The epidemiology of multiple sclerosis: new data in mortality and cognitive impairment from Hungary

Ph.D. thesis

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Original publications directly related to the Ph.D thesis

I. **Sandi D**, Rudisch T, Füvesi J, Fricska-Nagy Z, Huszka H, Biernacki T, Langdon DW, Langane É, Vécsei L, Bencsik K. The Hungarian validation of the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) battery and the correlation of cognitive impairment with fatigue and quality of life. Mult Scler Relat Disord. 2015 Nov;4(6):499-504.
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I. Biernacki T, **Sandi D**, Szekeres D, Füvesi J, Kincses ZT, Rózsa C, Mátyás K, Kása K, Matolcsi J, Zboznovits D, Burány Z, Langane É, Vécsei L, Bencsik K. What are the strongest contributing factors to the health-related quality of life in patients with multiple sclerosis? Qual Life Res. 2018. (Under review).

II. Biernacki T, **Sandi D**, Bencsik K, Vécsei L. Medicinal chemistry of multiple sclerosis: focus on cladribine. Med Chem. 2018. (Under review)

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1. **Sandi D**, Kasa K, Biernacki T, Szekeres D, Zboznovits D, Pyreschitz A, Fuvesi J, Kincses ZT, Rozsa C, Matolcsi J, Szerp P, Langane E, Vecsei L, Bencsik K. Prevalence of cognitive impairment among Hungarian patients with relapsing-remitting multiple sclerosis and clinically isolated syndrome Mult Scler. 2015;21:(S 11.):723-724.

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List of abbreviations

10/36: 10/36 Spatial Recall Test
95%CI: 95% confidence intervals
ANOVA: analysis of variance
BDI-II: Beck's Depression Inventory
BICAMS: Brief International Cognitive Assessment for Multiple Sclerosis
BVMT-R: Brief Visuospatial Memory Test Revised
CI: cognitive impairment
CIS: clinically isolated syndrome
CNS: central nervous system
CoD: cause(s) of death
COWAT: Controlled Oral Word Association Test
CVD: cardio- and cerebrovascular diseases
CVLT-II: California Verbal Learning Test 2nd Edition
DKEFS: Delis-Kaplan Executive Function System
DMT: disease modifying therapy
EDSS: Expanded Disability Status Scale
FIS: Fatigue Impact Scale
F/M: female-to-male ratio
GA: glatiramer-acetate
GDP: gross domestic product
HC: healthy control
ICD10: International Classification of Diseases, 10th revision
IFN-β: Beta-interferon
IQR: Inter-quartile range
JLO: Judgment of Line Orientation
MACFIMS: Minimal Assessment of Cognitive Functions in Multiple Sclerosis
MRI: magnetic resonance imaging
MS: multiple sclerosis
OR: odds ratio
PASAT: Paced Auditory Serial Addition Test
PPMS: primary progressive multiple sclerosis
PRMS: progressive-relapsing multiple sclerosis
PwMS: people with multiple sclerosis
QoL: quality of life
R-BRB: Rao's Brief Repeatable Battery
RIS: radiologically isolated syndrome
RRMS: relapsing-remitting multiple sclerosis
SD: standard deviation
SDMT: Symbol Digit Modalities Test
SMR: Standardized Mortality Ratio
SPMS: secondary progressive multiple sclerosis
SRT: Selective Reminding Test

Summary

Introduction

Multiple Sclerosis (MS) is a chronic, demyelinating, neurodegenerative disease of the central nervous system (CNS). It is predominantly the disease of the Caucasian race, more frequent in woman, and shows higher prevalence rates in the North. Hungary counts among the "middle-risk" countries with a prevalence rate of 83.7/100000. Until the last two decades, MS was thought to only affect the quality of life the patients, yet data emerging predominantly from Scandinavia and North-America proved that it holds an almost threefold mortality risk and a ~10 years reduced life expectancy, with almost two-thirds of the patients dying of MS-related causes.

Based on the natural course of the disease and the attributes of activity and progression, MS can be categorized to two basic clinical courses: relapsing and progressive MS. Relapsing MS can be either active or inactive relapsing-remitting (RRMS) course, or inactive or active clinically isolated syndrome (CIS – in the latter case, it means conversion to RRMS). Progressive MS can be either primary or secondary progressive, which can be active and progressing, inactive but progressing, non-progressing but active, or inactive and non-progressing. The older concept of "benign" MS has been abandoned, as several studies showed that after a longer follow-up periods, most of the "benign" patients reach high EDSS scores and converted to secondary progressive course. This led to the search of those unseen symptoms that can be present during the initial, seemingly benign phase of MS. Studies found that many of these patients suffer from psychopathological symptoms, such as cognitive impairment (CI), fatigue, depression and anxiety. CI is a frequent, yet underdiagnosed symptom of MS with prevalence rates 43-70%. It seriously worsens the quality of life of the patients, being one of the most important factors for unemployment. MS patients however do not become demented; the most frequently affected domains are information processing speed, visual and verbal memory. Some scattered data showed, that men seemingly are more often affected. However, measurement of CI is not easy as it requires specialists, special equipment and it is highly time-consuming. Thus, in 2011, a committee of neurologist and neuropsychologists created the Brief International Cognitive Assessment for Multiple Sclerosis (MS) battery for the quick, yet still sensitive screening of CI in MS. Fatigue is the most common symptom of MS, with virtually every patient experiencing it during some period. Depression is also very frequent, with a life-time prevalence nearing 50%. Both are reported to be overwhelmingly important factors regarding the quality of life of the patients. The evaluation of both symptoms can be done by self-report: one of the most sensitive and widely-used battery for fatigue is the Fatigue Impact Scale (FIS) and the Beck's Depression Inventory (BDI-II) for depression.

Aims

In our three separate assessments, we aimed to determine the causes of death and the mortality risk of the Hungarian MS patients; to validate the BICAMS battery to Hungarian

and to give the prevalence of CI among the Hungarian MS patients and assess any potential risk factors of developing it.

Patients and methods

In our first evaluation, we examined 740 patients treated at the MS outpatient unit of the Department of Neurology of the University of Szeged, of which 121 died during the period. The causes of death were established from the pathological records or the medical certificates of the cause of death. We calculated the standardized mortality ratios (SMR) and assessed the survival times with Gehan-Breslow test. In our validation study of the BICAMS battery, we enrolled 65 RR-MS patients and 65 age, sex and education matched healthy control (HC) subjects whom were tested retested after 3 weeks. The patients also completed the FIS battery. Group differences were calculated by paired sample T-tests, the test-retest reliability was measured by intraclass correlation coefficients. To analyse the difference between the test-retest performances, two-way repeated measures ANOVA - with the BICAMS battery being the single composite outcome - and one-way repeated measures ANOVA were utilized. To assess impact of fatigue on cognition, we examined the correlations between the BICAMS and the FIS batteries. In our study of the prevalence and risk factors of CI, we enrolled 553 RRMS and CIS patients from three Hungarian MS centres (Szeged, Budapest, and Eger). Age at screening, age at disease onset, disease duration, EDSS score, sex and educational levels were the analysed social-demographic factors. The BICAMS battery was used to assess CI, the BDI-II battery to assess depression. We used Fisher exact tests, chi-square tests and one-way ANOVA to find differences between the key demographic and clinical data and utilized a logistic regression model to assess the predictive factors.

Results

Two-third of our patients died of MS-related causes. The overall SMR was 2.52, with solely MS-related causes being the reason for this elevated mortality risk. We found negligible difference between the sexes, yet regarding the different courses, PPMS patients' SMR was 4.10, significantly higher than RR/SPMS patients (2.34; $p<0.001$). PPMS patients survived for less than half the time (14 years) than RR/SPMS patients (35 years; $p<0.001$). During our validation study, we found significant difference ($p\leqslant 0.001$, $p=0.017$ in the first CVLT-II assessment) between the performance of MS patients and members of the HC group in both sessions. The test-retest correlation were very strong ($r>0.8$; $p<0.001$; $r=0.678$, $p<0.001$ between the CVLT-II assessments). We found that the HC group performed significantly ($p=0.020$) better during the retest as compared to their original performance than the patients and this difference can solely be attributed to the CVLT-II performances. There was significant negative correlation between the patients' cognitive function and fatigue scores ($r<-0.3$, $p<0.05$).

In our epidemiological survey of cognition, 316 (57.1%) patients had CI. Sex, educational level and EDSS score were all significant predictors (OR: 2.71, $p<0.001$; OR: 1.94, $p=0.023$; OR: 0.47, $p=0.003$ respectively). CI was significantly ($p<0.001$) more frequent among men (70.1%) than women (52.0%) and educational level and EDSS score were only a significant predicting factor among women. The prevalence of cognitive dysfunction among women with

college or university degree was significantly ($p<0.001$) less common (39.4%) than in women lower educational levels (57.4% - 12-15 years of learning; and 66.7%- <12 years of learning). Women with higher EDSS scores (>2 points) had a prevalence of 69.9%, while in women with EDSS score between 0-2 points, the prevalence was significantly lower (42.8%, $p<0.001$). No such differences were found among men.

Discussion and conclusion

Our survey yielded similarly high ratio of MS-related cause of death and higher mortality risk in the Hungarian MS patients than in earlier assessments from Nordic countries and North-America, with a markedly elevated risk among PPMS patients. Our survey highlights that this higher mortality risk does not depend on any outside factors, only on the disease itself with us being the first group to give such data from Central-Eastern Europe.
We showed, that the Hungarian version of the BICAMS battery, the third validated version during the time of publication, is valid and reliable tool for measuring CI in MS. We also found some connection between subjective fatigue and CI, that could warrant further assessments of the relationship between the two psychopathological symptoms.
We found a similarly high prevalence of CI among our patients as in other, earlier assessments. Men are more susceptible to CI, and it seems, that higher educational level and lower EDSS scores are only associated with better cognitive performance in women. We are the first to report, however, such differences between the sexes regarding the predictive factors of CI among MS patients.

I. Introduction

Multiple sclerosis (MS) is a chronic autoimmune and neurodegenerative disease of the central nervous system (CNS), characteristically displaying signs of inflammation, demyelination and axonal damage (Trapp et al., 1998). Its name originates from the first pathological findings after the dissection of diseased patients' brain: several plaques are macroscopically visible in different parts of the CNS (multiple) and these plaques are stiffer to touch than normal brain tissue (sclerosis). It is one of the leading reasons of disability among young adults and it seriously worsens the quality of life (QoL) of patients: when compared to other autoimmune diseases, people with MS (PwMS) perceive their QoL to be the worst (Rudick et al., 1992).

I.1. Epidemiology of MS

On the general basis, MS is considered to be a rare disease: there are approximately 2.5 million patients worldwide (Browne et al., 2014). Yet, there are several factors determining susceptibility to it. It is generally the disease of the Caucasian race: among Africans and African-Americans, it is much rarer, just as among the Gypsy population of Hungary (Dobson and Giovannoni, 2019; Kalman et al., 1991). It also shows a North-South gradient as the prevalence of MS is the highest in Scandinavia, Canada and the Northern parts of the United States of America (with prevalence rates well over 200/100 000), while it gradually decrease with nearing the equator, where it is a rarity (Beck et al., 2005; Heydarpour et al., 2015; Mackenzie et al., 2014; Simonsen et al., 2017). Similarly to other autoimmune diseases, women are more often affected; the man-women ration is 1:2-3 (Bostrom et al., 2013; Celius and Smestad, 2009; Zsiros et al., 2014). Also, age is an important factor: the disease generally manifests in early adulthood or in the early middle ages (20-45 years) in approximately 80% of the cases (Confavreux et al., 1980). Yet, in ~10% of the patients, the first symptoms of MS appear much earlier, in childhood; and in about 10% of the patients, the disease starts at an older age (>50 years) (Louapre et al., 2017; Sandi et al., 2018).

