DOI:10.14753/SE.2022.2680

SEMMELWEIS EGYETEM

DOKTORI ISKOLA

Ph.D. értekezések

2680.

ILJICSOV ANNA KATALIN

Klinikai neurológiai kutatások
című program

Programvezető: Dr. Kovács Tibor, egyetemi docens

Témavezető: Dr. Simó Magdolna, egyetemi adjunktus

DOI:10.14753/SE.2022.2680

EPIDEMIOLOGIC FEATURES OF MULTIPLE SCLEROSIS IN HUNGARY, BASED ON ADMINISTRATIVE HEALTHCARE DATA

PhD thesis

Anna Iljicsov

János Szentágothai Neurosciences Doctoral School

Semmelweis University

Supervisor:	Magdolna Simó, MD, Ph.D
Official reviewers:	Andrea Mike, MD, Ph.D
	András Terebessy, MD, Ph.D
Head of the Complex Examination Committee:	Lilla Reiniger, MD, Ph.D
Members of the Complex Examination Committee:	Judit Áfra, MD, Ph.D
	Zoltán Hidasi, MD, Ph.D

Budapest

2022

DOI:10.14753/SE.2022.2680

Table of contents

DOI:10.14753/SE.2022.2680

List of abbreviations

ATC = Anatomical Therapeutic Chemical classification system

BPPV = benign paroxysmal positional vertigo

CIS = clinically isolated syndrome

DMD = disease-modifying drug

ICD-10 = International Classification of Diseases, 10th edition

NHIF = National Health Insurance Found

NMOSD = neuromyelitis optica spectrum disease

MS = multiple sclerosis

PSP = progressive supranuclear palsy

DOI:10.14753/SE.2022.2680

1. Introduction
(with the scientific background and relevant literature)

Multiple sclerosis (MS) is a chronic demyelinating and degenerative disease of the central nervous system with supposed autoimmune origin. Typically it is diagnosed in adults aged 20-40 years, meaning that patients have to live with this condition for decades and struggle with its challenges for example in employment, and family planning. Even using modern, effective disease-modifying drugs (DMDs), primary or secondary axonal degeneration may lead to irreversible physical, psychical and cognitive disability with a negative impact on mobility, independence, quality of life and productivity of patients.

In MS Barometer 2020 [1], published by European Multiple Sclerosis Platform, it is reported that MS affects almost 1.2 million people in Europe. In this survey substantial inequalities were confirmed even among European countries, for example regarding the use of DMD treatment and rate of MS-patients with employment. According to numerous recent studies, the prevalence of MS increases in every world region [2; 3] due to various plausible factors discussed below. Thus, from 2013 to 2020 the estimated number of MS-patients has increased from 2.3 million to 2.8 million, mirroring a rise in global prevalence (29.3/100.000 in 2013 versus 43.9/100.000 in 2020), but significant differences are found among regional rates of prevalence, incidence and sex-ratio of MS. The better knowledge about regional epidemiologic features and trends also can help to understand the still ambiguous role of various environmental and genetic factors in the pathomechanism of the disease.

Long-term treatment and complex management of MS is a burden for the health care system, social services and caregivers as well [3; 4; 5]. Given the rapidly evolving scene of costly immunomodulatory drugs, optimal allocation of resources and planning of health services require accurate data on the number and age-distribution of patients affected by the disease.

DOI:10.14753/SE.2022.2680

2. Objectives

Given the absence of nationwide MS-registry, in Hungary only regional studies were conducted on the epidemiology of MS until 2020 [6-13]. Therefore, we aimed to describe prevalence, incidence and age-distribution of patients living with MS in the whole country. We have analyzed anonymized administrative data supplied by the National Health Insurance Fund (NHIF). This method has its advantages, like that it represents practically the total population, it is cost-effective and the registered data are standardized. Its limitations include the risk of suboptimal data quality and lack of detailed clinical information on subjects. However, we believe that at present date the analysis of health claim data gives the best estimation of incidence and prevalence of MS in Hungary.

