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Ballegooijen, H. van; Hiele, K. van der; Enzinger, C.; Voer, G. de; Visser, L.H.

**Citation**

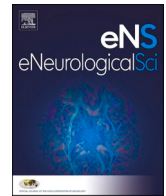
Ballegooijen, H. van, Hiele, K. van der, Enzinger, C., Voer, G. de, & Visser, L. H. (2022). The longitudinal relationship between fatigue, depression, anxiety, disability, and adherence with cognitive status in patients with early multiple sclerosis treated with interferon beta-1a. *Eneurologicalsci*, 28. doi:10.1016/j.ensci.2022.100409

Version: Publisher's Version

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Downloaded from: <https://hdl.handle.net/1887/3513804>

**Note:** To cite this publication please use the final published version (if applicable).



# The longitudinal relationship between fatigue, depression, anxiety, disability, and adherence with cognitive status in patients with early multiple sclerosis treated with interferon beta-1a

Hanne van Ballegooijen<sup>a</sup>, Karin van der Hiele<sup>b</sup>, Christian Enzinger<sup>c</sup>, Gert de Voer<sup>d</sup>, Leo H. Visser<sup>e,\*</sup>, on behalf of the CONFIDENCE Study Group

<sup>a</sup> IQVIA Netherlands, Real World Evidence, Netherlands

<sup>b</sup> Department of Psychology, Health, Medical and Neuropsychology Unit, Leiden University, Leiden, Netherlands

<sup>c</sup> Medical University of Graz, Graz, Austria

<sup>d</sup> Merck BV, Schiphol-Rijk, The Netherlands, an affiliate of Merck KGaA, Germany

<sup>e</sup> St Elisabeth Tweesteden Hospital, Tilburg, the Netherlands

## ARTICLE INFO

### Keywords:

Anxiety  
Depression  
Fatigue  
Disability  
Adherence  
Cognitive status  
Multiple sclerosis  
Interferon beta-1a

## ABSTRACT

**Background:** Cognitive dysfunction is common in multiple sclerosis and may worsen with reduced treatment adherence. We examined longitudinal relationships between anxiety, depression, fatigue, disability and adherence with cognitive status in patients with relapsing-remitting multiple sclerosis (MS) treated with interferon beta-1a in four countries.

**Methods:** The Confidence study is a prospective study in 165 people with MS with four visits (baseline/12/24/36 months). Physical and psychological symptoms were assessed using standardized questionnaires. Adherence was calculated as the number of injections divided by number of expected injections. Cognitive status was assessed by the Brief Repeatable Battery of Neuropsychological Tests and converted to a global Z-score.

**Results:** At baseline, mean age was  $35.7 \pm 11$  years and 66% were female ( $n = 109$ ). Adherence to treatment was very high throughout the study (>99%). A depression score  $\geq 8$  was significantly associated with a higher risk of low cognitive status compared with a lower score (0–7): relative risk 1.79 (1.14–2.83) adjusted for education and time since diagnosis. The *P*-value-for-time was not significant ( $P = 0.304$ ) meaning that associations existed since baseline and remained stable during follow-up.

**Conclusion:** Our findings provide evidence for a longitudinal association between depression and low cognitive status in patients treated with interferon beta-1a in routine medical practice.

## 1. Introduction

Cognitive dysfunction in multiple sclerosis (MS) has become a subject of increasing research interest over the past two decades. Impaired cognitive function has been observed in 40–65% of patients with MS in neuropsychological studies and may already occur in the early stages of the disease, even in patients without significant physical disability [1–3]. The pattern of cognitive impairment in MS is characterized by deficits in sustained attention, information processing speed, recent memory and conceptual reasoning, while language and the intellectual functions are preserved [1].

Cognitive dysfunction may worsen with reduced treatment

adherence due to disease progression [4,5]. Symptoms such as anxiety, depression, fatigue, and disability are frequently prevalent in patients with MS [6] and may further worsen cognitive status, although a causal relationship has not been established yet [7,8]. These factors considerably impact patients' daily activities and quality of life [6]. In a prospective study, poor medication adherence was associated with cognitive deficits such as memory and attention difficulties, but also with depression and anxiety [9]. MS patients with anxiety disorders were almost five times more likely than MS patients without anxiety disorders to exhibit problems adhering to their disease modifying therapies. Poor adherence was also associated with memory difficulties, anxiety, depression, neuroticism, and low conscientiousness [9].