Hungary counts among the "middle-risk" countries considering the prevalence of the disease. The first epidemiological data arose in 1961. According to this report, the crude prevalence of MS was 20/100 000 in Hungary (Lehoczky and Halasy-Lehoczky, 1961). In the '80s, Pálffy et al. found that the prevalence of MS in Baranya County was 37/100 000 (Prange et al., 1986). In Csongrád County, the crude prevalence of MS was shown to be 62/100 000 by Bencsik et al. in 1998 (Bencsik et al., 1998). In 2013, a new epidemiological study was conducted that reported the standardized prevalence of MS in Csongrád County to be 83.7/100 000 (Zsiros et al., 2014).

This increase in prevalence rate however is not surprising. Early diagnostic criteria – in the absence of magnetic resonance imaging (MRI), liquor diagnostic tools etc. – only relied on the clinical manifestations of the disease, stating that MS was ultimately a pathological diagnosis (Schumacher et al., 1965). In the ‘80s, with the creation of the Poser diagnostic criteria, which placed the patients into definitive MS, probable MS and not MS categories based on the clinical course and paraclinical findings, the diagnosis became more definitive and could be achieved earlier than before (Poser et al., 1983). With MRI being widely utilized, the new McDonald criteria relied heavily on its use, permitting the diagnosis of MS after only one clinical attack (McDonald et al., 2001). Since 2001, this diagnostic criteria has been revised three times, last time in 2017 (Polman et al., 2011; Polman et al., 2005; Thompson et al., 2018). As the technology of MRI evolved, it started to play a pivotal role not only in the diagnosis of the disease, but for the regular follow-up of disease activity, which is extremely important for measuring the efficacy of the utilizable disease modifying therapies (DMTs). In 2016, the MAGNIMS group published their own MRI diagnostic guideline, further specifying the MRI criteria for early diagnosis and follow-up (Filippi et al., 2016). All these evolution in the diagnostic tools have culminated in the earlier and surer diagnosis of MS, which in turn led to an increasing prevalence and incidence worldwide.

I.2. Mortality in MS

For until the last three decades, MS was considered to be a disease only affecting the patients’ QoL and having no effect on the lifespan and mortality. Since however, this view has radically changed.

The first study dedicated to the topic was carried out in Scotland and was published in 1987 (Phadke, 1987). It found, that approximately 2/3 of the patients die due to MS-related causes (Phadke, 1987). As MS progresses, it leads to severe disability and patients become immobile and bedridden. Thus, the causes of death (CoD) are the complications of long-term bed riddance: decubitus and consequential sepsis, urosepsis and pneumonia (Phadke, 1987). Since then, other assessments were carried out and found that MS-related CoDs are responsible for the death of 47-75% of the patients (Bronnum-Hansen et al., 2004; Leray et al., 2007; Phadke, 1987; Sadovnick et al., 1991). The other most common causes of death are similar to the general first world population, namely cardio- and cerebrovascular diseases (CVD) and malignancies (Bronnum-Hansen et al., 2004; Grytten Torkildsen et al., 2008; Phadke, 1987). On the contrary, suicide rates are constantly reported to be higher among PwMS as compared to the general population (Bronnum-Hansen et al., 2005; Feinstein and Pavisian, 2017;

Fredrikson et al., 2003).

The first data concerning the lifespan of the patients arose from Denmark in 2004 (Bronnum-Hansen et al., 2004). It was the result of a 40-years follow-up assessment from the Danish MS registry. It found, that PwMS live approximately 10 years shorter, than their life expectancy at birth(Bronnum-Hansen et al., 2004). Other evaluations carried out in North America and North-Europe found this loss of years to be 6-12.8 years (Hader, 2010; Kingwell et al., 2012).

MS holds a great mortality risk for the patients beyond the reduced life expectancy. Several evaluations has shown that PwMS have an about three-fold mortality risk as compared to the general population (Sumelahti et al., 2010). Patients with the primary progressive (PPMS) form have been shown to have a higher risk as compared to the initially relapsing forms (Grytten Torkildsen et al., 2008; Kingwell et al., 2012). Patients, in whom MS manifested before the age of 18, have a four-fold risk of dying, which is similar to the mortality risk of type II diabetes mellitus and higher than some common malignancies diagnosed in the early phases (de Marco et al., 1999; Hooning et al., 2006; Sumelahti et al., 2010). Some evaluations found that women have a slightly higher relative risk of dying than man, but those results are somewhat controversial (Bronnum-Hansen et al., 2004; Kingwell et al., 2012; Sumelahti et al., 2010).

I.3. Natural history of MS

The two main clinical attributes of the disease can be specified as the activity and the progression of the disease. Activity can be described as the acute onset of new neurological symptoms that end up partially or completely remised (relapse) or – as a newer concept - new or enlarging, potentially contrast-enhancing lesions on the MRI scan (Lublin et al., 2014). Progression is the phenomena that describes the steady, yet irreversible worsening of symptoms and signs of MS over 6 months or more (Lublin et al., 2014). Based on these attributes, several clinical courses of the disease were defined by Lublin and colleagues in 1996 (Lublin and Reingold, 1996). The most common form is the relapsing-remitting (RRMS) form, which is characterized by the above described relapsing, remitting periods (Lublin and Reingold, 1996). After a time, a large proportion of these patients convert into the secondary progressive (SPMS) phase, which is characterized by steady progression instead of relapses (Lublin and Reingold, 1996). About 10-15% of the patients never experience the relapsing phase, and the disease is defined by steady progression from the beginning, thus it is called PPMS (Lublin and Reingold, 1996). A small proportion of patients experience this progressive phase at the same time with relapsing phase, this course was labelled relapsing-

progressive MS (RPMS) (Lublin and Reingold, 1996). Also, a so-called benign course of the disease was described, where patients do not exhibit meaningful activity or progression after the initial attack, meaning that during a period of fifteen years, the patients' Expanded Disability Status Scale (EDSS) score did not exceed 3 points and they rarely suffered relapses (Lublin and Reingold, 1996).

However, this type of clinical phenotypisation needed to be revised as our knowledge of MS expanded. New clinical courses had to be defined based on the new information and the found link between clinical characteristics and paraclinical investigations. In 2014, Lublin and colleagues published a revision of the originally defined phenotypes and introduced new aspects of MS as well (Lublin et al., 2014). As a new concept, clinically isolated syndrome (CIS) was introduced: CIS is now recognized as the first clinical presentation of a disease that shows characteristics of inflammatory demyelination that could be MS, but has yet to fulfil criteria of dissemination in time (Lublin et al., 2014). As for the classical clinical courses, a new concept was developed, with activity and progression incorporated into the definitions. Now we recognize two initial subtypes of MS: relapsing and progressing subtypes (Lublin et al., 2014). Relapsing MS can be either RRMS, which can be active or not active, and CIS can also be not active or active, in which case it fulfils the diagnostic criteria for dissemination in time and space, it means conversion to RRMS (Lublin et al., 2014). Progressive patients can be PPMS patients, with progressive accumulation of disability from the onset, or SPMS patients with progressive accumulation of disability after an initial relapsing phase (Lublin et al., 2014). Progressive patients can be either active and progressing, active but non-progressing, non-active but with progression and non-active and non-progressing (Lublin et al., 2014). The benign term was excluded as a disease course indicator per se, as new data arose from several studies describing the natural history of the disease (Lublin et al., 2014). Ebers and colleagues have shown, that the initial phase of the disease – defined by reaching the milestone of EDSS score 3 points, the threshold for the beginning of irreversible neuronal damage – show a grand variation in time (Ebers, 2001). Patients with higher initial activity and severity of progression will reach this threshold earlier (Ebers, 2001). But from EDSS 3 points, to EDSS 6 points, this variation disappears, meaning that after reaching the first signs of irreversible neuronal damage, the gradual worsening of the patients goes down in the same manner (Ebers, 2001). Thus despite a patient appearing to have the benign course in the 15 years, when followed-up after the initial years, will still reach EDSS score 6 points with the same speed as the other patients do. This was an important reason (among others) that initialized the search for other signs and symptoms of MS that may not be incorporated into

the EDSS system but can be prevalent during the first, seemingly inactive phase of the disease. Evaluations discovered that among benign patients, fatigue is as prevalent, as in other courses; that approximately 50% of these patients exhibit signs of cognitive dysfunction; that a grand proportion of "benign" patients are burdened by depression, anxiety or other psychiatric conditions, which are not yet routinely examined and followed-up (Amato et al., 2006a; Correale et al., 2012; Sayao et al., 2007; Ton et al., 2017). These information may propose, that the activity in this group seems low because the disease does not manifest in the somatic symptoms of MS, yet in the psychopathological domains.

I.4. Psychopathological symptoms of MS

Aside from the somatic manifestations of the disease, there are several other symptoms burdening MS patients which are psychological in nature and therefore much harder to recognize or to measure. These symptoms are cognitive impairment (CI), depression, fatigue and anxiety.

I.4.1. Cognitive impairment in MS

Classically, cognition was believed to remain largely intact through the course of the disease. Original descriptions of the disease counted moria and euphoria among the cognitive symptoms, which only appear at the very end of the disease (Charcot and Harris, 1991).

In heavy contrast to this, in the recent two decades, data emerged showing that CI is a very common and heavily debilitating symptom of MS. Its prevalence was shown to be 43-70% by different evaluations (Chiaravalloti and DeLuca, 2008). It seriously worsens the QoL of the patients in almost all aspect of life. MS patients with CI have reduced physical independence and competence in daily activities, such as claiming their ability for safe driving (Goverover et al., 2007; Marcotte et al., 2008; Rao et al., 1991b). These patients report impaired social lives and higher rates of divorce as compared to cognitively healthy patients (DeLuca et al., 2015). Also it reduces the patients' coping mechanism, medical adherence and rehabilitation potential thus negatively impacting medical management (Bruce et al., 2010; Ehrensperger et al., 2008; Langdon and Thompson, 1999). In some assessments, CI is indicated to be the strongest predictor of MS patients' becoming unemployed (Honarmand et al., 2011; Morrow et al., 2009).

Importantly, cognitive dysfunction is not global among PwMS (rarely can it be described as dementia) (Langdon, 2011). There are several cognitive domains that are – to various degree - characteristically affected by the disease including attention, information processing

efficiency, executive functioning, short-term and long-term memory (Langdon, 2011). Of these, information processing speed, visual and verbal memory seems to be the most vulnerable (Langdon, 2011).

Cognitive dysfunction can appear at any stage of the disease. It was found that it can begin very early in patients with CIS and also a small but substantial portion of patients with radiologically isolated syndrome (RIS) showed signs of CI (Amato et al., 2012a; Glanz et al., 2007). It was also found that CI can manifest as an acute relapse of the disease (Morrow et al., 2011). There is evidence showing that MS may primarily present with cognitive (and pathophysiological) symptoms with minimal or no other neurological systems involved (Calabrese et al., 2015). It was reported, that sadly, once CI appears, there is a very small chance for any improvement (DeLuca et al., 2015). There were very sparse data on the possible predictive factors for developing or the worsening of CI: only recently an Italian assessment found that man are more susceptible to CI, and there were some minimal data showing that people with higher EDSS scores are more prone to cognitive dysfunction (DeLuca et al., 2015; Patti et al., 2015).

The only real biomarkers for CI in MS are magnetic resonance imaging (MRI) parameters. Global brain atrophy, and regional atrophy of the thalamus, hippocampi, frontal cortex and basal ganglia show good correlation with CI (Brass et al., 2006; DeLuca et al., 2015; Houtchens et al., 2007; Koenig et al., 2014; Morgen et al., 2006). The enlargement of white-matter lesions in the corpus callosum and the appearance of grey-matter lesions are linked to CI (Diker et al., 2016; Rossi et al., 2012). Some recent studies found connection with the dysfunction normal-appearing white matter or the default mode networks with cognitive decline in MS (Bonavita et al., 2011; Rocca et al., 2010).

