

Kertas Asli/Original Articles

A Narrative Review on Biopsychosocial Predictors of Cognitive Impairment among Multiple Sclerosis Patients: Directions for Malaysia Studies

(Satu Tinjauan Naratif Mengenai Peramal Biopsikososial Kemerosotan Kognitif dalam Kalangan Pesakit Sklerosis Berbilang: Halatuju Arah Kajian di Malaysia)

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ABSTRACT

Cognitive impairment is the most disabling symptoms of Multiple Sclerosis (MS). Researchers have been studying factors that could predict cognitive impairment among MS patients hoping to alleviate its consequences and gather indicators of the disease progression. However, there were limited up-to-date articles that review the predictors of cognitive impairment among MS patients. In Malaysia, the topic about cognitive functioning in MS was absent. This review aims to identify and synthesize the research evidence concerning biopsychosocial variables on cognitive impairment among this population for future directions in Malaysia researches. A narrative review was performed by identifying research articles from year 2004 to 2019 through PubMed, EBSCOhost, Scopus and Google Scholar. Full-text articles meeting the selection criteria were included for qualitative synthesis. A total of 12 studies were included. Studies included in this paper found that age, course of disease and anxiety predicts cognitive functioning. Mixed results were found among variables such as gender, disability, fatigue, burden of lesion, depression and educational level. Stress was correlated with cognitive functioning but it was not a significant predictor. Although many factors were found to affect cognitive functioning among MS patients, evidence provided from this review indicates that their relationships might not be linear and direct.

Keywords: predictors; cognitive impairment; multiple sclerosis; Malaysia

ABSTRAK

Kemerosotan kognitif adalah gejala Sklerosis Berbilang (MS) yang paling melumpuhkan. Para penyelidik telah mengkaji faktor-faktor yang dapat meramalkan kemerosotan kognitif dalam kalangan pesakit MS dengan harapan dapat mengurangkan akibatnya dan mengumpulkan petunjuk perkembangan penyakit. Walau bagaimanapun, artikel terkini yang mengkaji peramal kemerosotan kognitif dalam kalangan pesakit MS masih terhad. Di Malaysia, kajian mengenai fungsi kognitif di MS masih tiada. Kajian tinjauan ini bertujuan untuk mengenal pasti dan mensintesis bukti penyelidikan mengenai penentu biopsikososial atas kemerosotan kognitif dalam kalangan populasi ini untuk menentukan hala tuju penyelidikan di Malaysia pada masa depan. Kajian naratif dilakukan dengan mengenal pasti artikel penyelidikan dari tahun 2004 hingga 2019 melalui PubMed, EBSCOhost, Scopus dan Google Scholar. Artikel teks penuh yang memenuhi kriteria pemilihan telah dimasukkan untuk sintesis kualitatif. Sebanyak 12 kajian telah dimasukkan. Kajian yang dimasukkan mendapati bahawa usia, tahap penyakit dan kegelisahan meramalkan fungsi kognitif. Hasil bercampur didapati dalam pembolehubah seperti jantina, ketakupayaan, kelesuan, beban lesi, kemurungan dan tahap pendidikan. Tekanan mempunyai kaitan dengan fungsi kognitif tetapi ia bukan peramal yang signifikan. Walaupun terdapat banyak faktor mempengaruhi fungsi kognitif dalam kalangan pesakit MS, hasil kajian tinjauan ini menunjukkan bahawa hubungan mereka berkemungkinan tidak linear dan secara langsung.

Kata kunci: peramal; gangguan kognitif; sklerosis berbilang; Malaysia

INTRODUCTION

Multiple Sclerosis (MS) is a chronic autoimmune neurological disorder that causes inflammation and destruction to the central nervous system. It typically affects the multifocal areas of white matter, the cortical and

deep gray matter leading to cerebral atrophy (Lucchinetti et al. 2011; Popescu & Lucchinetti 2012). There are four stages of MS: relapsing remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS) and progressive-relapsing MS (PRMS). The precise causes of MS are unknown, and only a few risk factors comprise

of genetic and environmental factors have been identified to date, yet with modest effect (Leray et al. 2016). MS could contribute to the mortality of patients through progressive disability, increased risk of infection, cardiovascular diseases and maybe cancer (Leray et al. 2016; Marrie et al. 2015).

