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

Summary of the Ph.D. thesis

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Szeged,

2019.06.14.

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.
IF: 1.150

II. **Sandi D**, Zsiros V, Füvesi J, Kincses ZT, Fricska-Nagy Z, Lencsés G, Vécsei L, Bencsik K. Mortality in Hungarian patients with multiple sclerosis between 1993 and 2013. J Neurol Sci. 2016 Aug;367:329-332.
IF: 2.295

III. **Sandi D**, Biernacki T, Szekeres D, Füvesi J, Kincses ZT, Rózsa C, Mátyás K, Kása K, Matolcsi J, Zboznovits D, Burány Z, Langane É, Vécsei L, Bencsik K. Prevalence of cognitive impairment among Hungarian patients with relapsing-remitting multiple sclerosis and clinically isolated syndrome. Mult Scler Relat Disord. 2017 Oct;17:57-62.
IF: 3.199

Cumulative impact factor: 12.758.

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. 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.

MS is a rare disease: there are approximately 2.5 million patients worldwide. It is generally the disease of the Caucasian race, it shows a North-South gradient and it affects women more often It generally manifests in early adulthood or in the early middle ages (20-45 years) in approximately 80% of the cases. Hungary counts among the "middle-risk" countries considering the prevalence of the disease. According to the latest epidemiological survey from 2013 the standardized prevalence of MS is 83.7/100 000.

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 in 1987 and found, that approximately 2/3 of the patients die due to MS-related causes. The first data concerning the lifespan of the patients arose from Denmark in 2004. It found, that PwMS live approximately 10 years shorter, than their life expectancy at birth. Furthermore, several evaluations has shown that PwMS have an about three-fold mortality risk as compared to the general population. Patients with the primary progressive (PPMS) form have been shown to have a higher risk as compared to the initially relapsing forms. Patients, in whom MS manifested before the age of 18, have an even higher risk of dying, en par with some malignancies.

The two main clinical attributes of the disease can be specified as the activity and the progression of the disease. Based on these attributes, four basic clinical courses of the disease were defined by Lublin and colleagues in 1996: The most common, relapsing-remitting (RRMS) form, the secondary progressive (SPMS) form, in about 10-15% of the cases the PPMS form and the rare relapsing-progressive form (RPMS). 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. However, this type of clinical phenotypisation needed to be revised. In 2014, by Lublin and colleagues,

clinically isolated syndrome (CIS) was introduced as a new concept, and now we recognize two initial subtypes of MS: relapsing and progressing subtypes. 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 means conversion to RRMS. Progressive patients can be PPMS or SPMS patients and can be either active and progressing, active but non-progressing, non-active but with progression and non-active and non-progressing. The benign term was excluded as new data arose about the natural history of the disease. Ebers and colleagues have shown, that the initial phase of the disease – defined by reaching the milestone of EDSS score 3 points -, show a grand variation in time, but from EDSS 3 points to EDSS 6 points, this variation disappears. This was an important reason (among others) that initialized the search for other signs and symptoms that can be prevalent during the first, seemingly inactive phase. Evaluations discovered these to be patopsychological in nature: fatigue is as prevalent, as in other courses; approximately 50% of these patients exhibit signs of cognitive dysfunction; and grand proportion of "benign" patients are burdened by depression, anxiety or other psychiatric conditions.

Classically, cognition was believed to remain largely intact through the course of the disease. In contrast, it was found recently, that CI is a very common symptom of MS with prevalence rates 43-70%. It seriously worsens the QoL of the patients in almost all aspect of life. In some assessments, CI was even indicated to be the strongest predictor of MS patients becoming unemployed. CI is not global among PwMS. Information processing speed, visual and verbal memory are the most often affected domains. It can appear at any stage of the disease, even in CIS and radiologically isolated syndrome (RIS) stages. It was also found that CI can manifest as an acute relapse of the disease and MS may primarily present as cognitive symptoms with minimal or no other neurological systems involved. 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. The only real biomarkers for CI in MS are magnetic resonance imaging (MRI) parameters: global and some regional brain atrophy, the enlargement of white-matter and the appearance of grey-matter lesions, the dysfunction normal-appearing white matter or the default mode networks are connected with CI in MS.