I.4.1.1. Measurement of cognitive impairment in MS

Measuring CI is usually not a routine task of neurologists. It is done by assigning different questionnaires designed to measure one (or more) specific cognitive domain to the patient. Yet, different diseases tend to affect different domains, hence the tests used should be directed towards the domains usually affected by the disease. As noted above, in MS, various cognitive functions may decline due to the disease.

Therefore during the past decades, several composite batteries were created for a deeper measurement of CI. Of these, the two most frequently utilized are Rao's Brief Repeatable Battery (R-BRB) and the Minimal Assessment of Cognitive Functions in Multiple Sclerosis (MACFIMS) (Benedict et al., 2006; Rao et al., 1991a).

Both batteries include longer assessments (5 and 7) that measure the most commonly declining cognitive domains in MS. Both batteries include the Symbol Digit Modalities Test (SDMT), the Paced Auditory Serial Addition Test (PASAT) and the Controlled Oral Word Association Test (COWAT) for the measurement a visual and auditory processing speed and language (Rao et al., 1991a). Other than these, R-BRB utilizes the 10/36 Spatial Recall Test (10/36) for visual memory and the Selective Reminding Test (SRT) for verbal memory (Rao et al., 1991a). In the MACFIMS, visual memory is measured by the Brief Visuospatial Memory Test Revised (BVMT-R) and verbal memory is assessed by the California Verbal Learning Test Second Edition (CVLT-II) (Benedict et al., 2006). The MACFIMS also included the Judgment of Line Orientation (JLO) for evaluating the spatial processing and the Delis-Kaplan Executive Function System (DKEFS) for higher executive functions (Benedict et al., 2006). Both batteries have been validated to several language and have been used efficiently for the measurement of CI.

However, there are limitations for the usefulness of such batteries in clinical practice. Both test require long time for administration (45 and 90 minutes) which clinical practitioners don't have in the outpatient units. Furthermore, some of these tests require special equipment also not routinely available in clinical settings. Last but not least, the administration of these batteries require a neuropsychologist, thus making the routine administration of these batteries all but impossible. For these reasons, the need for the creation of a well-composed but simple screening tool arose that could be applied to routine use, requires no special personnel or tool yet still sensitively measures CI in MS.

I.4.1.2. The Brief International Cognitive Assessment for Multiple Sclerosis

The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) battery was created in 2011 by a panel of neurologists and neuropsychologists (Langdon et al., 2012). They aimed to develop a sensitive screening tool for CI in MS. They agreed on the following consensus criteria that the battery should conform to in order to be useful (Langdon et al., 2012):

1. Administration should not require more than 15 minutes.
2. It should not require any special personnel, tool or training.
3. The battery should be able to be administered easily in the clinical setting.
4. It should measure the most frequently affected cognitive domains in MS: information processing speed, visual memory and verbal memory.

After the thorough and careful review of the international literature, they identified six

eligible questionnaires that met these criteria: two for each cognitive domains. After that, they developed a scoring system for both psychometric values and clinical applicability and the members of the panel rated all sex tests. Based on these ratings, they chose three questionnaires that now comprise BICAMS: the SDMT, the first three immediate recall trials of the BVMT-R and the first five immediate recall trials of CVLT-II (Langdon et al., 2012).

1. The SDMT is the measure of the information processing speed. It is given to the participant as a sheet of paper containing nine symbols in pseudo-randomized lines. All symbols are paired with a number in a key at the top of the sheet. During the assessment, the patient first undergoes a short practice of 10 symbols. After, they have to pair as many of the symbols with the numbers as they can in 90 seconds. Both a written and an oral version of the test exist: with the written version, the patients have to write the correct digits on the paper, whereas in the oral version the patient is required to say the correct number out loudly while the administrator notes them. The dependent variable is the total number of correct responses (Smith, 1982).
2. The CVLT-II is a long battery designed for the in depth evaluation of verbal memory. BICAMS utilizes only the first five immediate recall trials of CVLT-II, which is comprised of a list of 16 words in 4 semantic categories. During administration, the examiner reads the list aloud at the approximate speed of 1 word/second. After, the patients have to recall as many of the words as they can and repeat them back to the administrator. The order is arbitrary and there is no time limit for the assessment. The dependent variable is the total number of correct words recalled during the five trials (Delis, 2000).
3. The BVMT-R is also a longer questionnaire designed for measuring the visual memory of the patients. BICAMS utilizes only the first three immediate recall trials. When administrating the test, the patients are given a blank sheet of paper divided into six equal parts and a pencil or a pen. Then the administrator shows them a matrix of 6 abstract designs for a learning period of 10 seconds. After, the patients are required to reproduce those on the blank paper as accurately as they can. Each design receives a score of 0, 1, or 2 based on accuracy and the location. There is no time limit for this test and the dependent variable is the total points received for the reproduced designs during the three trials (Benedict, 1988).

The committee recommended that the battery should not be used within 1 month of recovery from relapse or within 1 month of steroid therapy, because it can negatively affect memory

functions (albeit reversibly) (Langdon et al., 2012). It was also concluded that the evaluations should be conducted annually or bi-annually (Langdon et al., 2012).

I.4.2. Depression

The aetiology of depression and mood disorders – not unlike in other disorders – are multifactorial. Thorough investigations aimed to determine the biological, psychological and social factors of developing depression in MS.

It seems, that genetic factors do not play a significant role in the association of MS and depression as family history do not seem to increase the risk (Joffe et al., 1987; Johansson et al., 2014). MRI studies however have shown, that frontal and temporal lobe atrophy and lesion volume correlate with the appearance of depression in PwMS (Feinstein et al., 2014). Some new data point toward the importance of inflammatory processes in the development of depressive symptoms (Patten et al., 2017). The earliest DMTs (the beta-interferons [IFN-β]) have been associated with inducing depression-like symptoms or episodes in treated patients (Patten et al., 2017). Yet, as was expected, evaluations committed to the assessment of psychosocial variables (such as how MS affects young patients' interpersonal relations and career leading to various sorts of stressors) found, that these are very important contributors to the development of depressive symptoms in PwMS (Beal et al., 2007).

However the aetiology might be, nonetheless, depression remains a frequent problem among MS patients. Epidemiological surveys differ greatly on its prevalence, with a reported pooled rate of 30.5%, but these differences could be traced back to the different methodologies of evaluation (Boeschoten et al., 2017). Assessments that identified depression with structured interviews or by a clinical examination as a depressive disorder, yielded lower rates, with a pooled prevalence of 20.6% and a range of 1.3-44.1% (Boeschoten et al., 2017). Yet other studies, which utilized depression rating-scales and identified patients by a cut-off point with clinically relevant depressive symptoms, resulted in the pooled prevalence of 35.0% with a range of 9.3-76.2% (Boeschoten et al., 2017).

Depression is a serious burden to PwMS. It heavily worsens the patients QoL in virtually all levels: it was found to be a contributor to health-related QoL almost as strong as physical disability itself by several evaluations (Berrigan et al., 2016; Carta et al., 2014). It can lower the adherence to medical treatment, and potentially aggravate other symptoms, such as fatigue, pain or anxiety, multiplying their impact on QoL (Feinstein et al., 2014). It is also known, that depression can cause pseudo-dementia, or worsen the already existing cognitive disabilities again possibly aggravating its impact on PwMS (Feinstein et al., 2014). Importantly, it was established as well, that the risk of suicide is much higher in MS than in

the general population, and the link between depression and suicide is strong and well-understood (Bronnum-Hansen et al., 2005).

As was mentioned above, the evaluation of depression can be done following multiple directions. Yet, during the three-monthly visits of the patients in the outpatient units, screening tools are the most useful, as they are reliable, yet easily administered and scored and they sensitively reveal clinically relevant depressive symptoms. Many of these tools are self-filling questionnaires, as they are the least time-consuming but still very effective. One of the most frequently utilized such questionnaire is the Beck's Depression Inventory (BDI-II) (Beck, 1996).

BDI-II consists of 21 items, all are related to an aspect of depression and all contain four possible choices of response ranging in intensity. Every response can be scored from 0 to 3 points, with 3 being the most intense answer (Beck, 1996). The maximum achieved score can be 63 points (Beck, 1996). The cut of is 13 points; any patient reaching 13 or more points can be regarded to have clinically relevant depressive symptoms (Beck, 1996).

I.4.3. Fatigue

Though fatigue is a common word, the medical definition of it as a pathological symptom cannot be given easily. It is described as a complex symptom defined by three underlying components: 1. asthenia/daytime tiredness, 2. pathological exhaustibility and 3. worsening of symptoms due to stress (Iriarte et al., 2000).

In light of MS, fatigue can be either primary or secondary. Primary fatigue is caused by the pathophysiology of the disease itself: loss of connectivity between cortical and subcortical structures due to lesion burden; mediators released due to immune-mediated inflammation; and neuroendocrine dysfunctions due to damage in the central regulatory regions of the CNS (Patejdl et al., 2016). Secondary fatigue is related to other symptoms of MS, pain, comorbidity or side-effect of DMTs (Patejdl et al., 2016). Importantly, secondary fatigue can accompany primary fatigue and worsen its effect.

Fatigue frequently appears as the initial symptom of the disease before any other measureable, easily evaluated signs of the disease appear (Kister et al., 2013; Runia et al., 2015). It can be easily over-looked or "brushed-away" as simple tiredness or lack of motivation, which is a grand problem, because fatigue is the most common symptom of MS. Its prevalence was measured up to 95%, thus it appears at some point in effectively every MS patient's life (Kister et al., 2013). Furthermore, the majority of the patients report it to be one of the worst, while a sizeable proportion (15%) to be the worst symptom of the disease (Fisk et al., 1994a).

Thus, this symptom has a profound negative effect on the patients' perceived QoL independently from physical disability, disease duration, disease course or other social or clinical parameters (Benedict et al., 2005). Interestingly however, despite it can hypothetically affect cognitive functions, no strong connection has been found to date (Morrow et al., 2009).

Because of its nature, fatigue is hard to measure and to objectify. No gold-standard exist for its evaluation, and to date, it is based on self-reported questionnaires, such as the Fatigue Impact Scale (FIS) (Fisk et al., 1994b). The FIS battery comprises of 40 questions, divided into 3 subscales: 20 questions about the social aspects of fatigue, 10 questions about the physical and 10 questions about the cognitive aspects (Fisk et al., 1994b). The answers are scored from 0 (minimal degree) to 4 (severe degree) points, 160 points in total (Fisk et al., 1994b). The cut-off can vary, but it is usually given at ≥40 points (Losonczi et al., 2011).

II. Aims

Our aims with the reported evaluations were to:

1. Determine the causes of death, the standardized mortality ratios (SMR) and the survival times from disease onset among the Hungarian MS patients with any possible difference between the sexes or the different clinical courses of the disease from January 1st 1993 to January 1st 2013.
2. Validate the BICAMS battery to Hungarian language.
3. Assess any possible connection between cognitive performance and fatigue.
4. Determine the prevalence of CI among Hungarian RRMS and CIS patients.
5. Determine the possible differences in regard to CI between sexes and patients with different educational levels.
6. Find any possible risk factors for developing CI among RRMS and CIS patients in Hungary.

III. Patients and methods

III.1. Mortality and causes of death among Hungarian MS patients

III.1.1. Patients

The MS outpatient's clinic of the Department of Neurology of the University of Szeged is responsible for the health care of all MS patients from Csongrád- (population: 419.366) and parts of Bács-Kiskun- (population: 522.312) and Békés- (population: 357.740) counties (total number of the population the unit is responsible for is approximately 900.000 people) in the southern region of Hungary (Hungarian Central Statistical Office). All MS patients were included into the Multiple Sclerosis Register of the Department of Neurology of the University of Szeged since 1993 (Bencsik et al., 2017).

