Impact of cognitive impairment on quality of life and work productivity of relapsing-remitting multiple sclerosis patients: a systematic literature review

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Introduction

- Multiple sclerosis (MS) is a chronic, immune-mediated, inflammatory, demyelinating disease of the central nervous system[1]
- In 2020, approximately 2.8 million people were living with MS worldwide[2]
- An estimated 85% of patients with MS have relapsing-remitting MS (RRMS)[3]
- Common symptoms of MS include visual disturbances, sensory loss, limb weakness and gait abnormalities, fatigue, cognitive impairment, and emotional problems[1,4]
  - Up to 65% of patients with MS have cognitive impairment, or dysfunction in the domains and subdomains of cognition defined in the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition[5,6]
- Cognitive impairment may have a significant impact on patient quality of life (QoL) and work productivity[7-10]

Objective

- To conduct a systematic literature review to summarize the available evidence on the impact of cognitive impairment on QoL and work productivity in patients with RRMS

Methods

PICOS framework

- The population, intervention, comparator, outcomes, and study type (PICOS) framework was used to prespecify eligibility criteria and identify all relevant studies (**Table 1**)

Literature search

- EMBASE, MEDLINE, and MEDLINE-IN-PROCESS (via PubMed) were systematically searched on July 7, 2020
- Conference abstracts published at key meetings in the field of MS between 2017 and 2020 were also reviewed
  - No hand searches were conducted as the major conferences of interest were indexed in EMBASE

Table 1. PICOS framework

PICOS component	Selection criteria
Population	Adult (≥18 years) patients with RRMS
Intervention	No restrictions
Comparator	No restrictions
Outcomes	• Correlation between cognitive performance and QoL (both measured via MS-specific and validated questionnaires) • Correlation between cognitive performance (measured via MS-specific and validated questionnaires) and work productivity (presenteeism, absenteeism, and time off work) • A **threshold ± 0.3** (correlation coefficient or Z-score) has been used to determine correlation between 2 components
Study type	Observational studies (including retrospective, prospective, cohort, and cross-sectional studies). Case studies, letters, editorials, SLRs, NMAs, and RCTs were not included
Date	• Publications dating 2008–2020 • Conference abstracts dating 2017–2020
Language	English

Term	Parameters of interest
Cognitive function	MS-specific tools measure cognitive function (eg, BICAMS) Cognitive functions often measured in MS: • Information processing • Memory • Attention and concentration • Executive function (planning and prioritizing) • Visuospatial functions (visual perceptional and constructional abilities) • Verbal fluency (word finding)
Quality of life	MS-specific tools measure QoL QoL measurements often include: • **Physical and occupational functions** (eg, impairment of mobility, balance, driving, sleep, leisure activities) • **Psychological state** (eg, depression, fatigue, emotional well-being, mood, anxiety, fear of falling)
Work productivity	Presenteeism, absenteeism, employment status, time off work, and lost wages

BICAMS, Brief International Cognitive Assessment for MS; MS, multiple sclerosis; NMA, network meta-analysis; PICOS, population, intervention, comparator, outcomes, and study type; QoL, quality of life; RCT, randomized controlled trial; RRMS, relapsing-remitting multiple sclerosis; SLR, systematic literature review.