Measuring CI is usually not a routine task of neurologists. However, 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). Both batteries include longer assessments that measure the most commonly declining cognitive domains, however, there are limitations for the usefulness of such batteries in clinical practice. Both test require long time for administration (45 and 90 minutes), special equipment and a neuropsychologist, thus making the routine administration of these batteries all but impossible in clinical routine. For these reasons, the need for the creation of a well-composed but simple screening tool arose that is easy to use but sensitively measures CI in MS.

The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) battery was created in 2011 by a panel of neurologists and neuropsychologists. 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:

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 three questionnaires that comprise BICAMS: the Symbol Digit Modalities Test (SDMT), the first three immediate recall trials of the Brief Visuospatial Memory Test Revised (BVMT-R) and the first five immediate recall trials of the California Verbal Learning Test (CVLT-II). The SDMT is the measure of the information processing speed, the CVLT-II evaluates verbal memory and the BVMT-R measures visual memory. The committee recommended that the evaluations should be conducted annually or bi-annually.

The aetiology of depression and mood disorders – not unlike in other disorders – are multifactorial. 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. Howe frontal and temporal lobe atrophy and lesion volume correlate with the appearance of depression in PwMS . Some new data point toward the importance of inflammatory processes in the development of depressive symptoms as well. However the aetiology might be, depression remains a frequent problem among MS patients. Epidemiological surveys differ greatly on its prevalence, with a

reported pooled rate of 30.5%. Depression is a serious burden to PwMS, it heavily worsens the patients QoL in virtually all levelsand it is also known, that depression can cause pseudo-dementia, or worsen the already existing cognitive disabilities. Depression can be easily assessed by self-reporting questionnaires. One of the most frequently utilized such questionnaire is the Beck's Depression Inventory (BDI-II). The total received points can be 63, the cut-off value is 13 points.

Fatigue – medically - 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. It can be either primary (which is caused by the pathophysiology of the disease itself) or secondary (related to other symptoms of MS like pain, comorbidity or side-effect of DMTs). It frequently appears as the initial symptom of the disease and it is the most common symptom of MS with prevalence rates up to 95%. 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. Interestingly however, despite it can hypothetically affect cognitive functions, no strong connection has been found to date. Fatigue is usually measured by self-reported questionnaires, such as the Fatigue Impact Scale (FIS). The FIS battery comprises 3 subscales: social, physical and cognitive aspects. Total received points can be 160 points. The cut-off can vary, but it is usually given at ≥40 points.

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

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- and parts of Bács-Kiskun- and Békés- counties (total number of the population the unit is responsible for is ~900.000 people) in the southern region of Hungary. All MS patients were included into the Multiple Sclerosis Register of the Department of Neurology of the University of Szeged since 1993. 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. The socio-demographic data 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. The different courses of MS were determined per the Lublin-criteria from 1996.

The CoD was determined from the pathological records or the medical certificates of the cause of death. 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 as the ratio of the observed to the expected numbers of deaths. For the analysis of survival time from MS onset 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

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 were obtained from the Multiple Sclerosis Register of Szeged. 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.