Recently, the global prevalence of MS has increased, at least among women (Leray et al. 2016). In Malaysia, MS is considered as uncommon with an estimated prevalence of one to two per 100 000 population (Chong & Tan 2008). Similar with the global prevalence, there were more Malaysian females than male MS patients, with a ratio of 5:1; Malays were mostly affected, followed by Chinese, Indians and a small portion of indigenous Malaysian from East Malaysia (Viswanathan et al. 2013). However, these numbers may be underreported. According to the Multiple Sclerosis Society Malaysia (2015), it was estimated that 1000 Malaysian was suffering from MS, but only about 400 to 500 were diagnosed and on treatment due to poor public awareness about this disease. Furthermore, MS has an usual onset during young adulthood (Kinsinger, Lattie & Mohr 2010) and diagnosed between age 20 to age 50 (Krokavcova et al. 2010). According to the data released by Department of Statistics Malaysia (2018), young adults constitutes most of the national workforce (69.7%). This shows that the impact of MS on this population could be detrimental to the country's work productivity if the disease is left undiagnosed and untreated.

Cognitive impairment is recognized as one of the leading causes of disability (Braley et al. 2016) among MS patients that has a direct impact on health-related quality of life at all stages of MS (Mitchell et al. 2005). It often involves working memory (Griffiths et al. 2005; Scherer et al. 2007), sustained attention (Arnett & Strober 2011), information processing speed (Bodling, Denney & Lynch 2012), learning (Ferreira 2010), executive functioning and visuospatial skills (Loftisa, Huckansa & Morasco 2010). Deficits in cognitive functioning reduces the quality of life of MS patients by losing job opportunities (Ruet et al. 2013), hindering social participation (Leocani, Colombo & Comi 2008) due to diminishing competence in daily activities (Goverover et al. 2007), affecting driving safety (Marcotte et al. 2008) and poses risk of having mental illness (Rao et al. 1991). Considering the effect of cognitive impairment among MS patients, researchers have been investigating factors that could affect cognitive functioning among this population for clinical utility. However, there were limited up-to-date articles that review the predictors of cognitive impairment among MS patients. In Malaysia, the topic about cognitive functioning in MS has yet to be explored. By looking into the relationship of multiple factors on cognitive impairment among MS patients, proper early intervention plan can be carried out

to alleviate the challenges experienced across cognitive domains. Therefore, this narrative review aims to provide a comprehensive overview of predictors on cognitive impairment among MS patients and suggestions for future directions in Malaysia researches.

METHODOLOGY

A narrative review was performed using databases that included PubMed, EBSCOhost, Scopus and Google Scholar. Research articles were searched using as descriptors: predictors, factors, cognitive impairment, multiple sclerosis, Malaysia, published from 2004 to 2019, written in English, investigated at least four cognitive domains, in which there were clearly defined study design, sample size, selection criteria, assessment tools and detailed correlation and regression statistical analysis. Articles that were review papers, irrelevant, written in other languages and without abstract or full-text were excluded. After going through the selection process of identification, screening and determining eligibility, 12 studies were included in this review (Figure 1) and summarized (Table 1) in terms of factors investigated, sample size, outcome measures and findings. The findings of these studies were presented and discussed.

FINDINGS RELATED TO PREDICTORS OF COGNITIVE IMPAIRMENT AMONG MS PATIENTS

Three major domains of factors are biological, psychological and social that can be broken down into various predictors.

BIOLOGICAL FACTORS

Age. Ageing was also found to be negatively associated with cognitive functioning among MS patients specifically in several recent studies (Borghini et al. 2013; Nabavi et al. 2016; Nunnari et al. 2015; Papadopoulou et al. 2013; Heled, Aloni & Achiron 2019). For instance, Nabavi and colleagues (2016) compared 147 MS patients (112 females, 35 males) with 100 healthy controls and found that age is positively correlated with deficits in verbal memory, visuospatial memory, information processing speed, working memory and attention.