\* Corresponding author at: Department of Neurology, Hilvarenbeekseweg 60, 5022 GC Tilburg, Netherlands.

E-mail address: [lh.visser@etz.nl](mailto:lh.visser@etz.nl) (L.H. Visser).

<https://doi.org/10.1016/j.ensci.2022.100409>

Received 14 December 2021; Received in revised form 24 May 2022; Accepted 7 June 2022

Available online 14 June 2022

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There is some evidence from small cross-sectional studies that anxiety, depression and fatigue are related with cognitive impairment in MS patients [10,11]. In addition, also increased disability has been linked prospectively with cognitive impairment [12]. Few studies examined the long-term effects of adherence to treatment and physical and psychological symptoms with cognitive performance in patients treated with IFN  $\beta$ -1a [13].

We examined the longitudinal relationship between fatigue, depression, anxiety, disability and adherence with cognitive status using the Brief Repeatable Battery of Neuropsychological Tests in patients with RRMS treated with IFN  $\beta$ -1a in four countries in routine medical practice. Hereafter, we use “people with MS” instead of RRMS to be more inclusive.

## 2. Materials and methods

### 2.1. Study design and patients

The assessment of cognition, fatigue, depression, anxiety and adherence Study (the Confidence Study) is a prospective, multi-center study conducted in four European countries with 50 hospital sites (Austria  $n = 5$ , Belgium  $n = 11$ , Slovakia  $n = 9$ , the Netherlands  $n = 25$ ) between June 2012 and May 2017. The study was originally aimed to investigate the relationship between cognitive status and depression, anxiety, fatigue, adherence, disability, MS related costs in people with MS patients treated with subcutaneous IFN  $\beta$ -1a (Rebif®, Merck Europe B.V.).

The patients were recruited from neurology departments and all patients were between 18 and 65 years, had a diagnosis of RRMS according to the McDonald 2010 criteria [14], an Expanded Disability Status Scale (EDSS) score  $< 4$ , were relapse-free within 30 days before the baseline visit, and treatment naïve or had recently started treatment with IFN  $\beta$ -1a within 6 weeks before the start of the study. IFN  $\beta$ -1a was administered in multi-dose cartridges either by an autoinjector (e.g., RebiSmart®) or by prefilled syringes according to the recommended dose 44  $\mu$ g (or 22  $\mu$ g) injected subcutaneously thrice weekly.

Exclusion criteria were treatment with IFN  $\beta$ -1a for more than 6 weeks before informed consent, women pregnant or breast-feeding and/or planning to become pregnant, current severe depression and/or suicidal ideation, severe disability and/or any neurologic or severe psychiatric disorder (e.g., psychosis), history of alcohol/drugs abuse, history of traumatic brain injury with residual symptoms that interfered with the cognitive test performance. A current diagnosis of major depressive disorder and/or suicidal ideation was defined according to the Diagnostic and Statistical Manual of Mental Disorders-fifth edition DSM-5 criteria.

The study included a baseline visit and three follow-up visits, scheduled approximately 12 months apart as part of routine medical care (M0, M12, M24, M36). In total 170 men and women were screened for inclusion and 166 individuals were eligible for inclusion of which 1 did not attend the baseline visit, making a total of 165 for the analytical sample for the baseline visit. After the baseline visit, 47 patients dropped out as described in the flow diagram (Fig. 1), resulting in 118 patients that completed visit 1, 71 patients that completed visit 2 and 56 patients that completed visit 3. Overall, 101 patients discontinued the study prematurely and eight patients were lost to follow-up. The main reasons for early discontinuation were treatment change ( $n = 27$ ), lack of efficacy ( $n = 24$ ), adverse reactions ( $n = 23$ ), and other reasons ( $n = 27$ ).

The study was performed in accordance with the principles of the Declaration of Helsinki and all applicable national regulatory requirements, including approval from local ethic committees. Written informed consent was obtained from all patients before the start of the study.