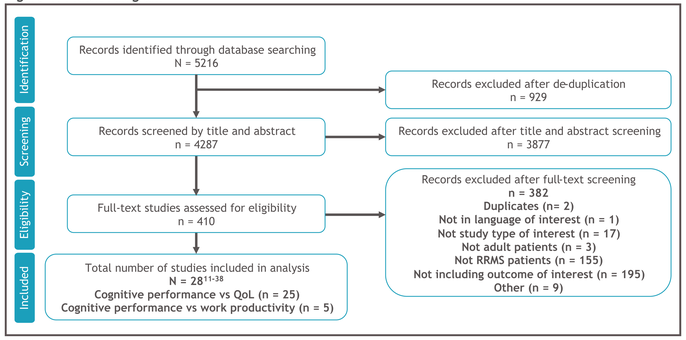
Results

Included studies

- A total of 5216 citations were captured from EMBASE, MEDLINE, and MEDLINE-IN-PROCESS. After removal of duplicates, 4287 citations were assessed for inclusion at title and abstract screening stage, and 410 of these were further reviewed as full texts
- In total, 28 studies were included (**Figure 1**)[11-38]
- Most studies used a prospective design (n = 21); of these, 11 were cross-sectional (**Figure 2**)
  - A total of 15 studies were based on clinic or hospital databases, and 6 studies used data from MS centers
- Of the 28 included studies, 14 were conducted in the European Union,* 8 in the United States, 2 in Canada, 1 in Brazil, 1 in Egypt, 1 in Jordan, and 1 in Australia
- Study sample size ranged from 35 to 699 patients

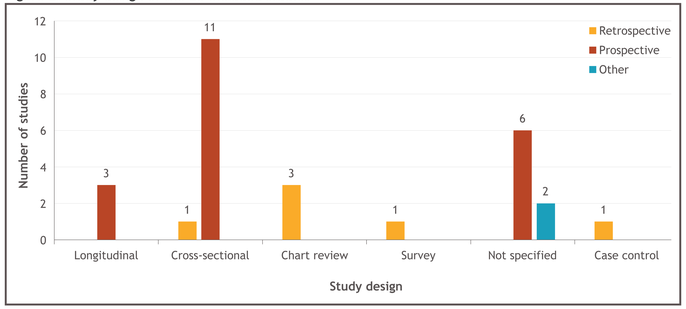
*Two studies included sites in the United Kingdom while it was an EU member country

Figure 1. PRISMA diagram



PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; QoL, quality of life; RRMS, relapsing-remitting multiple sclerosis.

Figure 2. Study design of the 28 included studies



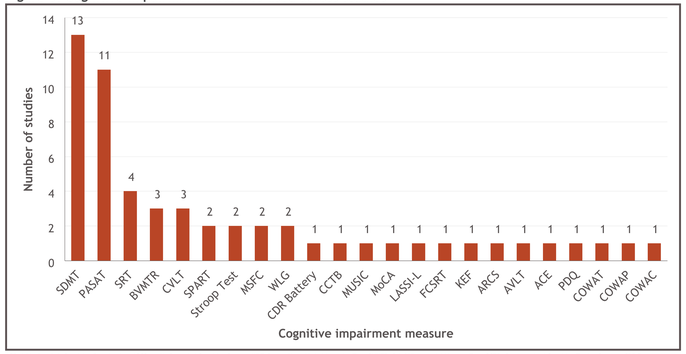
Baseline demographics

- The majority of patients in the included studies were women aged 34.3 – 47.2 years
- The average time since diagnosis ranged between 2.6 and 13.8 years
- Across all studies, no patients had an Expanded Disability Status Scale score > 7.0
- Patients' previous disease-modifying therapies used varied quite markedly across studies and within studies
  - Products used included natalizumab (n = 6),[19,27,29-31,34] fingolimod (n = 6),[19,27,29-31,34] beta interferons (n = 4),[12,19,27,34] and unspecified interferons (n = 2)[30,31] among others

Tools to assess cognitive impairment

- The most common tool used to measure cognitive impairment was the Symbol Digit Modalities Test (n = 13), which assesses divided attention (a subdomain of complex attention) and visual scanning, tracking, and motor speed (subdomains of perceptual-motor function)
- Paced Auditory Serial Addition Test was the second most common tool (n = 11), used to assess auditory information processing speed and flexibility as well as calculation ability
- Tools used to assess cognitive impairment across and within the studies are shown in **Figure 3**