Gender. Although females are more affected by MS (Heled, Aloni & Achiron 2019), males perform poorer in cognitive assessments. A large sample study done by Savettieri et al. (2004) on 503 MS patients (320 females, 183 males)

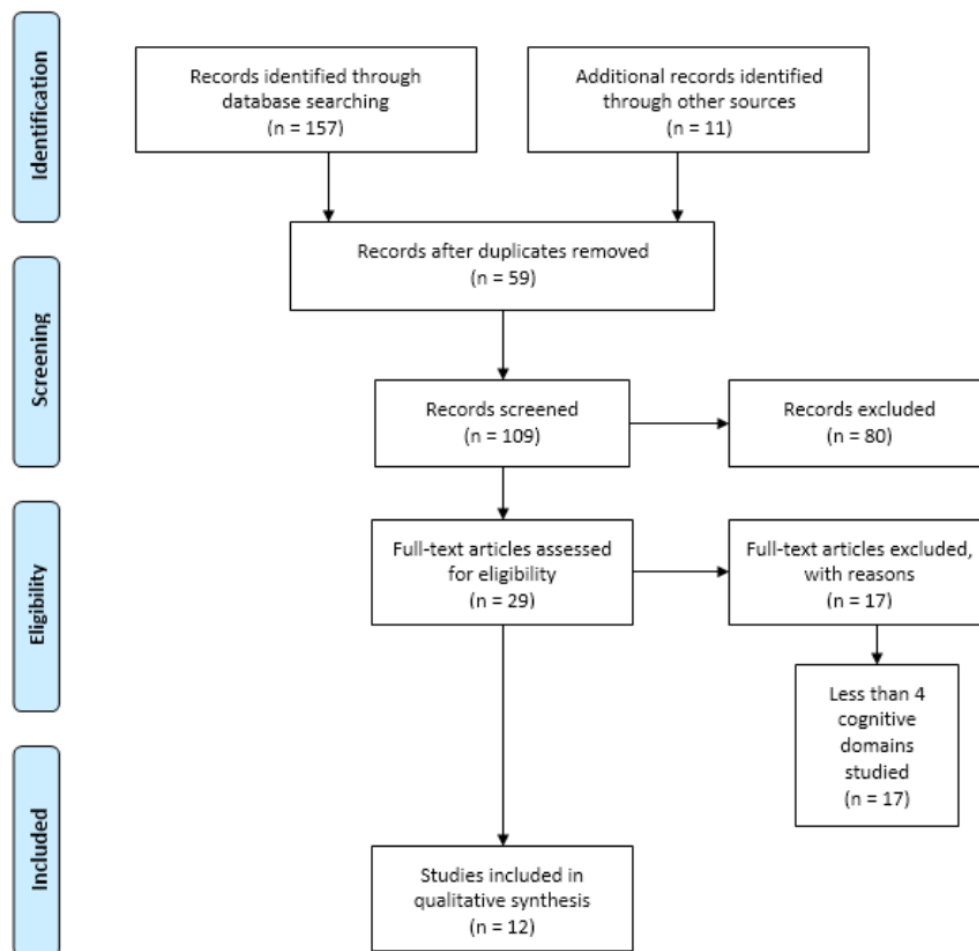


FIGURE 1. Flowchart illustrating the study selection process in accordance with the PRISMA guidelines

supported this claim by comparing between patients with mild and severe cognitive impairment. Worse performance in verbal memory and visuospatial memory among males were found compared to females. However, Heled, Aloni and Achiron (2019) found that female MS patients aged below 39 performed poorer in cognitive assessments than males. This shows that gender probably affects cognitive functioning among MS patients differently throughout different life stages.

Disability. Disability was found to be negatively correlated with cognitive functioning among MS patients (Heled, Aloni & Achiron 2019; Nabavi et al. 2016; Niino et al. 2014). For example, Heled, Aloni and Achiron (2019) conducted a study on 183 MS patients (125 females and 58 males) found that disability positively correlates with cognitive impairment and predicted information processing speed. In addition, a larger comparison study done by Niino

and colleagues (2014) between 184 MS patients with 163 health individuals yields the similar findings that disability is negatively correlated with verbal memory, visuospatial memory, information processing speed, working memory and attention. However, Nabavi et al. (2016) did not find any significant relationship between disability and working memory and attention. This could be due to difference in stages of MS among patients in their study that should be investigated as predictor.