After informed consent, trained personnel checked the eligibility criteria, collected information on demographics, MS history, and examined physical and psychological symptoms, and cognitive function.

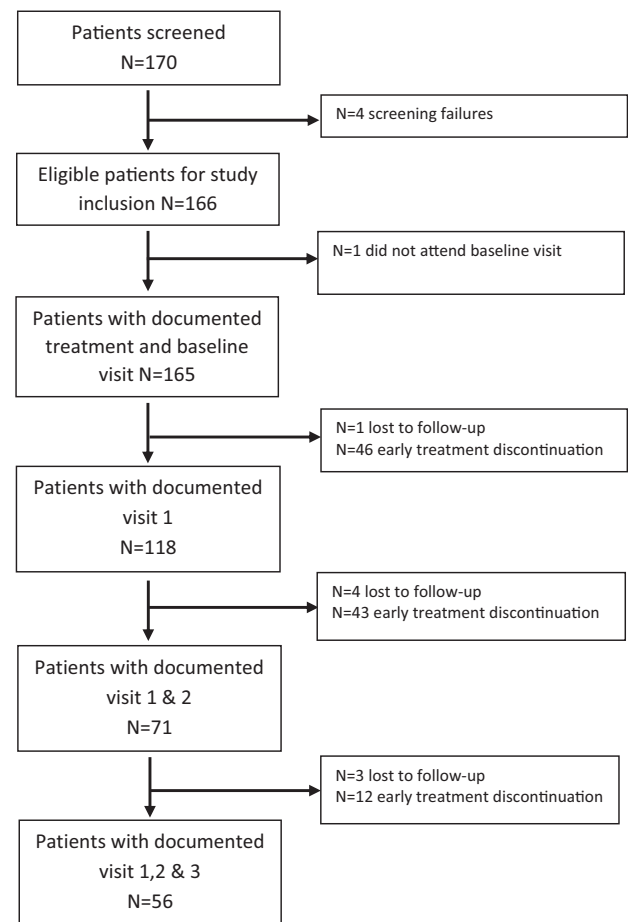


Fig. 1. Flow diagram of Confidence Study patients. Visit 1: 12 months; visit 2: 24 months; visit 3: 36 months.

### 2.2. Assessment of physical and psychological symptoms

Four physical and psychological symptoms (disability, fatigue, depression, anxiety) and adherence were assessed at baseline and at the follow-up visits. Fatigue was evaluated by means of the Modified Fatigue Impact Scale (MFIS) [15]. This 21-item tool assesses the effects of fatigue in terms of the three domains physical, cognitive, and psychosocial functioning. All items were evaluated on a 5-point scale from 0 to 4, with higher scores indicating greater impact of fatigue on the patient's activities.

The Hospital Anxiety and Depression Scale (HADS) was used to evaluate depression and anxiety [16]. The HADS is divided into two 7-item subscales, each ranging from 0 (no depression or anxiety) to 21: the depression subscale (HADS-D) and the anxiety subscale (HADS-A). A score between 0 and 7 on either subscale is considered a normal result. HADS scores were analyzed dichotomously to evaluate clinically meaningful changes: patients with a score  $< 8$  were considered not anxious or not depressed, whereas patients with a score  $\geq 8$  were considered anxious or depressed [17].

Disability was measured by means of the EDSS [18]. The scale ranges from 0 (normal) to 10 (death). As per inclusion criteria, patients had to have a EDSS score  $< 4.0$  to be eligible.

Adherence to treatment with IFN  $\beta$ -1a was measured by means of the injection data stored electronically on the RebiSmart® device or by using the data from patient diaries in which injection data were recorded. Adherence since last visit was defined as the number of injections administered since last visit divided by the number of expected injections since last visit expressed as percentage. Also, the number of missed doses since the last visit was recorded.