In the assessed 20 years, 740 MS patients were treated for MS at our centre, with a total follow-up person years of 10303 years. Two-hundred and four were men (27.5%, 2806 person years), 536 were women (72.5%, 7497 person years). The F/M ratio was 2.63:1. Six-hundred and eighty-eight patients had RR or SP disease course (93%, 9733 person years) and 52 patients PPMS (7%, 570 person years). During the period of our evaluation, 121 patients (16%) died, 46 men and 75 women: 23 suffered from PPMS, 98 from RR/SPMS. Forty patients (33%) received DMTs (IFN-β, glatiramer-acetate [GA] or mitoxantrone), the mean duration of treatment was 6.2 (95% CI: 5.1-7.3) years, and the EDSS score at the beginning of the treatment was 3.3 (95% CI: 2.5-4.0).

III.1.2. Methods

The socio-demographic data such as the sex, the date of birth, the date of MS onset, the course of the disease and the date of death of the patients were obtained from our Register. Between 1993 and 2001, the diagnosis was based on the Poser diagnostic criteria, after 2001, the McDonald diagnostic criteria were used (McDonald et al., 2001; Poser et al., 1983). The different courses of MS were determined per the Lublin-criteria from 1996 (Lublin and Reingold, 1996).

The CoD was determined from the pathological records (in case of 53 patients) or the medical certificates of the cause of death provided by the families (in case of 68 of the patients). Data on the number of deaths and the CoDs in the Hungarian general population distributed by sex, age and calendar year were derived from the website of the Hungarian Central Statistical Office. The SMRs were calculated: it is the ratio of the observed to the expected numbers of deaths (Andersen and Vaeth, 1989). The expected numbers of deaths were calculated by

multiplying the age-, sex- and time-specific person-years of observation by the respective age-, sex- and time-specific population death rate (Andersen and Vaeth, 1989). SMRs and 95% confidence intervals (95%CI) were calculated with the assumption that the numbers of deaths followed a Poisson distribution. For the analysis of survival time from MS onset of the sexes and patients with different clinical courses, Gehan-Breslow test was utilized.

The study was approved by the Human Investigation Review Board of the University of Szeged (approval number 3267) in accordance with the Helsinki Declaration.

III.2. The Hungarian validation of the BICAMS battery

III.2.1. Patients and healthy control group

Sixty-five patients treated at the MS Outpatient's Unit of the Department of Neurology of the University of Szeged and 65 healthy controls (HC) matched in age, sex and years of education were recruited. Sixteen were men, 49 women; 31 members of both groups studied ≤12 years, and 34 of them studied for at least 13 years. All sociodemographic data on the patients including age, age at disease onset, disease duration and EDSS score were obtained from the Multiple Sclerosis Register of Szeged (Bencsik et al., 2017). Among the patients there was no pre-selection applied for CI.

Inclusion criteria were:

A. Age between 18-65 years.
B. First language is Hungarian.
C. RRMS patients.
D. All patients were in remission during the evaluation.
E. EDSS score 0-6.5.

Exclusion criteria were:

A. CIS, SPMS or PPMS for homogeneity of the population.
B. Patients undergoing acute infection or an acute relapse.
C. Diagnosed psychiatric, mood or personality disorder among both groups as they can cause CI.
D. History of chronic alcohol or drug abuse among both groups as they can also cause CI.

III.2.2. Methods

The validation was conducted per the international standards given in 2012 (Benedict et al., 2012).

1. The CVLT-II list of words were translated and retranslated from English to Hungarian and

vice versa respectively (the other two tests did not require translation due to their nature).

2. The relevant parts of the tests manuals were translated into Hungarian.

3. The initial testing, and after 3 weeks, the retesting of the participants between December 2013 and March 2014. In our evaluation, we used both the oral and the written version of SDMT. Also for the assessment of the correlations between the cognitive state and fatigue, all 65 patients had completed the Hungarian version of the FIS (Losonczi et al., 2011). For the evaluation of connection with FIS, we used the first BICAMS tests of the patients.

Paired sample T-tests were utilized for the measurement of differences between the patients and the HC group. The test-retest reliability and the correlation between BICAMS and FIS were assessed by Pearson correlation coefficients. To analyse the difference between the test and retest performances, two-way repeated measures ANOVA with the result of the BICAMS battery being a composite outcome was utilized, and one-way repeated measures ANOVA to assess the differences by the battery-types that compose the BICAMS battery. For the statistical analysis, SPSS 21.0 software was used.

Informed consent was obtained from all individual participants included in the study. The study was authorized by the Ethics Committee of the University of Szeged (authorization number 127/2013).

III.3. The prevalence of cognitive impairment and its risk factors among Hungarian RRMS and CIS patients

III.3.1. Patients

The study was conducted between February 2014 and November 2015. In total, 553 (28 CIS and 525 RRMS) patients were enrolled from three Hungarian MS centres. Four-hundred and four from the MS outpatients' clinic of the Department of Neurology of the University of Szeged; 111 from the MS outpatients' clinic of the Jahn Ferenc Dél-Pest Hospital in Budapest and 38 from the MS outpatients' clinic of the Markhot Ferenc Hospital in Eger.

One-hundred and fifty-seven patients were man, 396 women, classified into 3 categories depending on their educational level: 123 patients in the first group with less than 12 years of education, indicating they did not obtain a high school degree; the second group, 209 patients for the second group whom either finished high school or after high school obtained some qualification but not a degree from college or university (12-15 years of education); and 221 patients for the third group whom obtained college or university level of graduation (16 or more years of education). Additionally, all the patients currently enrolled to college or

university were placed in the third group. Regarding the therapy, 90 patients received no DMTs; 169 patients received IFN-β, 129 patients GA, 31 patients teriflunomide, 33 patients dimethyl-fumarate therapy; 56 patients were on natalizumab, and 41 patients on fingolimod. Additionally, 1 patient was involved in the daclizumab, 1 in the LINGO-1 and 1 in the siponimod clinical trials.

All sociodemographic data on the patients including age, age at disease onset, disease duration and EDSS score were obtained from the Multiple Sclerosis Register in case of the centre of Szeged, or from the outpatient treatment reports from the other centres (Bencsik et al., 2017).

The inclusion and exclusion criteria were the same as in the aforementioned BICAMS validation study, with the exception of the inclusion of CIS patients.

III.3.2. Methods

We evaluated the patients' cognitive state with the Hungarian version of the BICAMS battery (Sandi et al., 2015). As no consensual threshold on CI for BICAMS has been proposed yet, we used the thresholds given in the manuals of the separate tests (-1.5 standard deviation [SD] below the average for SDMT; T-score 40 or below for BVMT-R and CVLT-II) (Benedict, 1988; Delis, 2000; Smith, 1982). We identified patients with CI, whom had abnormal scores on one or more tests, a criterion proposed by Dusankova et al. in 2012 in their own BICAMS validation process(Dusankova et al., 2012). The BDI-II was utilized to assess depression: all patients with a score of 13 or above were classified as depressed (Beck, 1996).

To determine the predictors of CI, a univariate logistic regression model was used. For the evaluation of the differences in CI and depression between the sexes and patients with different levels of education, Fisher's exact test and chi-square tests were used. To assess the differences between key clinical and demographic factors (age, age at disease onset, disease duration, EDSS score) one-way ANOVA was utilized.

Informed consent was obtained from all individual participants included in the study. The study was approved by the Human Investigation Review Board of the University of Szeged in accordance with the Helsinki Declaration (authorization number 127/2013).

IV. Results

IV.1. Mortality and causes of death among Hungarian MS patients

The demographic data of our patients sorted by sex and the course of the disease are presented in Table 1. The mean age at death was 54.2 (95%CI: 52.0-56.5) years in the whole cohort, and the mean final EDSS score was 6.5 (95%CI: 6.1-6.9) points.

Table 1: Demographic data of the deceased patients by sex and clinical course

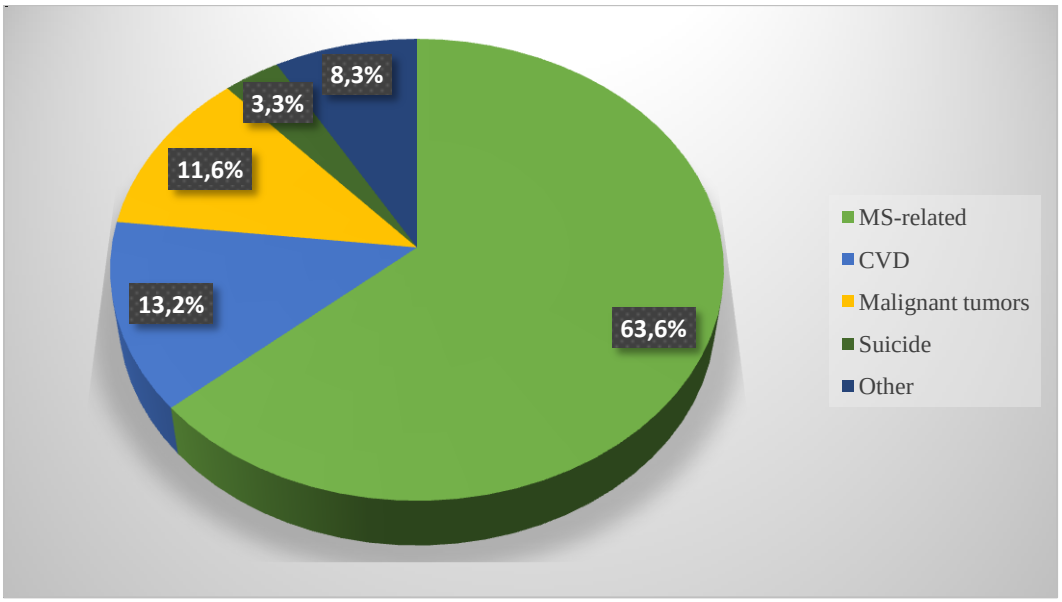
	Total (N=121)	Sex		Clinical course	
		Men (N=46)	Women (N=75)	RR/SP (N=98)	PP (N=23)
Mean age at death (95%CI) [years]	54.2 (52.0-56.5)	53.3 (52.0-56.6)	54.8 (49.9-57.2)	53.5 (50.9-56.0)	57.5 (53.3-61.8)
Final EDSS (95%CI) [points]	6.5 (6.1-6.9)	6.5 (6.0-7.1)	6.5 (6.0-7.0)	6.2 (5.7-6.7)	7.4 (6.8-8.1)

95%CI, 95% confidence interval; EDSS, Expanded Disability Status Scale; RR, relapsing-remitting; SP, secondary progressive, PP, primary progressive

IV.1.1. Causes of death

Seventy seven (63.6%) of the 121 patients died due to MS-related causes, which were the effects of long-term disability such as bronchopneumonia, sepsis and infection of the urogenital tract (ICD10: G35, A00-B99, J00-J99). In the other 44 cases (36.4%), CoDs were categorized as CVD (stroke, acute myocardial infarct and aortic rupture, [ICD10: I20-I25, I60-I69, I71]), malignant tumours (ICD10: C00-D09), suicide (ICD10: X71-83) and other causes (hepatic failure, pulmonary emboli, [ICD10: K70-77, I26-I41]). CVD was the CoD of 16 patients (13.2%), malignant tumours in 14 cases (11.6%), 4 people committed suicide (3.3%) and 10 patients (8.3%) died of the causes labelled “other” above (Figure 1). For comparison, CVD are responsible for 35.6%, malignancies for 28.0%, suicide for 1.5%, hepatic failure and pulmonary emboli for 8.1% and the causes labelled as “MS-related” for the 6.0% of deaths in the Hungarian general population.

Figure 1: The causes of death in the Hungarian MS population by percentage



MS, multiple sclerosis; CVD, cardio-and cerebrovascular diseases.

IV.1.2. Mortality risk

During the observed 20 years, 121 patients died, while the expected number of deaths based on the data from the general population was 47.93; the SMR was 2.52 (95%CI: 2.10-3.01) (Table 2). The SMR for MS-related CoDs was 105.34 (95%CI: 83.13-131.60), while SMRs for other causes were all below or approximately 1.00 (Table 2).