Disease duration. Disease duration is the number of years from onset, which is defined as the year of the first episode of focal neurological dysfunction indicative of MS, to time of physical disability assessment in a non-exacerbated state (Smestad et al. 2010). Mixed results were found in the relationship between disease duration and cognitive impairment. Some studies found correlation between disease duration with cognitive impairment

TABLE 1. Studies investigating the predictors of cognitive impairment among MS patients

References	Sample Size	Factors	Outcome Measures	Findings
(Savettieri et al. 2004)	<i>N</i> = 503 63.6% female 100% MS patients	Gender	RAVLT CDL EDSS BDI MDB	Male MS patients showed greater cognitive deterioration in VM and VSM.
(Diamond et al. 2008)	<i>N</i> = 68 73.5% female 70.6% MS patients	Fatigue Depression	Digit Span CVLT VTSAT ROCFT EDSS MFIS CES-D	Depression and physical fatigue had the greatest influence on VM, VSM and IPS.
(Smestad et al. 2010)	<i>N</i> = 123 69.1% female 100% MS patients	Course of disease Disease duration	SDMT PASAT HVLTR CVMT Stroop test	Course of disease and disease duration are correlated with VM, VSM, IPS, WM and Attention.
(Borghetti et al. 2013)	<i>N</i> = 582 69.9% female 52.1% MS patients	Age Course of disease Depression Disability Disease duration Educational level	BRB-N EDSS FSS HADS	Age, course of disease, depression and educational level are predictors of VM, VSM, IPS, WM and Attention among MS patients. Disease duration and disability are predictors of VM, VSM, IPS, WM and Attention only among relapsing-remitting patients.
(Papadopoulou et al. 2013)	<i>N</i> = 91 63.7% female 100% MS patients	CL volume	SDMT PASAT-3 FSMC CES-D	CL volume is positively correlate with deficits in IPS, WM and Attention but is not a significant predictor.
(Karadayi et al. 2014)	<i>N</i> = 61 67.2% female 50.8% MS patients	Anxiety Depression Disability Disease duration	MMSE SDLT SCT Stroop Test RAVLT EDSS FSS HAM-D HAM-A	Disease duration and disability is correlated with VM, IPS, WM and Attention. Depression and anxiety are not correlated with VM, IPS, WM and Attention.
(Niino et al. 2014)	<i>N</i> = 347 73.2% female 53% MS patients	Fatigue Depression Disease duration Disability Education duration	BRB-N EDSS FSS BDI-II	Subjective fatigue is not correlated with VM, VSM, IPS, WM and Attention. Disease duration, depression and disability is negatively correlated with VM, VSM, IPS, WM and Attention. Education duration is positively correlated with VM but not VSM, IPS, WM and Attention.
(Nunnari et al. 2015)	<i>N</i> = 60 66.7% female 100% MS patients	Age Depression Disability Disease duration Fatigue	BRB-N EDSS FSS BDI-II	Age predicts VM. Disability predicts VM and Attention. Disease duration predicts VM. Depression is a significant predictor for VM, VSM, IPS, WM and Attention. Fatigue is not a significant predictor for any cognitive function.

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(Nabavi et al. 2016)	<i>N</i> = 247 76.5% female 59.5% MS patients	Age Educational level Depression Disability Fatigue	BRB-N EDSS FSS BDI-II	Age is positively correlated with CI. Educational level is negatively correlated with CI. Depression is negatively correlated with IPS, WM and Attention but not VM and VSM. Disability is negatively correlated with VM, VSM and IPS, but not WM and Attention. Fatigue is negatively correlated with VM, VSM, IPS, WM and Attention.
(Ribbons et al. 2017)	<i>N</i> = 322 81.1% female 100% MS patients	Anxiety Depression Stress	ARCS DASS	Depression, anxiety and stress are correlated with memory, VSM and Attention. Anxiety is the significant predictor of memory, VSM and Attention.
(Curti et al. 2018)	<i>N</i> = 60 70% female 100% MS patients	CL number	BRB-N Stroop test	Total CL number predicted VM, IPS, WM and Attention.
(Heled, Aloni & Achiron 2019)	<i>N</i> = 183 63.3% female 100% MS patients	Age Disability Disease duration Gender	EDSS NeuroTrax	Age is positively correlated with IPS and Attention. Disability is positively correlated with CI. Disease duration is not correlated with VM, VSM, IPS, WM and Attention. Women showed greater general cognitive deterioration.