Studies working with administrative data for nationwide estimations of epidemiologic features of different diseases are more and more common (regarding MS, see details in Discussion), but methodology for case ascertainment is variable, mostly depending on the type, content and extent of available datasets. Therefore, even previously published methods have to be adapted and preferably validated for the actually researched databases. Indeed, we have first developed and validated a case definition of „administrative MS-patient" – I present this work in the first part of this thesis in chapters Methods and Results. Our methodology has been already published [14]. Applying this administrative case definition on the NEUROHUN database and an independent database of pharmacy dispension, we could estimate the number of incident and prevalent MS-patients, as well as ratio of patients treated with immunomodulatory drugs and trends of their changes between 2010-2015. These epidemiologic features also have been published [14]. Finally, it made possible the analysis of sex- and age-distribution of people living with MS in Hungary, and its changes during a decade. These results have been recently published as well [15].

In this thesis I intend to give an insight and summary of this ongoing research about epidemiology of MS in Hungary, using a new approach: analysis of health claim data. The contain of this thesis is based on the two already published studies mentioned above [14; 15].

DOI:10.14753/SE.2022.2680

3. Methods

Briefly, our first step was establishing an administrative case definition of MS and validating it on a cohort of consecutive patients of the Department of Neurology, Semmelweis University, Budapest. After showing a high concordance between administrative and clinical classification of non-MS and MS-patients, as well as excellent specificity and sensitivity, this case definition was applied on the nationwide database and thus we could determine the number of MS-patients yearly, and calculate prevalence and incidence of MS in Hungary each year during the observational period. We have also analyzed the changes in age-distribution of prevalent and incident patients during these years. An independent database of drug refills between 2010-2016 was merged with the healthcare utilization database, with a linkage of subjects by their unique pseudonymized number. It made possible the examination of drug refilling history of administrative MS-patients.

3.1 Features of healthcare system of Hungary

In Hungary the total resident population (almost 10 million persons) receive health care coverage through the country's universal, single-payer state health insurance system. Each individual is assigned at birth a unique nine-digit number (social security identifier) for lifetime, and all public healthcare services include the registration and use of this number for personal identification. Service providers are obliged to submit reports each month for reimbursement purposes to the NHIF, which is responsible for archiving and processing of these electronic data.

People living with MS can receive complex management in one of the cca. 35 MS-centers of Hungary, and importantly, the prescription of MS-specific disease-modifying drugs is exclusively authorized for neurologists affiliated to one of these centers. It has to be mentioned here that NHIF restricts reimbursement of DMDs to clinically definite MS, therefore in Hungary their prescription with financial support is not possible in clinically or radiologically isolated syndrome.

3.2 Setting of database

We have studied the NEUROHUN database that captures data submitted to the NHIF by healthcare providers with contract – including all public and contracted private hospitals

and outpatient specialist services –, from 2004 to 2016. For each individual, the anonymized database contains basic patient features (year of birth, gender, postal code of residence) and data on all hospitalizations, all outpatient specialist care or diagnostic services used during the observational period. Of note, it does not include reports of general practitioners, which are submitted separately to the NHIF. If a person died during the observational period, the date of death was provided by the Central Statistical Bureau of Hungary and linked to the subject.

For each submitted claim towards the NHIF the provider has to declare the date of care, the specialty and institution of provider and at least one diagnosis using the 10th International Classification of Diseases (ICD-10) codes. NEUROHUN database captures all primary (for hospitalized inpatients and outpatients) and all secondary diagnoses (for hospitalized inpatients) reported for each claim.

More specifically, the NHIF provided anonymized data on all individuals, who has received at least once a neurological or cerebrovascular diagnostic code between 1st January 2004 and 31st December 2016 (for detailed list of queried diagnoses, see APPENDIX 1). This database (called NEUROHUN version 1) contained healthcare consumption data of 4.29 million subjects. Of them, we have identified all subjects who were given at least once the diagnostic code assigned for MS (G35) as primary or secondary diagnosis. It resulted an "MS-database" of nearly 34,400 subjects.

An independent database of outpatient pharmacy refills was also provided by NHIF, with a notable difference in the covered time interval: only from 1st January 2010 to 31st December 2016. It contains the commercial name, the chemical name, the ATC code and the amount of the prescribed drug, the ICD-10 code of the indication (limited to one single diagnosis), the specialty of the prescribing physician and the date of refill. These data are linked to the patient. The database does not cover over-the-counter medication use.