### 2.3. Cognitive status

Cognitive function was assessed by the Brief Repeatable Battery of Neuropsychological tests (BRB-N) with an administration time of 25–30 min [19,20]. We applied two parallel versions for repeated testing to avoid a learning effect. The BRB-N includes: 1) the Selective Reminding Test (SRT) to assess verbal memory, including long-term storage (STR-S), long-term retrieval (STR-R) and delayed recall (STR-D) scores; 2) the 10/36 Spatial Recall Test (10/36) to assess visuospatial learning (SPART-S) and delayed recall (SPART-D); 3) the Symbol Digit Modalities Test (SDMT) to assess attention, visual precision search and executive functions; 4) the Paced Auditory Serial Addition Task 2 and 3 s (PASAT 2–3) to assess the maintenance of attention, and 5) Word List Generation (WLG) to assess associative verbal fluency. These tests were selected to explore most of the cognitive functions while minimising overlap.

We obtained the global cognitive function (BRB-N Z) for all study visits by calculating the mean of the Z scores from the four cognitive domains (verbal memory, visual memory, attentional/executive, fluency) according to Sepulcre et al. [21]. Z-verbal memory = (Z SRT-S + Z SRT-R + Z SRT-D)/3; Z-visual memory = (Z-10/36 SPART-S + Z-10/36 SPART-D)/2; Z-attentional/executive = (Z PASAT3 + Z PASAT2 + Z SDMT)/3; Z-fluency = Z WLG. The total BRB-N = (Z-verbal memory + Z-visual memory + Z-attentional + Z-fluency)/4. Lower scores indicate a lower cognitive status. The Z-score represents the deviation from the mean per standard deviation: 0 no deviation, 1 represents 1 standard deviation (SD) larger than mean.

### 2.4. Other measurements

Demographic and clinical data were extracted from the electronic medical records. Other variables were collected prospectively by means of standardized electronic forms. Relapse was defined as the appearance of a new symptom or worsening of an old symptom, attributable to MS, accompanied by an appropriate new neurological abnormality or focal neurological dysfunction lasting at least 24 h in the absence of fever, and preceded by stability or improvement for at least 30 days. Relapses were recorded by frequency and relapse severity grade.

Adverse drug reactions associated with the treatment with IFN  $\beta$ -1a, whether observed clinically or reported by the patient were documented during the entire study period according to the MedDRA terminology version 18.0 [22].

### 2.5. Statistical analysis

The data of all patients who received at least one injection of IFN  $\beta$ -1a after enrolment were included in the data analysis and outlined per visit. We defined cognitive status based on the global Z-score and tabulated baseline characteristics by median cognitive status <median low cognitive status vs  $\geq$  median high cognitive status to create equal size groups since the sample size was rather small. For the main analyses, we included the largest possible sample. A patient with two missing values for one test (e.g., the SRT) was not taken into account while a patient with one missing value was taken into account. As sensitivity analysis, we also present the complete-case analysis without any missing values for any of the cognitive function measures ( $N = 141$  for the baseline analysis).

Normality of the continuous variables was checked by visual inspection of Q-Q plots. The physical and psychological symptoms and adherence as well as the outcome measure BRB-N Z-global score are displayed for the baseline and the 3 follow-up visits as mean and standard deviation for normally distributed variables and as median and interquartile range (IQR) for skewed variables.

To assess the longitudinal relationship in 5 separate association models between the physical and psychological symptoms and adherence with cognitive status, we applied a binominal generalized estimating equation (GEE) analysis expressed as relative risks and 95%

confidence intervals. Due to the high correlation between follow-up measures within patients, we used an exchangeable correlation structure [23]. We present a crude model (unadjusted) and a model adjusted for education (3 categories) and time since MS diagnosis (months). The reference group was high cognitive status. To measure the rate of cognitive decline by the physical and psychological symptoms and adherence during follow-up, we added an interaction term (symptom\*time) to the model. The symptoms anxiety and depression were analyzed dichotomously while EDSS, MFIS and adherence were analyzed continuously and per 1-SD increment.

A 2-sided  $P$ -value of 0.05 was considered statistically significant and analyses were conducted using SAS, version 9.4.

## 3. Results

### 3.1. Study population

The mean age of the 165 patients was  $35.7 \pm 11$  years and 66% were female ( $n = 109$ ) (Table 1). Most of the patients were included in Slovakia (56%) followed by the Netherlands (29%), Belgium (8%) and Austria (7%). The majority obtained secondary education 65% ( $n =$

**Table 1**  
Baseline characteristics of study patients by cognitive status in 165 patients with relapsing-remitting MS.