Note. VM = verbal memory; VSM = visuospatial memory; IPS = information processing speed; WM = working memory; RAVLT = Rey Auditory Verbal Learning Test; CDL = Copying Drawings with Landmarks; EDSS = Expanded Disability Status Scale; BDI = Beck Depression Inventory; MDB = Mental Deterioration Battery; CVLT = California Verbal Learning Test; VTSAT = Visual Threshold Serial Addition Test; ROCFT = Rey-Osterrieth Complex Figure Test; MFIS = Modified Fatigue Impact Scale; CES-D = Center for Epidemiologic Studies – Depression; CL = cortical lesion; SDMT = Symbol Digit Modalities Test; PASAT = Paced Auditory Serial Addition Test; HVLT-R = Hopkins Verbal Learning Test-Revised; CVMT = Continuous Visual Memory Test; BRB-N = Brief Repeatable Battery of Neuropsychological Tests; FSS = Fatigue Severity Scale; HADS = Hospital Anxiety and Depression Scale; FSMC = Fatigue Scale for Motor and Cognitive Functions; MMSE = Mini-Mental State Examination; SDLT = Serial Digit Learning Test; SCT = symbol cancellation test; HAM-D = Hamilton Depression Rating Scale; HAM-A = Hamilton A

(Karadayi et al. 2014; Niino et al. 2014; Smestad et al. 2010). According to Smestad et al. (2010), it was found that disease duration was associated with verbal memory, visuospatial memory, information processing speed, working memory and attention among 123 MS patients (85 females, 38 males). Niino and colleagues (2014) found weak association between disease duration with similar cognitive functioning. Heled, Aloni and Achiron (2019) found that disease duration is not associated with general cognitive impairments. In another instance, a large sample study done by Borghi and colleagues (2013) among 303 MS patients (212 females, 91 males) showed that disease duration and disability are the significant determinants of verbal memory, visuospatial memory, information processing speed, working memory and attention but only among patients with RRMS.

Course of disease. Course of disease significantly correlated (Smestad et al. 2010) and predicted (Borghi et al. 2013) verbal memory, visuospatial memory, information

processing speed, working memory and attention among MS patients.

Fatigue. Literature showed mix results on the study regarding the relationship between fatigue and cognitive impairment among MS patients. It was found that fatigue positively correlated with deficits in verbal memory, visuospatial memory, information processing speed, working memory and attention (Nabavi et al. 2016) and significantly predicted information processing among MS patients (Diamond et al. 2008). However, contradictory result was yielded by Nunnari and colleagues (2015) among 60 MS patients (40 females, 20 males) that fatigue was not a significant predictor for any cognitive functioning and only weakly associated with verbal memory. This might be because their study did not include healthy control. To investigate further, Niino and colleagues (2014) conducted a large sample study comparing 184 Japanese (135 females, 49 males) MS patients with 163 healthy controls (119 females, 44 males) and found that subjective fatigue do not

associate with and predict functioning in verbal memory, visuospatial memory, attention, information processing and working memory in MS patients.

Location and burden of lesion. Burden of lesion is often measured by grey matter damage, which is measured either as cortical lesion (CL) or as cortical atrophy. Total CLs number was also found to predict cognitive impairment in verbal memory, information processing speed, working memory and attention in comparing between 30 MS patients with CL and 30 MS patients without CL (Curti et al. 2018). According to Curti et al. (2018), frontal lobe is the most affected region by CL, followed by temporal and parietal lobe. On the other hand, according to Papadopoulou and colleagues (2013), even though CL volume was correlated with information processing speed, working memory and attention, white matter damage significantly predicted cognitive impairment instead.

PSYCHOLOGICAL FACTORS

Depression. Various studies found that depression was associated with verbal memory, visuospatial memory, attention, information processing and working memory in MS patients (Nabavi et al. 2016; Niino et al. 2014), impacting especially information processing speed and attention (Nunnari et al. 2015). A contradictory study done by Karadayi and colleagues (2014) comparing 31 MS patients (21 females, 10 males) with 30 healthy controls (20 females, 10 males) found that depression is not associated with cognitive impairment. It may be because comparison was not made between depressed and non-depressed MS patients.

Anxiety. A large-scale study done by Ribbons et al. (2017) among 322 MS patients (261 females, 61 males) using short version of the Depression Anxiety Stress Scales (DASS-21; Henry & Crawford 2005) found that even though depression, anxiety and stress were correlated with cognitive impairment, only anxiety emerged as the sole significant predictor.

Stress. Ribbons and colleagues (2017) found that stress was correlated with memory, visuospatial memory and attention among MS patients.