The protection of personal data was guaranteed, since the NHIF had centrally anonymized the original social security identifiers before providing this database for research. This encrypted identifier was used for record linkage between the clinical and pharmacy databases. The studies were performed after the approval of the Ethics Committee of Semmelweis University, Budapest (Approval No: SE TUKEB 88/2015), and data were handled in accordance with personal data protection regulations.

3.3 Criteria of administrative case definition

A unique code (G35) is assigned for multiple sclerosis in ICD-10, which is widely used in clinical practice. In Hungary, it is the only code authorized to be indicated on prescriptions of DMDs.

Marrie et al. were among the first authors who had published on validity of different case-definitions of MS using regional administrative data [16]. As NEUROHUN database and their database didnot cover exactly the same sources of informations (for example reports of general practitioners), we had to adapt and modify their case definition. Our primary aim was to have high specificity, so that the „administrative MS-patients" would be almost surely really MS-patients. Therefore, even at the cost of probably excluding some „real MS-patients" we have established a rather strict administrative case definition of MS. Thus, we considered an individual as a person living with MS if he or she had fulfilled all of the following 3 criteria:

i) between 2004 and 2016 receiving the ICD-10 diagnostic code of MS (G35) at least 3 times meaning 3 separate medical contacts. The registration of G35 could have happened either as inpatient or outpatient in any of the hospitals or any outpatient services of the country. Of note, we have ignored when diagnosis had been given on the occasion of laboratory, imaging, pathology or other diagnostic services used, because in these cases the pre-coded diagnosis might be only a suspected one (that justifies examination).

ii) at least one of the above mentioned ≥3 claims for MS was submitted by a neurologist, ie. registered during hospitalization on a neurology ward or on an occasion of using neurological outpatient care. This criterion was intended to confirm the diagnosis.

iii) during the observational period, receiving G35 codes in at least 2 different calendar years that can be consecutive or not. Hereby, we aimed to exclude those individuals who had been examined for suspected MS which was finally ruled out.

Of those 34,400 persons who had at least once received the code of MS, we excluded the occasions when G35 was given when laboratory, imaging, pathology or other diagnostic services were used, see first criterion. Of the remaining 30,238 individuals only 48% (14,437) fulfilled all the three administrative criteria and are therefore considered as MS-patients. The numbers of people who fulfil 0 or 1 or 2 or 3 criteria are shown on **Figure 1**. It also

demonstrates that 90% of subjects had been given a G35 diagnostic code at least once by a neurologist. The other two criteria, ie. number of submitted G35 code (16.700 subjects) and in 2 separate calendar years (15.875 subjects) are true for the 48% and 46% of them, respectively.