	Total group	Low cognitive status $\leq$ median BRB-N	High cognitive status $>$ median BRB-N
N	165	82	83
<b>Demographics</b>			
Age (years)	35.7 $\pm$ 11.0	38.9 $\pm$ 12.0	32.7 $\pm$ 8.8
Sex			
Female	109 (66%)	54 (66%)	55 (66%)
Male	56 (34%)	28 (34%)	28 (34%)
Country			
Austria	10 (7%)	2 (2%)	8 (10%)
Belgium	14 (8%)	5 (6%)	9 (11%)
Slovakia	93 (56%)	55 (67%)	38 (46%)
the Netherlands	48 (29%)	20 (25%)	28 (34%)
Educational level			
Primary	14 (8%)	8 (10%)	6 (7%)
Secondary	106 (65%)	63 (77%)	43 (52%)
Tertiary	45 (27%)	11 (13%)	34 (41%)
Smoking habit			
Smoker	18 (11%)	10 (12%)	8 (10%)
Non-smoker	147 (89%)	72 (88%)	75 (90%)
Alcohol consumption			
Yes	24 (15%)	7 (9%)	17 (21%)
No	141 (85%)	75 (91%)	66 (79%)
<b>Treatment history</b>			
Time since MS diagnosis, months	3.6 [2.2–7.4]	4.5 [2.9–15.7]	2.9 [1.7–5.7]
Time between last relapse and baseline (months)	3.3 [2.3–5.1]	3.9 [2.3–5.8]	3.1 [2.3–4.9]
Number of relapses within last 12 months	1 [1–2]	1 [1–2]	1 [1–2]
<b>Type of injector</b>			
Rebismart®	125 (76%)	54 (66%)	72 (87%)
Manual	6 (4%)	2 (2%)	4 (5%)
Other	33 (20%)	26 (32%)	7 (8%)
<b>Co-medication</b>			
Anti-depressants use	7 (4%)	4 (5%)	3 (4%)
Anti-anxiety use	5 (3%)	3 (4%)	2 (2%)
Psychostimulants use	3 (2%)	2 (2%)	1 (1%)
<b>Psychiatric disorders</b>			
Anxiety HADS-A $\geq$ 8	57 (34%)	34 (41%)	23 (28%)
Depression HADS-D $\geq$ 8	28 (17%)	16 (20%)	12 (15%)

Results are presented as number and percentage for categorical variables. Continuous variables are displayed as mean  $\pm$  SD. Skewed variables are presented as median (interquartile range). HADS-A and HADS-D: Hospital Anxiety and Depression Scale anxiety and depression.

106), 27% (n = 45) had tertiary education, and 8% (n = 14) had a primary education. Other medication classified as anti-depressants, anti-anxiety medication, psychostimulant, nootropic, or cognitive drug or anti-fatigue medication were documented for 7 (4%), 5 (3%) and 3 (2%) patients, respectively.

### 3.2. Treatment characteristics

At baseline, most patients 76% (n = 126) used the RebiSmart® device, 20% (n = 33) used another autoinjector, and 4% (n = 6) injected manually. The median duration of MS at baseline was 3.6 [IQR 2.2–7.4] months. The median number of relapse episodes per patient within the last 12 months before study entry was 3.3 [2.3–5.1]. After 3 years, 54 of the 56 patients (96%) reported an intention to continue treatment with IFN β-1a. The IFN β-1a dose of 44 µg was reported in most patients at all post-baseline visits: 89% at month 12, 89% at month 24, 95% at month 36. A dose of 22 µg was used by 11% of the patients at any post-baseline visit.

Of the patients remaining in study, most were relapse-free since the last visit: 92% (n = 108) at month 12, 90% (n = 64 at month 24, and 96% (n = 54) at month 36. During the study period meaning after the baseline visit, 79 patients reported 109 adverse reactions of which two were serious or of severe intensity. Patients can report multiple adverse reactions. The most common adverse reactions were influenza-like illness n = 31, injection site reaction n = 21, headache n = 14, injections site reaction n = 13, fatigue n = 12, and other side effects n = 18. Due to adverse reactions, 43 patients discontinued the study.