Table 2: Mortality risk in Hungarian MS patients

Causes of death	Expected number of death	Observed number of death	SMR (95%CI)
All causes	47.93	121.00	**2.52** (2.10-3.01)
MS-related	0.73	77.00	**105.34** (83.13-131.60)
CVD	18.98	16.00	**0.84** (0.50-1.34)
Malignancies	17.78	14.00	**0.79** (0.45-1.29)
Suicide	3.89	4.00	**1.03** (0.33-2.48)
Other	6.55	10.00	**1.53** (0.78-2.72)

SMR, standardized mortality rate, CVD, cardio- andcerebrovascular diseases

There was virtually no difference between the sexes: the SMR for men was 2.46 (95%CI: 1.82-3.25) and the SMR for women was 2.57 (95%CI: 2.03-3.20) regarding all CoDs. The SMR for MS-related causes were the highest in both sexes, but it was markedly lower in men

than women (Table 3). SMRs were virtually the same regarding CVDs, malignant tumors and suicide, yet men had a double risk of dying caused by hepatic failure or pulmonary emboli (Table 3).

Table 3: Mortality risk in Hungarian MS patients by sexes

	Men			Women		
Causes of death	Expected number of death	Observed number of death	SMR (95%CI)	Expected number of death	Observed number of death	SMR (95%CI)
All causes	18.71	46.00	**2.46** (1.82-3.25)	29.22	75.00	**2.57** (2.03-3.20)
MS-related	0.29	25.00	**86.23** (57.03-125.40)	0.44	52.00	**117.91** (88.97-153.40)
CVD	6.70	6.00	**0.90** (0.36-1.86)	12.28	10.00	**0.81** (0.41-1.45)
Malignant tumor	6.71	7.00	**1.04** (0.46-2.06)	11.07	7.00	**0.63** (0.28-1.25)
Suicide	2.02	2.00	**0.99** (0.17-3.27)	1.87	2.00	**1.07** (0.18-3.54)
Other	2.98	7.00	**2.01** (0.82-4.19)	3.57	4.00	**1.12** (0.36-2.71)

SMR, standardized mortality rate; CVD, cardio- and cerebrovascular diseases

Regarding the different clinical courses of MS, the SMR for RR/SPMS patients was 2.34 (95%CI: 1.91-2.84), while it was much higher, 4.10 (95%CI: 2.66-6.05), in case of patients with PPMS. The SMR for MS-related CoDs was almost double in PPMS patients than in the RR/SPMS group (Table 4). PPMS patients' survival risk associated with CVDs was higher than in RR/SPMS patients (Table 4). No PPMS patient committed suicide, while the survival risk associated with hepatic failure and pulmonary emboli was almost six-fold (SMR: 5.78) than in the RR/SPMS group (Table 4).

Table 4: Mortality risk in Hungarian MS patients by clinical courses

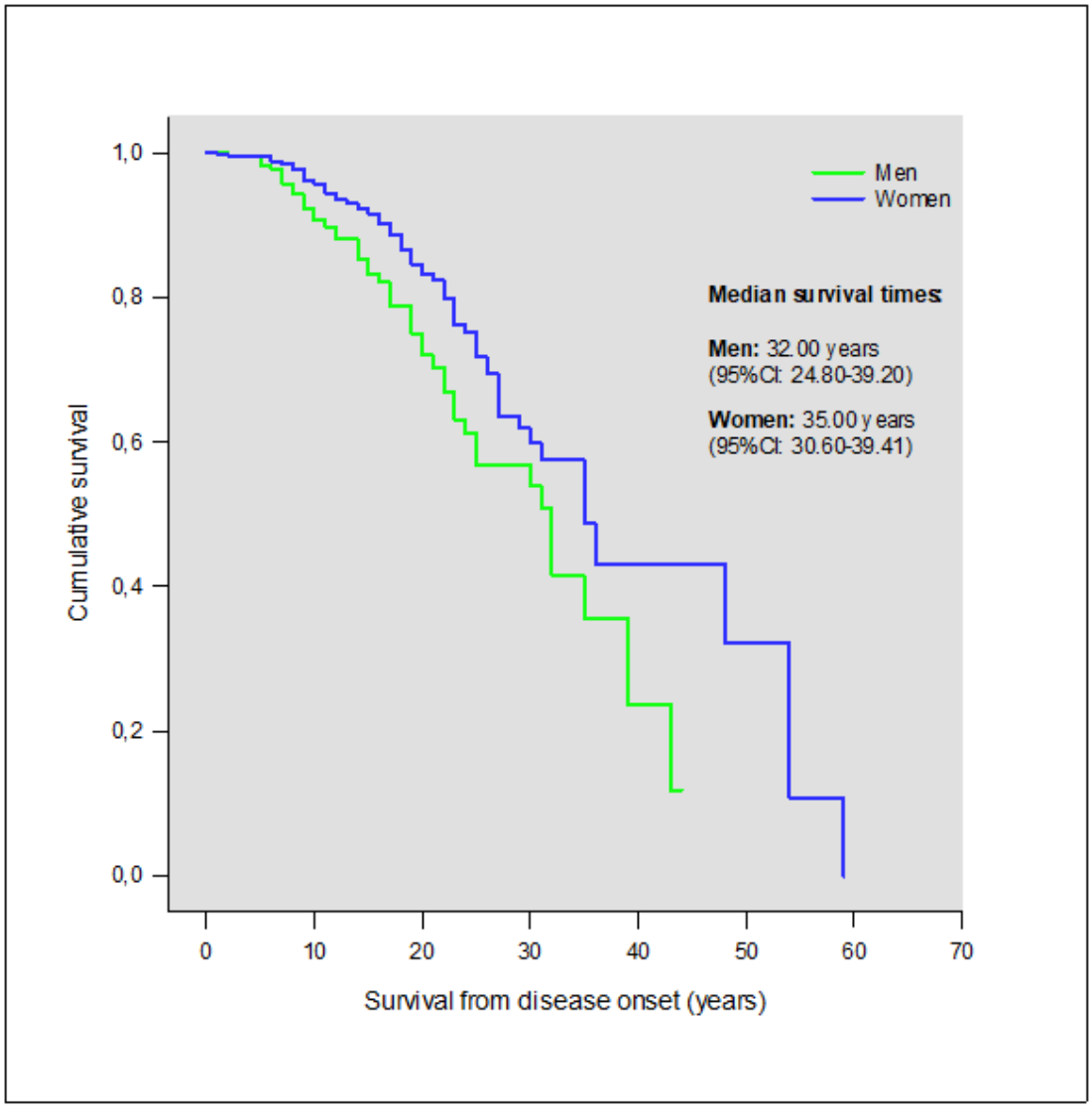
	RR/SPMS			PPMS		
Causes of death	Expected number of death	Observed number of death	SMR (95%CI)	Expected number of death	Observed number of death	SMR (95%CI)
All causes	41.90	98.00	**2.34** (1.91-2.84)	5.62	23.00	**4.10** (2.66-6.05)
MS-related	0.64	62.00	**96.42** (74.56-122.80)	0.09	15.00	**170.50** (99.05-274.80)
CVD	16.24	12.00	**0.74** (0.40-1.26)	2.65	4.00	**1.51** (0.48-3.67)
Malignant tumor	15.73	12.00	**0.76** (0.41-1.30)	2.09	2.00	**0.96** (0.16-3.16)
Suicide	3.49	4.00	**1.15** (0.36-2.75)	0.44	0.00	**0.00** (-)
Other	5.80	8.00	**1.38** (0.64-2.62)	0.35	2.00	**5.78** (0.97-19.10)

RR/SPMS, relapsing-remitting and secondary progressive MS; PPMS, primary progressive MS; SMR, standardized mortality rate; CVD, cardio- and cerebrovascular diseases

IV.1.3. Survival time

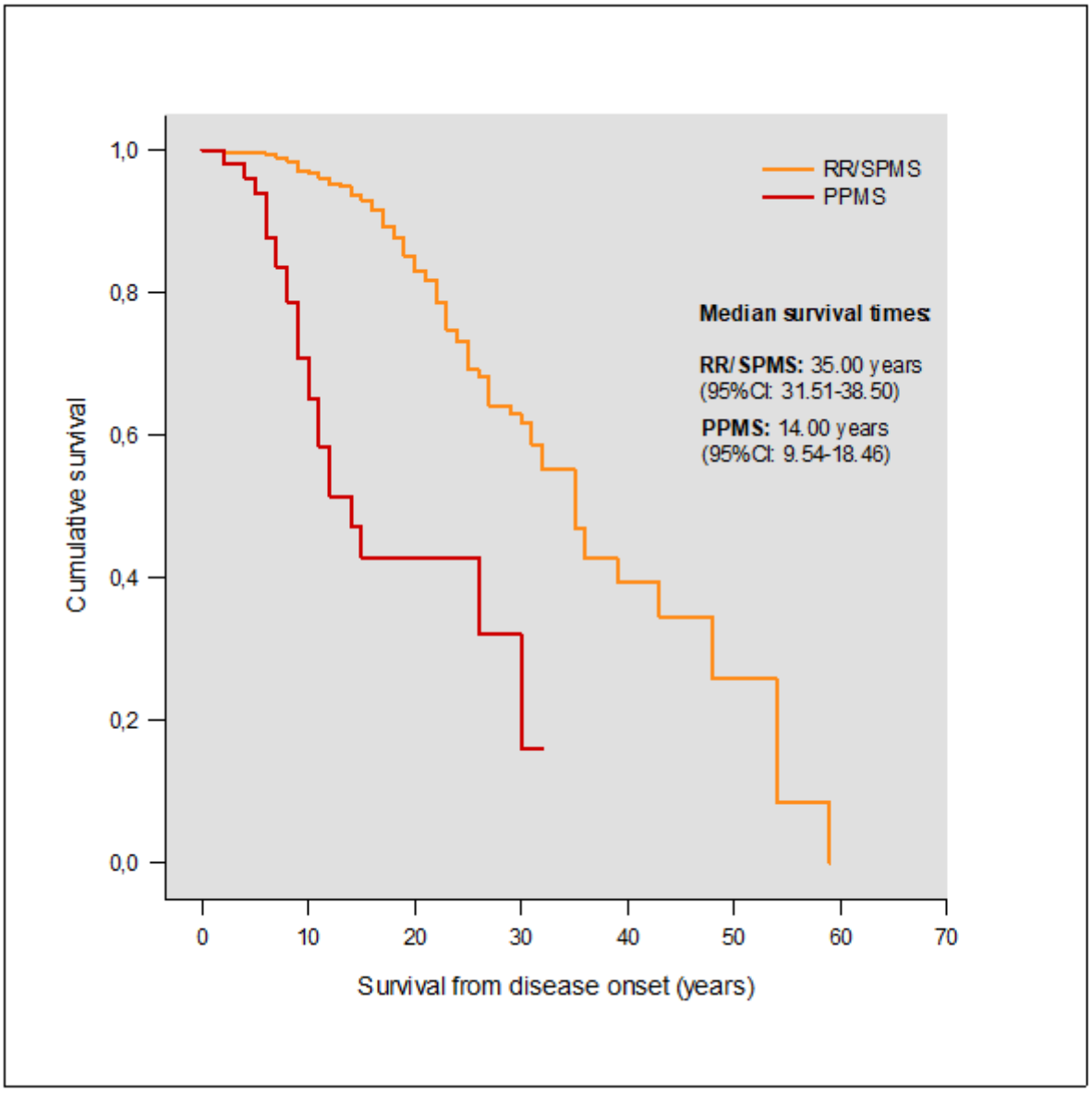
The median survival time from disease onset was 35 years in case of the whole MS population. Regarding the sexes, we found a statistically significant ($p<0.001$), yet clinically not relevant difference: the median survival time from disease onset for women was 35 years, while it was 32 years for men (Figure 2). However, the median survival times differed greatly between the different clinical courses ($p<0.001$): PPMS patients' median survival time from disease onset was 14 years, while it was 35 years in the RR/SPMS group ($p<0.001$) (Figure 3).

