight the predictive value of EDSS, education, and baseline cognition in cognitive trajectories.

These also raise questions about the reliability of general adjustments 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.

Depression significantly influenced SDMT in mixed MS populations at meta-regression and study-level correlation levels, although regression models were less clear. Although this appears to be a straightforward association, caution is needed when interpreting cognitive impairment in patients with concurrent depression due to the potential for pseudo-dementia, highlighting the importance of parallel testing for comorbid depression when evaluating cognitive functions in MS.

The impact of *fatigue* was less clear due to variability in testing methods and insufficient data. The commonly available FSS test suggested a significant negative effect at study-level correlations in mixed MS with contradictory findings at the meta-regression level, and non-significant negative association in RRMS populations, based on univariate meta-regressions and study-level correlations. One possible explanation is a study by Yigit et al. [34] investigating the interplay between depression and fatigue. They found that fatigue, as measured by the FSS score, significantly reduced SDMT scores, whereas depression had no significant effect. However, when both symptoms co-occurred, a significant decline in information processing speed was observed, particularly on the SDMT from the BiCAMS test. This suggests that depression may "amplify" the impact of fatigue, further worsening cognitive performance. Unfortunately, we lacked sufficient data to perform interdependence and multivariable regression analyses to explore this question further.

Sex (the proportion of females in the population) showed a moderate but consistent positive effect on SDMT in mixed MS populations, suggesting that a *higher proportion of females in the MS population tends to correlate with better cognitive performance*. This aligns with literature indicating reduced susceptibility to cognitive decline in females, possibly due to the neuroprotective effect of estrogen (reversing myelin damage [43]) and less gray matter damage [44]. This might explain the protection observed, especially in early-stage MS, which may also carry the potential risk of menopause [45].

Meta-regression data alone limit conclusions due to aggregation bias for *T25FW*, *T9HP*, and *treatment* effects. In general, there is weak evidence that T25FW and T9HP tests have a negative influence on SDMT score, with the T25FW test having a significant effect in mixed MS and RRMS, supporting the concept of "cognitive-motor interference" (CMi) or, alternatively, "dual-task interference" (DTi) [46] or "cognitive-postural interference" (CPI) [47], commonly referred to in the literature. They are associated with special neural correlates and the interactions of complex neural networks [48].

In terms of treatments, our results are inconsistent. The literature on DMTs suggests that their cognitive impact varies by specific therapeutic agents, focusing on these effects mainly as secondary or exploratory outcomes [49–54], with a limited number of studies assessing aggregated effects within broader classifications such as ours [55, 56]. Variability in treatment protocols and patient adherence further complicates this area, underscoring the need for robust clinical trials focusing on cognitive outcomes as primary endpoints.

4.1 | Strengths and Limitations

The strength of our study lies in the extensive dataset and comprehensive methodological approach, in line with established recommendations, which are critical for the evaluation of future association studies.

However, the main limitation is reliability and the fact that our study is a review of cross-sectional studies.

We used aggregated data to draw individual conclusions, introducing the "fallacy of the wrong level", where aggregated relationships may not apply individually. This leads to ecological

and aggregation bias, distorting relationships. Interdependence among predictors further complicates regression results, making it difficult to identify the contribution of each parameter to the dependent variable (SDMT scores). To address this, we followed Harrer's guidelines [18], analyzed results across different evidence levels, and conducted interdependence and multivariable regressions. Where study-level correlations/regressions and meta-regressions aligned, the effect strength was reliably estimated, ranking of the impact of predictors on cognitive impairment. Thus, the strategy developed to address these confounding factors and the resulting limitations represents a major strength of our study.

Cross-sectional data do not allow for conclusions about causal inferences or changes over time. Therefore, we can claim to have identified that certain clinical and sociodemographic parameters may act as potential risk factors for poorer cognitive screening performance in MS. Ideally, longitudinal data would enable us to assess how longitudinal cognitive *decline* in MS evolves in relation to these parameters. However, the number of available longitudinal studies was limited, and those that were available varied widely in terms of follow-up duration and population characteristics, making their integration into a quantitative synthesis infeasible.

4.2 | Implications for Clinical Practice and Research, and Future Directions

Our study confirms a controversial claim in the international scientific community: the physical status of patients with MS is a strong, independent factor influencing cognitive impairment that also significantly contributes to disability progression. Consequently, maintaining long-term EDSS stability is critical for clinical practice in MS care in order to preserve the social, familial, and existential integrity of our patients.

A clear implication for research is the multi-level analysis described, which may serve as a model for future association studies. In MS, a more sophisticated examination of patient-related factors influencing cognitive impairment should integrate neuropsychological test batteries—for example, BRB-N, MACFIMS, and BiCAMS [8, 57, 58]—with radiological markers (MRI parameters) and biomarkers, to capture multidomain functional aspects. This approach was not feasible in our study due to insufficient pooled data.

For the future, understanding the interaction of clinical and sociodemographic factors on cognitive performance may improve patient stratification and enable more targeted interventions, translating scientific findings into clinical practice—a top priority for the 21st century [59, 60].

5 | Conclusion

In multiple sclerosis, poorer performance on SDMT—a sentinel test for cognitive impairment—is shaped by a complex interaction of sociodemographic and clinical factors. Among these, overall physical status (as measured by the EDSS score) and educational attainment were found to be the strongest influencing factors. While preserving patients' physical well-being and slowing neurological progression remain critical, our findings also emphasize the protective role of higher education, suggesting that cognitive reserve may mitigate the impact of disease-related cognitive involvement and help maintain cognitive functions essential for preventing disability progression and preserving quality of life in MS.

Author Contributions

Katalin Lugosi: conceptualization, project administration, investigation, data curation, writing – original draft. **Marie A. Engh:** conceptualization, project administration, methodology, writing – review and editing. **Tamás Kói:** conceptualization, statistics, formal analysis, visualization, writing – review and editing. **Zsolt Molnár** and **Gábor Csukly:** conceptualization, writing – review and editing. **Klaudia Horváth** and **Emma Hargitai:** conceptualization, investigation, data curation, writing – review and editing. **Péter Hegyi:** conceptualization, funding acquisition, methodology, writing – review and editing. **Zsolt Mezei:** conceptualization, project administration, writing – review and editing, supervision. All authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript.

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Ethics Statement

The authors have nothing to report. The datasets used in this study can be found in the full-text articles included in the systematic review and meta-analysis.

Conflicts of Interest

Katalin Lugosi received speaking fees from Merck and Novartis, and conference attendance and travel grants from Biogen, Merck, Novartis, and Roche. Klaudia Horváth received conference attendance and travel grants from Merck, Novartis, and Roche. Zsolt Mezei received honoraria for lectures (directly) from Merck and Novartis and conference/travel grants and support (paid to the organizer) from Merck, Novartis, Roche, Sanofi Genzyme, and UCB. Marie A. Engh, Tamás Kói, Zsolt Molnár, Gábor Csukly, Emma Hargitai, and Péter Hegyi declare no conflicts of interest.

Data Availability Statement

Data in the article will be shared on reasonable request to the corresponding author.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** Supplementary Material. **Table S1:** Baseline characteristics of the included studies.