Figure 3. Cognitive impairment measures used across studies



ACE, Addenbrooke's Cognitive Examination; ARCS, Audio Recorded Cognitive Screen; AVLT, Rey Auditory Verbal Learning Test; BVMTR, Brief Visuospatial Memory Test; CCTB, Computerized Cognitive Testing Battery; CDR Battery, Cognitive Drug Research Battery; COWAC, Controlled Oral Word Association–Category; COWAP, Controlled Oral Word Association–Phoneme; COWAT, Controlled Oral Word Association Test; CVLT, California Verbal Learning Test; FCSRT, Free and Cued Selective Reminding Test; KEF, Kaplan Executive Function System; LASSI-L, Loewenstein-Acevedo Scale for Semantic Interference and Learning; MoCA, Montreal Cognitive Assessment; MUSIC, Multiple Sclerosis Inventarium Cognition; MSFC, Multiple Sclerosis Functional Composite; SDMT, Symbol Digit Modalities Test; PASAT, Paced Auditory Serial Addition Test; PDQ, Perceived Deficits Questionnaire; SPART, Spatial Recall Test; SRT, Selective Reminding Test; WLG, Word List Generation.

Impact of cognitive impairment on QoL and work productivity outcomes

- Correlation of cognitive impairment with QoL was assessed in 25 studies and with work productivity in 5 studies
- Most included studies assessed the correlation between cognitive impairment and depression (n = 16), fatigue (n = 9), and anxiety (n = 7) using MS-specific and generic QoL tools (**Table 2**)
- Studies found cognitive impairment to be positively correlated with depression, fatigue, and stigma and inversely correlated with social support, employment status, and mental health, regardless of cognitive domain
- No correlations were identified between cognitive impairment and anxiety, stress, or driving ability
- High performance in general cognition was strongly associated with increased rates of employment; however, correlations, or lack thereof, varied based on the cognitive domain being evaluated and across studies

Table 2. Correlations with QoL variables by cognitive domain

Cognitive domain	QoL outcomes with positive correlation	QoL outcomes with negative correlation	QoL outcomes with no correlation
Language[13,24,25,27,30,31,34,44]		**Fatigue***	Depression, anxiety, fatigue, general QoL, postural control, velocity sway, stress, driving
Episodic memory[13,14,16,18,25-27,34,37]		**Fatigue,*** general QoL	Depression, anxiety, fatigue, stress, physical QoL, mental QoL, general QoL, mobility, driving, neuroticism
Learning and long-term memory[13,14,19,20,24,27,29-31,37]		**Fatigue,* depression***	Depression, anxiety, fatigue, neuroticism, driving, general QoL, mobility
Complex attention[11,13,14,16,18-20,22-25,27,29-32,34,36,37]	**Fatigue,* physical QoL,* mental QoL,* fear of falling***	Fatigue, **depression,* sleep,*** mobility, **physical QoL***	Depression, anxiety, fatigue, physical QoL, mental QoL, general QoL, mobility, driving, dissociation, absorption, depersonalization, segment amnesia, fear of falling
Executive function[11-14,16,29-31,37]	Velocity sway	**Depression***	Depression, anxiety, fatigue, physical QoL, mental QoL, dissociation, absorption, segment amnesia, depersonalization, neuroticism, driving
Perceptual motor function[19,34,37]			Depression, anxiety, fatigue, stress, driving ability

*P<0.05
QoL, quality of life.

Limitations

- The main limitation of this study is that it was not feasible to conduct a quantitative synthesis of included studies owing to the heterogeneity of study outcomes and tools used to measure outcomes
- The large number of cognitive outcomes measured in the included studies that indicated correlation with QoL suggests that the relationship between cognition and QoL is not yet well understood and merits further research
- The dearth of longitudinal studies frustrates a more precise understanding of the relationship between cognitive impairment and QoL
  - The various cognitive subdomains may be better indicators of cognitive decline depending on how far patients' disease has progressed

Conclusions

- Results of this systematic literature review lend support to the association between cognitive impairment and:
  - Increased fatigue and depression
  - Decreased social support and mental and physical QoL
  - Employment status
- The associations identified suggest that cognitive factors contribute to reduced QoL in RRMS patients
- Study findings varied owing to the many outcome measures used across studies
- Further research is required to assess how cognitive impairment impacts MS-related QoL and work productivity, including absenteeism, presenteeism, and lost wages

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Disclosures

- **LA, JC, and MP:** Employees of Amaris Consulting at the time of development
- **JK:** Employee and shareholder of Bristol Myers Squibb
- **TT:** Employee and shareholder of Bristol Myers Squibb at the time of development

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