Figure 2: Kaplan-Meier survival curves representing survival from onset of the patients by sex, with median survival times and 95% confidence intervals



95%CI, 95% confidence interval

Figure 3: Kaplan-Meier survival curves representing survival from onset of the patients by disease course, with median survival times and 95% confidence intervals



RR/SPMS, relapsing-remitting and secondary progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; 95%CI, 95% confidence interval

IV.2. The Hungarian validation of the BICAMS battery

The mean age of the recruited patients was 41.9 (±8.9) years, the mean age at disease onset was 29.8 (±9.9) years, the mean disease duration was 11.1 (±7.6) years and the mean EDSS score was 2.5 (±1.8) points. The mean age of the HC group was 40.9 (±11.8) years, which is not significantly different from the patients group (p=0.610).

IV.2.1. Validity of the Hungarian BICAMS battery

The group data and the differences between the raw scores of the patients and HC group are shown in Table 5 during all 4 trials and the retests as well. MS patients performed significantly worse in all trials than the members of the HC group ($p \leq 0.001$ in all tests other than the first CVLT-II; where $p=0.017$).

Table 5: Differences between the performance of the patients and the healthy control group

Tests	Raw score (±SD)		Significance (p)
	Patients	HC group	
SDMT written	44.31 (± 11.76)	54.88 (± 10.32)	<0.001
SDMT written retest	49.38 (± 14.91)	62.31 (± 12.78)	<0.001
BVMT-R	22.54 (± 8.54)	26.68 (± 5.56)	0.001
BVMT-R retest	26.89 (± 8.21)	31.81 (± 4.13)	<0.001
SDMT oral	55.62 (± 15.48)	66.82 (± 12.44)	<0.001
SDMT oral retest	59.40 (± 18.29)	72.84 (± 13.88)	<0.001
CVLT-II.	55.37 (± 10.71)	59.03 (± 8.29)	0.017
CVLT-II. retest	61.77 (± 14.20)	70.58 (± 8.29)	<0.001

SD, standard deviation; HC, healthy control; SDMT, Symbol Digit Modalities Test; BVMT-R, Brief Visuospatial Memory Test Revised; CVLT-II, California Verbal Learning Test second edition

The correlation coefficients between the test and the retest performances are shown in Table 6. The overall correlations are very strong ($r>0.8$, $p<0.001$ during the SDMT and BVMT-R assessments; $r=0.678$; $p<0.001$ between the CVLT-II assessments). However, performance of the patients shows slightly stronger correlations than the HC group; the greatest difference is between the CVLT-II tests ($r=0.743$; $p<0.001$ in case of the patients, $r=0.453$; $p<0.001$ in case of the HC group).

Table 6: Correlation coefficients and significance levels

Tests	Overall		Patients		HC group	
	Correlation (r)	Significance (p)	Correlation (r)	Significance (p)	Correlation (r)	Significance (p)
SDMT written	0.874	<0.001	0.883	<0.001	0.796	<0.001
BVMT-R	0.864	<0.001	0.873	<0.001	0.805	<0.001
SDMT oral	0.830	<0.001	0.884	<0.001	0.664	<0.001
CVLT-II	0.678	<0.001	0.743	<0.001	0.453	<0.001

HC, healthy control; SDMT, Symbol Digit Modalities Test; BVMT-R, Brief Visuospatial Memory Test Revised; CVLT-II, California Verbal Learning Test second edition

The difference between test-retest scores of the patients and HC group was assessed, as we observed greater differences in the HC group than between the patients' scores and found weaker test-retest correlation within the HC group. A significant difference was found between the test-retest performances the patients and the HC group with a multivariate test where the result of the BICAMS battery was the single composite outcome (p=0.020, observed power=0.790). With multiple univariate analyses sorted by battery types, there was significant difference only in the CVLT-II performances (p=0.003, Table 7). This model satisfied the assumption of sphericity (p>0.05).

Table 7: Univariate tests of the test-retest performances between the patients and healthy controls

Within subject effects	Measure	p	Observed Power
Test-Retest and Patients-HC group	SDMT written	0.063	0.460
	BVMT-R	0.313	0.171
	SDMT oral	0.231	0.223
	CVLT-II	0.003	0.862

HC, healthy control; SDMT, Symbol Digit Modalities Test; BVMT-R, Brief Visuospatial Memory Test Revised; CVLT-II, California Verbal Learning Test second edition. The significant difference is highlighted in orange

IV.2.2. Connection between fatigue and cognitive performance

We observed significant, albeit moderate negative correlations (r<-0.3; p<0.05) between the patients' overall FIS scores and their cognitive performance in all parts of the BICAMS battery (Table 8). Regarding the different dimensions of FIS, the decline in the cognitive

correlated best with the physical dimension, then with the social dimension; and in the cognitive dimension the only significant correlations were observed with the oral SDMT and the CVLT-II results (Table 8).

Table 8: The correlation coefficients between the raw scores of the BICAMS subtests and the dimensions of the FIS questionnaire

	Total FIS points		Cognitive dimension of FIS		Physical dimension of FIS		Social dimension of FIS	
	Correlation (r)	Significance (p)	Correlation (r)	Significance (p)	Correlation (r)	Significance (p)	Correlation (r)	Significance (p)
SDMT written	-0.346	0.008	-0.248	0.052	-0.406	0,001	-0.293	0,023
BVMT-R	-0.322	0.014	-0.247	0.053	-0.351	0,006	-0.255	0,049
SDMT oral	-0.359	0.006	-0.279	0.028	-0.411	<0,001	-0.239	0,065
CVLT-II	-0.301	0.022	-0.311	0.014	-0.302	0,018	-0.316	0,014

SDMT, Symbol Digit Modalities Test; CVLT-II., California Verbal Learning Test II.; BVMT-R, the Brief Visuospatial Memory Test Revised (BVMT-R). The correlations which are not significant are highlighted.

IV.3. The prevalence of cognitive impairment and its risk factors among Hungarian RRMS and CIS patients

IV.3.1. Clinical and demographic data

We were able to recruit 553 patients for our multi-centered epidemiological study, which represent roughly 6.5% of the Hungarian MS population and about 8% of the CIS and RRMS patients in the country. All patients filled out the BICAMS battery, while 437 patients BDI-II assessment (some the patient did not fully complete the BDI questionnaire hence their score could not be reliably calculated or the patient did not consent at all to fill out the questionnaire). The mean age of our patients was 44.93±11.69 years, mean age at disease onset was 31.95±10.01 years, the mean disease duration was 13.05±8.05 years and the median EDSS score 2.0 (IQR: 2.0) points. One-hundred and sixteen patients (26.5%) showed signs of depression, but only in case of 17 (4%) patients, this could be categorized as “severe”.

In regard of the sexes, we found no significant difference between the rate of patients with different educational levels, disease duration, EDSS score and the rate of depression (Table 9). Yet men were approximately 4.5 years younger and 3.5 years younger at the onset of MS, which are statistically meaningful, yet clinically irrelevant differences (Table 9).

Table 9: Clinical and demographic data of the male and female participants

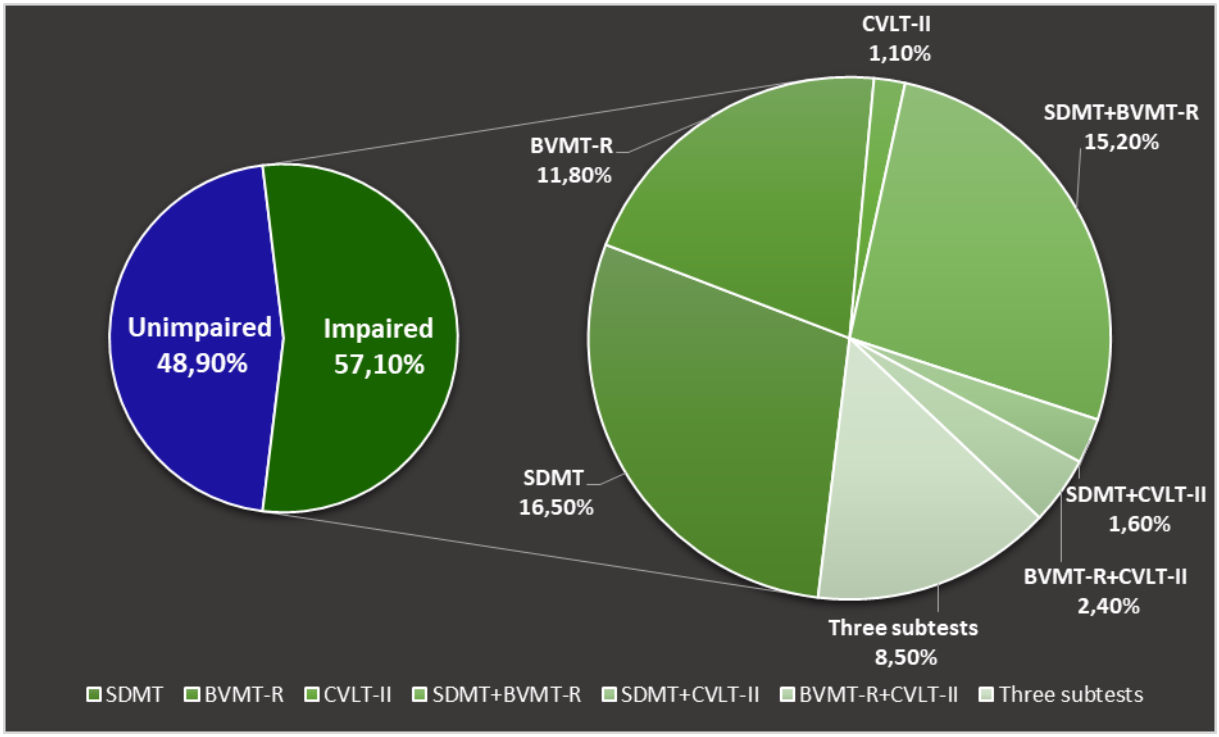
		Male	Female	Significance (p)
Age (+SD)		40.83 (±11.35)	45.24 (±11.49)	p<0.001
Age at disease onset (+SD)		29.59 (±9.58)	32.88 (±9.91)	p<0.001
Disease duration (+SD)		12.21 (±8.06)	13.35 (±8.00)	p=0.132
Median EDSS (IQR)		2.0 (2.0)	2.0 (2.0)	p=0.436
Education level	<12 years	42 (26.8%)	81 (20.5%)	p=0.254
	12-15 years	54 (34.4%)	155 (39.1%)	
	≥16 years	61 (38.9%)	160 (40.4%)	
Depression	Present	31 (23.8%)	85 (27.7%)	p=0.477
	Not present	99 (76.2%)	222 (72.3%)	

SD, Standard deviation.

IV.3.2. Prevalence of cognitive impairment and its predictors

Three-hundred and sixteen (57.1%) of our patients had some level of CI: 231 patients (41.7%) on the SDMT, 210 patients (38.0%) on the BVMT-R and 75 patients (13.6%) on the CVLT-II testing. Ninety-one patients (16.5%) had impaired scores solely on the SDMT, 66 patients (11.8%) only on the BVMT-R, and 6 patients (1.1%) only on the CVLT-II assessment. Eighty-four patients (15.2%) had impaired scores on both the SDMT and the BVMT-R, 9 (1.6%) patients on both the SDMT and CVLT-II, and 13 patients (2.4%) on both the BVMT-R and the CVLT-II assessments. Forty-seven patients (8.5%) had impaired scores on all three batteries. We found no significant difference regarding the clinical and demographic data between the patients with CI and those patients without it. Seven (25.0%) of our CIS patients had some level of CI as compared to 309 (58.8%) of the RRMS patients, which difference is significant (p=0.001).