### 3.3. Physical and psychological symptoms

The psychological symptoms anxiety and depression slightly increased after 12 months, which gradually attenuated after 24 and 36 months (Table 2). The mean anxiety and depression scores remained unchanged in more than 70% of the patients at month 12, 24 and 36. The mean fatigue scores (MFIS) steadily decreased over the study period. For the patients that remained in the study, adherence to treatment was very high throughout the study period (>99%) as indicated by the low number of missed doses per visit.

**Table 2**  
Physical and psychological symptoms and adherence over a 3-year period.

Symptoms		Baseline	M12	M24	M36
HADS-A (0–21)	N	165 5.9 ± 3.8	113 6.5 ± 4.2	70 6.0 ± 4.6	54 5.2 ± 4.5
HADS-D (0–21)	N	165 4.0 ± 3.5	113 4.6 ± 3.9	70 4.3 ± 4.2	54 3.9 ± 4.1
EDSS (0–10)	N	162 2.0 [1–3]	95 2.0 [1–3]	59 2.0 [1–3]	46 2.0 [0–3]
MFIS (0–84)	N	165 30.5 ± 4.9	113 32.7 ± 3.0	70 27.6 ± 1.7	54 25.1 ± 2.2
Adherence since last visit (%)	N	165 99.2 ± 4.9	118 98.8 ± 3.0	71 99.1 ± 3.2	56 98.4 ± 3.2
Number of missed doses since last visit	N	165 0 [0–3]	90 0 [0–3]	59 0 [0–5]	44 0 [0–1]

HADS-A and HADS-D: Hospital Anxiety and Depression Scale anxiety and depression, EDSS: Expanded Disability Status Scale, MFIS: Modified Fatigue Impact Scale.

Results are presented as number and percentage for categorical variables. Continuous variables are displayed as mean ± SD. Skewed variables are presented as median [interquartile range].

### 3.4. Cognitive status

The individual cognitive tests (SRT, both spatial recall tests and WL) indicated a gradually increasing trend towards the 24 months visit and a slight decrease for the 36-month visit (Table 3). The SDMT and both PASAT tests showed a decreasing trend over the study period. In general, we observed stable cognitive status in at least half of the patients after 12 months of treatment.

The longitudinal associations of physical and psychological symptoms and adherence with low cognitive status indicated that a higher anxiety score HADS-A (≥ 8) and a higher depression score HADS-D (≥ 8) were associated with a higher increased risk of a low cognitive status over the study period: the relative risk was 1.40 (1.02, 1.90) and 1.80 (1.17, 2.77), respectively, when compared with a lower anxiety or depression score (0–7) (Table 4). In the model adjusted for education and time since MS diagnosis, the relationship between anxiety and depression with cognitive function slightly attenuated and was only statistically significant for depression: relative risk 1.79 (1.14, 2.83). However, in none of the models, the interaction between the psychological symptoms and time was statistically significant (P interaction > 0.304), indicating that differences in symptoms scores existed since baseline and the association with cognitive function remained stable during follow-up. The other symptoms and adherence did not show significant associations with cognitive status.

In a sensitivity analysis restricting the analysis to a full case analysis, a higher anxiety score HADS-A (≥ 8) was associated with an increased risk of a low cognitive status: relative risk 1.57 (1.03, 2.39) when compared with a lower anxiety score (0–7) adjusted for confounders (supplemental Table 1). The results for a higher depression score HADS-D (≥ 8) compared with a lower depression score (0–7) slightly attenuated and were no longer significant 1.38 (0.86, 2.21). The other results for the physical and psychological symptoms and adherence did not materially change.

## 4. Discussion

In this longitudinal multi-country study, the relationship between physical and psychological symptoms and adherence with cognitive function was investigated in people with early MS treated with IFN β-1a. Cognitive function was assessed using the BRB-N, a global validated