The validation was conducted per the international standards given in 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. 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 connection between BICAMS and FIS were assessed by Pearson correlation coefficients. 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

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 (Szeged, Budapest,

Eger). One-hundred and fifty-seven patients were man, 396 women, classified into 3 categories depending on their educational level: 123 patients with less than 12 years, 209 patients with 12-15 years and 221 patients with 16 or more years of education. Additionally, all the patients currently enrolled to college or university were placed in the third group. Only 90 patients received no DMTs of the 553. All sociodemographic data on the were obtained from the Multiple Sclerosis Register in case of the centre of Szeged, or from the outpatient treatment reports from the other centres. The inclusion and exclusion criteria were the same as in the aforementioned BICAMS validation study, with the exception of the inclusion of CIS patients. We evaluated the patients' cognitive state with the Hungarian version of the BICAMS battery. We identified patients with CI, whom had abnormal scores on one or more tests. The BDI-II was utilized to assess depression: all patients with a score of 13 or above were classified as depressed. 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 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. 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. In the other 44 cases (36.4%), CoDs were categorized as CVD (stroke, acute myocardial infarct and aortic rupture), malignant tumours, suicide and other causes (hepatic failure, pulmonary emboli). 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. 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.

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). 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. 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. SMRs were virtually the same regarding CVDs, malignant tumours and suicide, yet men had a double risk of dying caused by hepatic failure or pulmonary emboli. 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. PPMS patients' survival risk associated with CVDs was higher than in RR/SPMS patients.

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

IV.2. The Hungarian validation of the BICAMS battery

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 $p=0.017$). The overall correlations between the test and the retest were 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).

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 The decline in the cognitive state 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.

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

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. 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, 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.

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).

A univariate logistic regression analysis was performed to identify any predictors of CI. Sex, educational level and EDSS score turned out to be significant predictors. Men had almost threefold risk to develop CI, the risk of CI was twice as high in patients with <12 years of education than in the other two groups, while patients with lower EDSS scores had approximately half the risk than patients with EDSS scores >2 points.

These predicting factors reflected in the prevalence rates: we CI in 70.1% of the man, while in only 52.0% of the women (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). 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).

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.

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. 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).

V. Discussion

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 and found that 62% of the patients died of MS and indicated that CVD and malignancies are the next most frequent CoDs. The forthcoming studies resulted in similar tendencies (43-75%). 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, but the range is generally between 10-20% similarly to our evaluation, and CVD seems to be the more common cause.

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). Earlier studies showed controversy in this. 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, but this was not the case in Hungary. Sadly, 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 .

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.

Some data showed, that PPMS patients’ mortality risk were higher than in RRMS patients. 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. We think, that as PPMS is more aggressive and it starts in older age it may partially cause this differences.

The median survival time from MS onset was 35 years for women and 32 years for men; in

case of PPMS patients', it was less than half than patients' with initially relapsing course (14 years and 35 years), which is in accordance to previous results .

V.1. 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. 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.

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. There are some sparse data showing that fatigued MS patients' information processing speed was slower than non-fatigued patients' . Our results may imply similar tendencies. Yet, as we did not investigate causal relationship in multivariable models, we cannot draw any clear conclusions further.

V.2. The prevalence of cognitive impairment and its risk factors among Hungarian RRMS and CIS patients

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 in the Czech Republic in 2012 and yielded similar results. 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). There are not many data regarding the prevalence of CI in CIS, yet those seem to be in line with our findings. 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 .

The only significant predictive factors for CI was sex, education and the EDSS score according to our results. Earlier assessments were controversial on this matter: Most of them similarly found sex, education and EDSS scores to be predictive factors, while some assessments did find association with other factors too. The explanation for this is not easy: the different sample-sizes and the utilized batteries and methods could be partly responsible for this controversy. 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. 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 .

According to our results, men are more vulnerable to cognitive dysfunction (70.1%) than women (52.0%). 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. The reason behind these differences in cognitive functions are even less well studied and understood: while certain genetic variables (the more frequent presence of the Apo-E ε4 allele in men for example) or the role of sex hormones (in particular, a possible protective effect of oestrogen), but these results were not reported specifically in MS. 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. Also, these studies found that higher cognitive reserve associated with higher educational levels is a protective factor against cognitive . 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 showing connection with cognition. Beside this, our colleges from the Neuroimaging Group (Király et al) showed healthy men have a faster rate of brain atrophy than healthy women. 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.

VI. Conclusions

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. and does not depend on any other outside factor.

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.

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.