Figure 4: The rate of cognitive impairment in the different subtests of the BICAMS battery



SDMT, Symbol Digit Modalities Test; BVMT-R, Brief Visuospatial Memory Test Revised; CVLT-II, California Verbal Learning Test 2nd Edition

A univariate logistic regression analysis was performed to identify any predictors of CI. Of the evaluated parameters, only sex, educational level and EDSS score turned out to be significant predictors (we dichotomized the EDSS score based on the median EDSS level). Men had almost threefold risk to develop CI, the risk of CI was twice as high in patients without a high school degree, than people with college and university degree, while patients with lower EDSS scores (0-2 points) had approximately half the risk than patients with EDSS scores >2 points.

These predicting factors reflected in the prevalence rates: we found some level of CI in 70.1% of the man, while in only 52.0% of the women ($p<0.001$). Men performed worse on all three subtests of the BICAMS battery (SDMT: 55.4% vs. 36.4%, BVMT-R: 48.4% vs. 33.8%, CVLT-II: 21.7% vs. 10.4%; $p<0.001$). The prevalence of CI among patients with <12 years of education was 68.3%, among patients with 12-15 years 60.8% and among patients with 16≤ years was 48.0% which significantly differed from the other two categories ($p=0.001$). Patients had a significantly higher rate of impaired scores on both the SDMT (53.7%, 41.6%, 35.3%; $p=0.004$) and the BVMT-R (48.0%, 39.7%, 30.8%; $p=0.006$) as the educational levels lowered, but there was no significant difference during the CVLT-II testing (17.1%, 14.8%,

10.4%; p=0.178). Among patients with EDSS scores between 0-2 points 49.7% had CI, while the prevalence was 72.9% among patients with higher EDSS scores (p<0.001) and those patients performed worse on all three BICAMS subtests (SDMT: 55.2% vs. 35.4%, BVMT-R: 53.1% vs. 31.1%, CVLT-II: 20.3% vs. 10.2%; p<0.001).

When we combined the predictors, and assessed both sexes with logistic regression analysis separately, we found that other than their sex, there is no other significant predictor of CI for man. The prevalence of CI did not significantly differ in any subgroups based on educational levels or EDSS scores, with the sole exception of the BVMT-R performance between men with different EDSS scores (Table 10).

Table 10: The rate of cognitive impairment among man with different educational levels, different EDSS scores

Predictor		All domain	p-value	SDMT	p-value	BVMT-R	p-value	CVLT-II	p-value
Education	*<12 years*	71.4%	0.949	64.3%	0.227	47.6%	0.687	19.0%	0.641
	12-15 years	68.5%		57.4%		44.4%		25.9%	
	≥16 years	70.5%		47.5%		52.5%		19.7%	
EDSS	*0-2 points*	66.7%	0.098	53.8%	0.405	40.9%	0.012	19.4%	0.422
	>2 points	79.7%		61.0%		62.7%		25.4%	

EDSS, Expanded Disability Status Scale; SDMT, Symbol Digit Modalities Test; BVMT-R, Brief Visuospatial Memory Test Revised; CVLT-II, California Verbal Learning Test 2nd Edition. The significant difference (p<0.05) is highlighted.

However educational level and the EDSS score both proved to be a significant predictor of CI in woman. Women with 12-15 years of education had an odds ratio (OR) of 1.79 (95%CI: 1.10-2.92; p=0.021), while women with <12 years of education had an even higher OR of 2.46 (95%CI: 1.34-4.52; p=0.004) as compared to women with a college or university degree. Women with low EDSS scores had an OR of 0.40 (95%CI: 0.24-0.65; p<0.001) as compared to women with higher EDSS scores.

Table 11: The rate of cognitive impairment among woman with different educational levels, different EDSS scores

Predictor		All domain	p-value	SDMT	p-value	BVMT-R	p-value	CVLT-II	p-value
Education	<12 years	66.7%	<0.001	48.1%	0.030	48.1%	<0.001	16.0%	0.083
	12-15 years	57.4%		36.1%		38.1%		11.0%	
	≥16 years	39.4%		30.6%		22.5%		6.9%	
EDSS	0-2 points	42.8%	<0.001	27.9%	<0.001	27.1%	<0.001	6.6%	0.001
	>2 points	69.9%		52.6%		48.9%		18.0%	

EDSS, Expanded Disability Status Scale; SDMT, Symbol Digit Modalities Test; BVMT-R, Brief Visuospatial Memory Test Revised; CVLT-II, California Verbal Learning Test 2nd Edition. The difference which is not significant is highlighted.

These differences appeared in the prevalence of CI: the higher the education, the lower the prevalence is (66.7% for women with <12 years of education, 57.4% for women with 12-15 years of education and 39.4% for women with 16≤ years of education; p<0.001); while the prevalence of CI is 42.8% among women with low EDSS scores and 69.9% with higher EDSS scores (p<0.001; Table 11). Women with higher EDSS performed worse an all three BICAMS subtests, while education affected the performance on SDMT and BVMT-R assessments, but not on the CVLT-II screening (Table 11).

V. Discussion

V.1. Mortality and causes of death among Hungarian MS patients

The data on mortality in MS comes principally from Northern Europe and North-America thus leaving “blank spots on the map”. Furthermore, these results show some controversy as well.

The first evaluation regarding CoDs in MS is from 1987, Scotland (Phadke, 1987). It found that 62% of the patients died of MS and indicated that CVD and malignancies are the next most frequent CoDs(Phadke, 1987). The forthcoming studies resulted in a wider range of MS-related CoDs up to 75%, but most of them put it between the narrow ranges of 55-62% (Bronnum-Hansen et al., 2004; Grytten Torkildsen et al., 2008; Hirst et al., 2008; Koch-Henriksen et al., 1998; Leray et al., 2007; Redelings et al., 2006; Sadovnick et al., 1991; Smestad et al., 2009; Sumelahti et al., 2010). Our study found that 64% of the patients died of MS-related causes, which is similar to most of these aforementioned evaluations.

CVD and malignancies (13% and 11% in our cohort, respectively) are the predominant none MS-related CoDs. Previous studies showed discrepancy as they found both lower and higher ratios regarding these diseases, but the range is generally between 10-20% similarly to our evaluation, and CVD seems to be the more common cause (Bronnum-Hansen et al., 2004; Goodin et al., 2012; Phadke, 1987).

The SMR for all CoDs was 2.52 in our population and this excess overall mortality risk was solely due to the excess deaths caused by MS (SMR: 105.34), with CVD and malignant tumours posing virtually the same mortality risk than in the general population (SMR: 0.84 and 0.79 respectively). Earlier studies showed controversy in this (Bronnum-Hansen et al., 2004; Grytten Torkildsen et al., 2008; Sumelahti et al., 2002). Yet we know, that the incidence of these diseases rise with the age of the patients and these are the leading CoDs among the elderly population. The mean age at death in our cohort was 54.2 years, so we conclude, that the majority of our patients most likely died before these diseases manifested or progressed to late phases. The majority of previous assessments found that the risk of suicide is higher among MS patients than in the general population (Bronnum-Hansen et al., 2005; Fredrikson et al., 2003). Interestingly, this was not the case in Hungary, as the risk of suicide was the same as in the general population (SMR: 1.03). A possible reason behind this is the sad fact, that Hungary is one of the leading countries in rate of suicide among the developed countries, just like Finland, where the mortality risk posed by suicide also did not differ from the general population (Sumelahti et al., 2010).

We found virtually no difference between the sexes regarding the overall SMRs in our assessment. Data on this are highly controversial: some studies yielded the same results, but others found that women have a higher mortality risk (Bronnum-Hansen et al., 2004; Kingwell et al., 2012; Leray et al., 2007; Ragonese et al., 2010; Sumelahti et al., 2010). Despite this, the relative risk of dying of MS-related causes was higher in women than in men in our patients, which was found in case of the evaluations showing higher mortality risk for women. It seems, that deaths due to malignancies, hepatic failure and pulmonary emboli are less frequent in women than in either men or the general population. A possible causative factor may be the higher rate of chronic alcoholism among men, but these results warrant further evaluations.

Both in British Columbia, Canada, and in Western-Norway PPMS patients' SMR rates and relative mortality risks were higher than in RRMS patients (Grytten Torkildsen et al., 2008; Kingwell et al., 2012). In our cohort, this difference was far more pronounced: SMR was 4.10 in PPMS patients while 2.34 in the initially relapsing group. The mortality risk due to MS-related causes and CVDs were almost twofold, the SMR due to hepatic failure and pulmonary emboli was fivefold in patients with PPMS. The differences between the clinical courses might explain these great differences. PPMS is more aggressive and patients become bedridden far earlier than initially relapsing MS; it starts in older age, so CVDs' prevalence might be higher among these patients. Last but not least, we note that in our cohort the rate of PPMS patients was lower than in the Norwegian and the Canadian population (7%, which corresponds to only 52 patients vs 10% and 12%), which could bias the results (Grytten Torkildsen et al., 2008; Kingwell et al., 2012).

The median survival time from MS onset was 35 years, 35 years for women and 32 years for men. Data from Canadian and Danish cohorts also describe longer median survival times for women than men, so our results are in line with the previously published ones (Bronnum-Hansen et al., 2004; Hader, 2010; Kingwell et al., 2012). PPMS patients' median survival time from MS onset (14 years) is less than half than patients' with initially relapsing course (35 years), which is in accordance to previous results (Grytten Torkildsen et al., 2008; Kingwell et al., 2012).

However, since our publication, some interesting new data have arisen. A recent study with 60-years follow-up period from Norway, published in 2017 showed, that PPMS patients have an almost two-fold mortality risk as compared to the RR/SPMS group, and a four-fold risk compared to the general population just like in our patients (Lunde et al., 2017). It was also revealed in this assessment, that age at disease onset is a crucial factor for life expectancy

even more so than we thought before: patients diagnosed at or before the age of 20 years had an SMR of 7.3, while patients diagnosed in their sixties had "only" 1.3 (Lunde et al., 2017). The most surprising result however shows, that the SMR rates decreased from 3.1 in the population with disease onset 1953-1974 to 0.7 in the population diagnosed during the DMT-era (1997-2012) (Lunde et al., 2017). Similarly, a recent assessment from Sweden, published in 2017, encompassing 54 years of follow-up between 1968 and 2012 reported a similarly marked decrease in the mortality risk in the last 12 years – while still remaining significantly higher than in the general population - as compared to the earlier periods (from a risk of 6.5 times between 1968-1980 to a risk of 1.7 times between 2001-2012) (Burkill et al., 2017).

Our study, as well as the previously published assessments were carried out on mixed cohorts involving a high proportion of patients who did not receive any therapy for MS, started it at the later phases of the disease or could not be changed to more effective therapy when needed unlike it can be done in the past couple of years (only about a third of our patients received any kind of DMTs). However, it is not due to any kind of mistreatment rather the fact, that the first DMTs were introduced in the middle '90s, and the more effective ones much later (in the middle 2000's or 2010's). Also, we observed a huge evolution in the diagnostic criteria and tools, making the diagnosis of MS far more exact and earlier than before. This means in our context, that the previous investigations (including ours) were in high proportion (but not exclusively) carried out on patients virtually demonstrating the natural course of disease. In the highlighted changing trends, we are probably witnessing the effect of early diagnosis and treatment to a degree. Yet – as the Norwegian authors suggested – these results should be interpreted cautiously, as the patients from the DMT era are still young, and the effect of treatment could not be analysed properly yet. Also, whether this trend is global or will it – hopefully - continue forward, still remains to be seen.