**Table 3**  
Cognitive status based on the Brief Repeatable Battery of Neuropsychological tests over a 3-year period.

Cognitive status	Baseline	M12	M24	M36
N	165	118	71	56
SRT (long-term storage)	9.7 ± 2.3	10.1 ± 2.5	10.2 ± 2.4	10.1 ± 2.5
10/36 Spatial Recall Test	21.8 ± 5.4	22.1 ± 4.6	23.9 ± 4.6	23.6 ± 4.9
10/36 Spatial Recall Test (delayed)	7.8 ± 2.3	8.3 ± 2.6	8.6 ± 1.9	8.5 ± 1.8
Symbol Digit Modalities Test	46.0 ± 14.4	44.2 ± 13.5	43.8 ± 14.5	42.6 ± 16.1
PASAT2 *(2 s)	27.0 ± 17.3	25.2 ± 18.2	24.8 ± 20.7	18.0 ± 20.6
PASAT3 (3 s)	40.4 ± 16.7	38.8 ± 19.2	37.3 ± 22.1	26.2 ± 27.1
Word List	26.3 ± 6.6	26.4 ± 7.4	27.9 ± 6.7	27.8 ± 6.5
Generation Test				
Total Z-score	−0.01	0.01	0.01	−0.08
BRB-N	[−0.52,0.48]	[−0.53,0.38]	[−0.59,0.43]	[−0.60,0.50]

\* SRT: Selective Reminding Test; PASAT: Paced Auditory Serial Addition Test; crude scores are presented for the separate cognitive tests.



**Table 4**  
Longitudinal association of physical and psychological symptoms with low cognitive status.

Symptoms and adherence	Crude model RR + 95% CI	Model 1 RR + 95% CI	P-value time model 1
HADS-A (0–7)	Ref 1.0	Ref 1.0	
HADS-A ( $\geq 8$ )	<b>1.40 (1.02, 1.90)</b>	1.36 (0.98, 1.89)	0.477
HADS-D (0–7)	Ref 1.0	Ref 1.0	
HADS-D ( $\geq 8$ )	<b>1.80 (1.17, 2.77)</b>	<b>1.79 (1.14, 2.83)</b>	0.304
EDSS (0–10)	1.07 (0.82, 1.39)	1.03 (0.78, 1.37)	0.723
EDSS per 1-SD increment	1.10 (0.86, 1.40)	1.07 (0.82, 1.38)	0.703
MFIS (0–84)	1.00 (1.00, 1.02)	1.00 (1.00, 1.02)	0.847
MFIS per 1-SD increment	1.15 (0.94, 1.40)	1.15 (0.94, 1.42)	0.810
Adherence (%)	0.99 (0.96, 1.02)	0.99 (0.96, 1.02)	0.976
Adherence per 1-SD increment	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	0.369

The results are derived from a binominal model expressed as relative risk and 95% confidence intervals.

Reference value is high cognitive status

Model 1: adjusted for education and time since MS diagnosis (months).

\*The RR is standardized to 1-SD increment for each visit.

HADS-A and HADS-D: Hospital Anxiety and Depression Scale anxiety and depression, EDSS: Expanded Disability Status Scale, MFIS: Modified Fatigue Impact Scale.

method of cognitive function. We observed that adherence to treatment was very high throughout the study period (>99%) among the patients who remained in the study. The fatigue score steadily decreased over 3 years of follow-up.

A higher score on the depression scale ( $\geq 8$ ) was significantly associated with a higher relative risk of low cognitive status adjusted for potential confounders. However, the associations between depression and cognitive status existed since baseline and remained stable during follow-up as the *P*-value for time was not significant ( $P = 0.304$ ), meaning that the rate of cognitive decline did not differ between the depression categories ( $\geq 8$  vs 0–7). The other symptoms and treatment adherence did not show significant associations with cognitive status.

#### 4.1. Comparisons to other studies

Our findings are not completely in line with those of other studies investigating the relationship between physical and psychological symptoms and adherence with cognitive dysfunction [12,24–28]. However, to the best of our knowledge, the current study is the first prospective study that investigated longitudinal relationships between physical and psychological factors and adherence with cognitive function in patients with MS.

Cross-sectional studies observed that higher levels of depression and anxiety were associated with lower processing speed in MS patients [25] and higher levels of anxiety were associated with lower working memory, and reduced verbal learning [28]. There is also some evidence from a small clinical population that anxiety is a predictor of cognitive dysfunction as measured by HADS-A and perceived cognitive impairment [29]. Also in cross-sectional studies, higher levels of the symptoms fatigue and disability were related to lower levels of cognition while in our study we did not observe such a relationship [24,27].