SOCIAL FACTORS

It was found that educational level negatively correlated with cognitive impairment (Nabavi et al. 2016) and significantly predicted verbal memory, visuospatial memory, information processing speed, working memory

and attention among MS patients (Borghi et al. 2013). However, according to Niino and colleagues (2014), significant positive association is only found between education duration and verbal memory, but not visuospatial memory, information processing speed, working memory and attention.

DISCUSSION AND CONCLUSION

Most studies included in this paper found that age, gender, disability, course of disease, burden of lesion, depression, anxiety and educational level predicts cognitive functioning.

Based on the findings, age and gender affects cognitive functioning among MS patients. However, the relationships may not be linear as demonstrated by Heled, Aloni and Achiron (2019); gender and life stages may have joint effect on cognitive functioning among this population. The findings that disease duration only had predictive ability in RRMS implies that the course of the disease might be more dominant in influencing cognitive functioning among MS patients.

Therefore, more future studies are needed to examine the influence of course of MS and disease duration on cognitive functioning among MS patients. In terms of fatigue, all the studies included in this paper examined subjective fatigue and produced mixed results in predicting cognitive functioning. This may suggest the gap of examining the role of objective fatigue in this matter. Some of the ways that can measure objective fatigue in MS patients are levels of oxygenated hemoglobin and stride velocity under single- and dual-task conditions (Holtzer et al. 2017). Although burden of lesion is often measured by grey matter damage, studies conducted by Papadopoulou and colleagues (2013) showed otherwise. However, their sample was generally an elder population. This also highlights the possibility that the influence of age on cognitive functioning among MS differs and the impact of CL might not be independent. The exploration of anxiety influencing cognitive impairment among MS patients was relatively new compared to depression. Anxiety is often comorbid with depression among female MS patients (Korostil & Feinstein 2007). Perhaps the common notion that anxiety comes as a feature of depression overshadows its significance. Although stress was found to positively associate with brain lesion among MS patient (Burns et al. 2014), which could indirectly tie to its impact on cognitive impairment, its direct impact on cognitive functioning among MS patients has yet to be widely examined. Memory function is affected among healthy individuals with posttraumatic stress disorders (PTSD) (Wingenfeld

& Wolf 2015). Since PTSD and stress dysregulation are prevalent among MS patients (Ribbons et al. 2017), it could be hypothesized that stress could be another factor affecting their cognitive function. Educational level is hypothesized to help protecting MS patients to withstand considerable disease burden without experiencing cognitive impairment through the concept of cognitive reserve (Filippi et al. 2010). However, findings from Niino et al. (2014) suggests that education may have a stronger effect in protecting verbal cognitive performance than non-verbal cognitive performance. In summary, although many factors were found to affect cognitive functioning among MS patients, there seems to be an indication of joint effect between several factors that could contribute to cognitive impairment among this population. Therefore, it may be worth examining the contribution of these factors a single research to capture a bigger picture.

Current review has a few limitations. This review excluded studies in other languages and unpublished studies, which might increase the risk of bias, and only 12 studies were included. In addition, the reviews' results in published journal articles can sometimes be limited. Despite its limitations, current review has a few advantages. The studies included in the review examines the factors towards all major cognitive deficits experienced by MS patients, which increases clarity on their effects. Furthermore, the validity and reliability of assessment tools administered by the included studies are well documented and established. Current review provides some future directions for researches in Malaysia regarding cognitive functioning among MS patients. Since MS is a medical condition, biological factors are often prioritized in patient management. However, psychological and social factors highlighted in current review show their predominant contribution in affecting cognitive functioning among this population. Therefore, a holistic view on biopsychosocial predictors on cognitive impairment among MS patients should be investigated, especially in Malaysia, given that such research is absent; there were only two epidemiological studies on MS done locally (Tan 1988; Viswanathan et al. 2013). Initiatives in exploring this field could increase societal awareness about this disease. Future studies should investigate some factors that are understudied and neglected, such as anxiety and stress, as both are commonly experienced by MS patients. Although a recent research in Malaysia was done in investigating the relationship between education and cognitive performance, such result may vary across population (Amir Hamzah et al. 2016). Therefore, it is important to study the prospective protective effect of educational level on specific cognitive functioning by targeting Malaysian MS patients.

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CONFLICT OF INTEREST STATEMENT

The Author(s) declare(s) that there is no conflict of interest.

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