V.2. The Hungarian validation of the BICAMS battery

Cognitive dysfunction is not easy to evaluate, despite being a frequent symptom of MS. To fill the need of a screening tool for CI, the BICAMS battery was created in 2011 (Langdon et al., 2012). During our validation process, we followed the methods proposed by the creators of the battery. We found significant differences ($p \leq 0.001$ in all tests other than the first CVLT-II screening; $p=0.017$ in the first CVLT-II screening) between the scores of the patients and the HC group, and we established good test-retest reliability with strong correlations ($r>0.67$, $p<0,001$). With this results we conclude, that the Hungarian version of the BICAMS battery is valid and useful in the everyday practice. We were the third team to validate and use the

battery after the original English, and the Czech (validated in 2012) counterparts (Dusankova et al., 2012; Langdon et al., 2012).

We found slightly lower differences between the test-retest scores and weaker test-retest reliability during the CVLT-II test, than the other two screenings in both groups, and it was more pronounced in the HC group. We suspected a significant learning effect behind this phenomenon. The HC group performed significantly ($p=0.020$) better at the retest period comparing to their original performance than the patients. This difference could solely be attributed to their CVLT-II ($p=0.003$) performance. We suspect the short interval of three weeks between the administrations and the use of the same form of the CVLT-II both to be an underlying reason (Benedict, 2005; Benedict and Zgaljardic, 1998). Furthermore, probably there was no novelty effect during the second administration, thus the anxiety of a new situation did not interfere with the performance during screening, further bettering the second performance (O'Neil-Pirozzi et al., 2010). The difference between the HC group and the patients is harder to explain, but it is a fact, that the control group consisted of individuals without any cognitive dysfunction. So we theorize, that despite the relative better performance of the MS patients during the retest period, their generally worse cognitive state prevented them from improving as much as the HC group, but this needs to be assessed further to be stated factually.

The relationship between fatigue and cognitive decline is not well understood and there are not many studies investigating it. Nevertheless, patients often report that fatigue impairs their cognitive abilities, yet most of the assessments failed to find any objective connection between the two psychopathological symptoms (Bailey et al., 2007; Bol et al., 2010; Johnson et al., 1997; Krupp et al., 1988; Morrow et al., 2010; Paul et al., 1998). However, there are some sparse data showing that fatigued MS patients' information processing speed was slower than non-fatigued patients' (Andreasen et al., 2010). Our results may imply similar tendencies: overall FIS points showed significant correlations with the patients' BICAMS scores ($r<-0.3$; $p<0.05$), and the strongest correlation was shown with the SDMT performances. Yet, as we did not investigate causal relationship in multivariable models, we cannot draw any clear conclusions further. Also, it is important that our patient pool was comprised of only 65 patients, and did not include any progressive PwMS, so evaluation on larger and heterogeneous populations are needed to get a clearer picture.

Since the publication of our study, BICAMS has been validated and adopted to several languages and cultures. It is utilized in Europe, North-America, South-America, Iran and Japan as well, encompassing 17 nations, with other validation studies under way (Costers et

al., 2017; Dusankova et al., 2012; Eshaghi et al., 2012; Filser et al., 2018; Giedraitiene et al., 2015; Goretti et al., 2014; Niino et al., 2017; O'Connell et al., 2015; Ozakbas et al., 2017; Polychroniadou et al., 2016; Sandi et al., 2015; Sousa et al., 2018; Spedo et al., 2015; Strober et al., 2009; Vanotti et al., 2016; Walker et al., 2016). In 2017, an Italian centre studied the effects of inducting BICAMS results into the cerebral function system of the EDSS score. Their results suggests, that a quarter of patients with EDSS≤4 points without integration of BICAMS is miscalculated and the disability underestimated (Sacca et al., 2017). Furthermore, in 2018, a guideline was proposed for the measurement of cognition in PwMS (Kalb et al., 2018). BICAMS (along with shorter and longer batteries) has been proposed for routine use. These new data further emphasize the usefulness of the battery and the importance of measuring CI.

V.3. The prevalence of cognitive impairment and its risk factors among Hungarian RRMS and CIS patients

As we discussed above, the routine assessment of cognition is still in its youth in regard of PwMS caused by several factors also described earlier. In our multi-centred evaluation, we found the prevalence rate to be 57.1% among the Hungarian MS population, with 58.8% in the RRMS group and 25.0% in the CIS group. When published, ours was the second prevalence data about CI in PwMS on a representative population cohort and the first to give data on CIS patients using the BICAMS battery. The first study with BICAMS was carried out by Dusankova and colleges in the Czech Republic in 2012 (Dusankova et al., 2012). They found the prevalence rate to be 55%, which is similar to our results and both are within the wider range of earlier assessments (43-70%) (Chiaravalloti and DeLuca, 2008; Dusankova et al., 2012). Importantly however, our study was carried out on an almost double-sized (553 patients), homogenous population as compared to the Czech assessment (which involved RRMS, RPMS, SPMS and PPMS but not CIS patients) (Dusankova et al., 2012). We did not evaluate progressive MS patients, which choice might have even raised the prevalence rate further, as CI seems to be even more frequent in the progressive courses (Zakzanis, 2000). There are not many data regarding the prevalence of CI in CIS, yet those seem to be in line with our findings (Hyncicova et al., 2017). These findings further emphasis the usefulness of the Hungarian BICAMS battery and its regular use in clinical routine.

Information processing speed was the most vulnerable cognitive domain in our evaluation (41.7%), followed by visuospatial memory (37.8%) with verbal memory seemingly be less affected (13.6%). These results were somewhat expected as other studies demonstrated

similar tendencies to various degrees, yet the rate of verbal memory impairment varied more than the other domains (Chiaravalloti and DeLuca, 2008).

The only significant predictive factors for CI was sex, education and the EDSS score according to our results, while no association was found with age, age at disease onset and disease duration. Earlier assessments were controversial on this matter. Most of the earlier studies similarly found sex, education and EDSS scores to be predictive factors, while in regard of age at disease onset and disease duration the picture is less clear. Some assessments found association with these factors, most, on the other hand, yielded similar results to (Amato et al., 2012b; Amato et al., 2006b; Bonnet et al., 2006; DeLuca et al., 2015; Patti et al., 2015). The explanation for this is not easy: the different sample-sizes and the utilized batteries and methods could be partly responsible for this controversy, yet without further, in depth assessments, we do not have a clear answer. Nonetheless, our results – and those in line with it - imply that not the disease duration, rather the activity of the disease is the more important factor in developing CI, yet – as was said – this is needed to be evaluated further.

Surprisingly, depression did not significantly affect cognition in our cohort, despite that it has been connected to cognitive dysfunction for a long time. However deeper analyses showed, that mainly moderate to severe levels of depression have a significant impact on cognitive functioning, while in our population of PwMS, the overwhelming majority of depressed patients fell into the mild category, explaining this finding (Siegert and Abernethy, 2005).

According to our results, men are more vulnerable to cognitive dysfunction (70.1%) than women (52.0%), and showed higher rate of cognitive impairment in all three evaluated domains. Yet, beside their sex, we found no other significant predictors while education and EDSS scores differentiated between women. The data on sex differences in MS patients are sparse at best. Despite these results show similar differences in the prevalence of CI, to our best knowledge, no other study found that education and EDSS score are only predictors in women (DeLuca et al., 2015; Patti et al., 2015). The reason behind these differences in cognitive functions are even less well studied and understood. Certain genetic variables were assessed as factors in developing more serious cognitive dysfunction such as the more frequent presence of the Apo-E ε4 allele in men which leads to more severe CI as compared to woman – but these evaluations are not specific to MS (Savettieri et al., 2004). Aside from this, the role of sex hormones was implied: in particular, a possible protective effect of oestrogens on cognitive function was found, but this was reported in other neurodegenerative conditions, most notably in Alzheimer’s and Parkinson’s disease, not in MS (Bove et al., 2014; Miller and Cronin-Golomb, 2010). Though, as we conducted an epidemiological study and did not

evaluate the genetic polymorphisms of the patients, these explanations are merely speculative.
The prevalence of CI was significantly lower among woman with higher education and lower EDSS scores in our study. These findings support previous assessments which established EDSS as a possible predictor of CI (Amato et al., 2006b). Also, these studies found that higher cognitive reserve associated with higher educational levels is a protective factor against cognitive (Amato et al., 2006b; Sumowski et al., 2014; Whalley et al., 2004). However, to our best knowledge, no previous assessment concluded that these phenomena are restricted to women. These surprising findings might partly be explained by results from MRI assessments. We now know, that MS patients suffer a faster rate of brain atrophy both on the global as well as in some different local levels (hippocampus, thalamus, basal ganglia) which structures show strong association with memory and other cognitive domains (Brass et al., 2006; DeLuca et al., 2015; Houtchens et al., 2007; Koenig et al., 2014; Morgen et al., 2006). Beside this, importantly, our colleges from the Neuroimaging Group (Király et al) showed healthy men show faster rate of brain atrophy than healthy women (Kiraly et al., 2016). We speculate, that the accelerated atrophy in MS patients combined with this inherently faster atrophy rate in men results in the faster disappearance of the cognitive reserve resulting in higher susceptibility to cognitive decline. Another important factor that we might consider, that male sex itself was shown to be a predictor for worse prognosis in MS patients (Weinshenker et al., 1991). It seems, this worse prognosis involves cognition as well.
In the past decade, some evidence emerged, that CI can possibly be managed. Data on the effect of DMTs on cognition is very limited, but in some assessments IFN-β and natalizumab showed positive effect regarding the cognitive state (Mattioli et al., 2015; Patti et al., 2013). The most promising data comes from cognitive rehabilitation studies, where some marked improvements were reported(Amato et al., 2013). Yet, these studies are mostly in the initial phases with low number of patients involved and short-time follow-up periods (Amato et al., 2013). Nevertheless, further evaluations are highly expected in this field and might open up new possibilities for treatment, but before this can happen, further, in depth analyses of CI in MS are highly needed.

VI. Conclusions

VI.1. Mortality and causes of death among Hungarian MS patients

As conclusion we can state that we are the first to give data on the CoD and the mortality risk of PwMS from Central-Eastern Europe.

We also conclude, that the observed elevated mortality risk in PwMS compared to the general population can be solely attributed the disease itself. This is underlined by the fact, that no other diseases SMRs were higher than in the general population, and that our results are very similar to previous assessments. In fact, those similar data mostly come from North-America and Scandinavia, despite the great differences between the social-economic and healthcare state of Hungary and these countries (For illustration, the gross domestic product [GDP] per capita in Hungary was 13 464 USD in 2013 as compared to 59 950 USD in Denmark and 52 393 USD in Canada (International Monetary Fund). In 2013, the life expectancy at birth in Hungary was 75 years, while it was 80 years in Denmark and 81 years in Canada (World Bank)) which shows that the mortality risk does not depend on any other outside factor other than MS itself.

VI.2. The Hungarian validation of the BICAMS battery

We can conclude, based on our results, that the Hungarian version of the BICAMS battery, which was the third version of its kind, is valid and can readily be used for the measurement of CI. Also, it seems that there can be a connection between fatigue and the cognitive decline in PwMS, thus it warrants further research into the topic.

VI.3. The prevalence of cognitive impairment and its risk factors among Hungarian RRMS and CIS patients

Cognitive decline is a frequent, yet still under-diagnosed symptom of MS. Man are more susceptible to cognitive decline than women and higher education and lower EDSS scores seems to be a protective factor only in women. This is possibly caused by the higher rate of brain atrophy leading to the faster elimination of cognitive reserve in men. To our best knowledge, we were the first to demonstrate this type of sex-difference in MS patients.

We confirmed a fairly high prevalence of CI among CIS and RRMS patients who were young, active and in relatively good physical condition. This is highly important, because despite a patient may seem to be symptom-free during a physical examination, the disease can still be active. We know that cognitive problems are one of the main factors determining the QoL of PwMS and perhaps the most important factor in the employment state. Thus, we conclude that

routine screening of the cognitive state is highly important because it can facilitate the best therapeutic decision for the patients thus helping to maintain a good QoL for them.

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Appendix

I.

II.

III.