One prospective multicenter study was conducted with a two year follow-up period in 300 people with MS in the Czech Republic [13]. This study investigated cross-sectional correlations between psychological symptoms and individual cognitive performance measures. At months 12 and 24, a small negative correlation was observed between higher PASAT values and lower fatigue scores.

In our study, we observed no association between adherence and cognitive status. However, mean adherence rates were constantly high over the entire observational period indicating that side effects were minor/tolerable. High adherence rates to IFN  $\beta$ -1a administered by RebiSmart® have also been observed previously [30,31]. Despite the high treatment adherence, the discontinuation rate in this study was much higher than in other studies of IFN  $\beta$ -1a using the RebiSmart® device, i.e., 28% during the first 12 months compared to 12% and 13% in two previous observational studies [30,32].

In contrast to these previous studies, the most frequent reason for treatment discontinuation was not related to adverse reactions, but to the need to change the patients' treatment. Shortly before study start and during the study period (2012–2017), several novel oral treatments for people with MS were approved in the European Union and reached the market. Several publications described MS patients' preferences for oral medication administration over injectable routes, merely due to the perception of the ease of use [33,34]. Thus, it is assumed that decisions from patients and/or physicians to switch to newly available oral treatments have probably increased the rate of early discontinuation in this study.

#### 4.2. Strengths and limitations

The strengths of our study are the inclusion of a representative real-world population of people with MS patients with a typical sex distribution, an early stage of MS (median interval to first manifestation was 4 months before inclusion), a low level of disability and low level of disease activity (median 1 relapse within the last 12 months). We used standardized validated and widely used methods to assess physical and psychological symptoms and cognitive function over 3 years follow-up [15–18,21] and longitudinal analyses adjusted for potential confounding factors.

Limitations of our study include the observational design and the lack of a control group. The rate of early discontinuation was higher than anticipated. At 36 months, 66% of the patients ( $n = 108$ ) discontinued the study early or were lost to follow-up. This has introduced a survivorship bias, which might have significantly diluted the results. The inclusion of a relatively young group of patients, at a very early stage after diagnosis, with a relatively low EDSS score and low disease activity might have reduced the range of possible outcomes.

It is known that cognitive dysfunction as well as the other evaluated symptoms increase with disease progression, i.e., accumulating contributions of the neurodegenerative part of the disease as well as inflammatory components (impairment during relapses, accrual of focal CNS lesions). Thus, the choice of including only patients with an EDSS score  $< 4$ , which is common in studies in which treatment efficacy is evaluated in RRMS, has likely introduced a selective group of people with mild MS.

#### 5. Conclusions

In conclusion, our study in routine medical practice supports a longitudinal relationship between depression and lower cognitive status. Adherence to interferon beta-1a was high during the entire study period, but we must acknowledge the high drop-out rate. The other symptoms and adherence did not show significant associations with cognitive status. Depression is often a 'hidden' psychological symptom for MS patients and the findings of our study support further clinical consideration and additional investigation in the treatment of depression for cognitive benefits. This will most likely also influence other benefits in the treatment of people with MS in a real-world population.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ensci.2022.100409>.

#### Funding

The study was jointly funded by affiliates of Merck KGaA, Germany:

Merck BV, the Netherlands; Merck GmbH, Austria; Merck NV, Belgium, and Merck SPOL. S R.O., Slovakia (CrossRef Funder ID: <https://doi.org/10.13039/100009945>).

### CRedit authorship contribution statement

**Hanne van Ballegooijen:** Methodology, Data curation, Writing – original draft, Visualization. **Karin van der Hiele:** Conceptualization, Methodology, Data curation, Writing – original draft. **Christian Enzinger:** Conceptualization, Writing – review & editing. **Gert de Voer:** Conceptualization, Writing – review & editing. **Leo H. Visser:** Conceptualization, Methodology, Data curation, Writing – original draft, Supervision.

### Acknowledgements

The authors thank all Confidence Study patients, physicians and study teams who participated in this study. The statistical analyses were supported by Elyonore Tsakeu & Rui Cai. Melissa van Tok an employee of Merck BV coordinated the finalization of the manuscript. Merck BV agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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