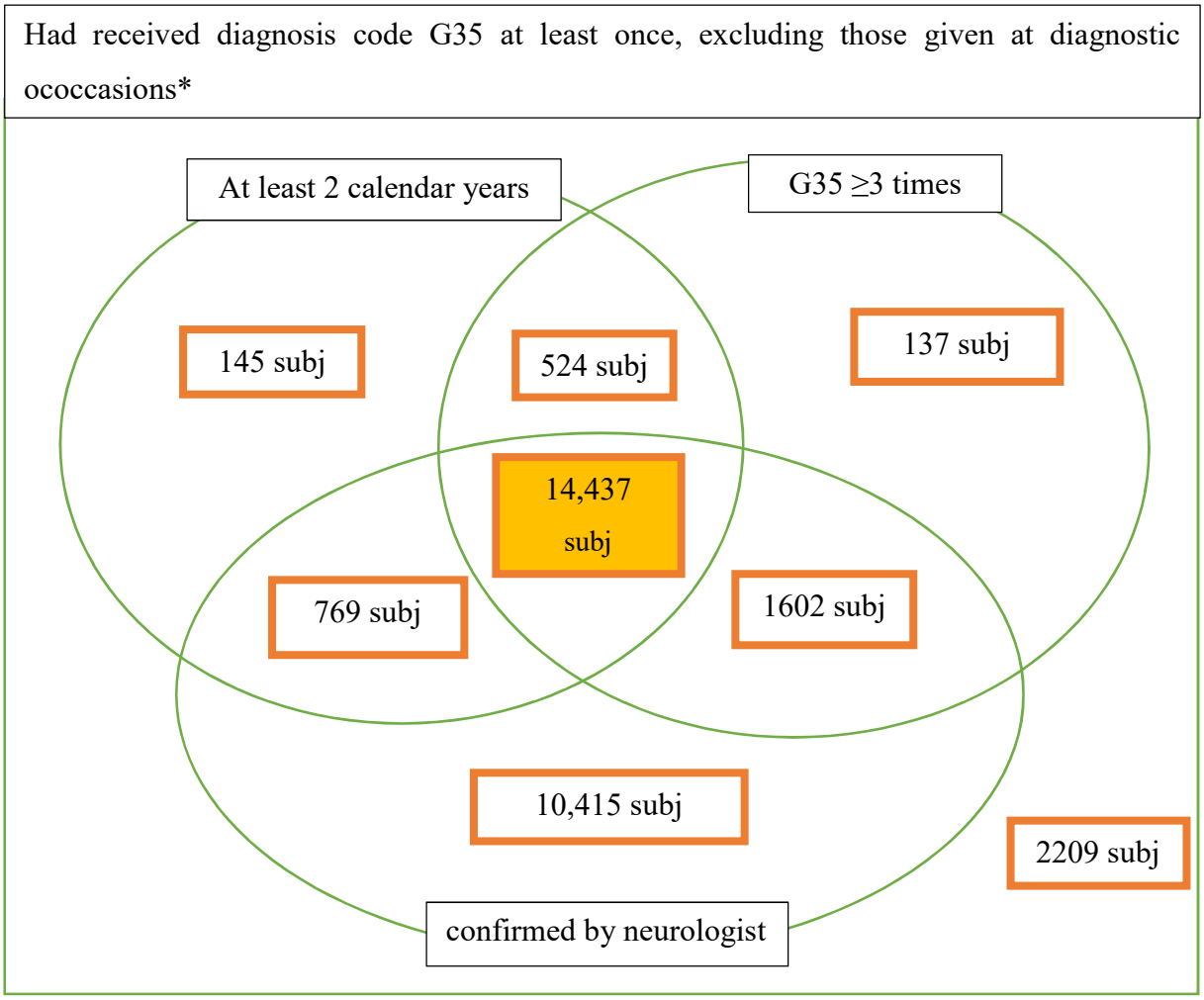


Figure 1. The subjects in the „MS-database" with the number of people fulfilling 1, 2 and 3 criteria of the administrative MS-case definition.

** diagnostic occasion: G35 diagnosis code was submitted when laboratory, imaging, pathology or other diagnostic services used, see first criterion*

3.4 Validation of administrative case definition with calculation of sensitivity and specificity

Before using it for epidemiological estimations, we performed the validation of the administrative case definition: we compared the concordance between administrative MS-cases and clinical diagnosis in medical documentation held by our department.

We had randomly chosen two 2-month-long periods (from 1st May 2011 to 30th June 2011, and from 1st May 2014 to 30th June 2014) from the observational period of the database. Using an automatized search in the integrated hospital healthcare IT system of our University (MedSol) we identified all subjects who were managed during that four months at our neurological department and were given an ICD-10 code of MS. We have included in the search all inpatient and outpatient services of our department, except for diagnostic (electrophysiology, ultrasound) and paramedical (physiotherapy, neuropsychology) services.

The second step was to find those anonymized individuals in the NEUROHUN database whose claim was submitted by our neurological services during the time periods in question and received a diagnostic code of G35. Then, we attempted to find a match of our patients (whose neurological documentation is held by Semmelweis University, Budapest), with one subject in the anonymized administrative database by their admission and discharge date, sex, year of birth, and service provider code.

When successful match occured, the clinical diagnosis of each patient was verified by reviewing their medical documents. A patient was considered as having MS when the McDonald criteria of 2005 [17] were fulfilled until the end of the observational period (31th December 2016). Using a later set of MS-diagnostic criteria (of 2010 [18] or 2017 [19]) might have resulted a higher number of „true" MS-patients, but would have possibly interfered retrospectively with the submitted code of diagnosis. When our medical documentation did not contain enough clinical data or the results of the ancillary examinations for establishing definitive diagnosis of MS, we considered the subject not having MS even if clinical data suggested it or G35 code was registered.

The third phase was the application of our administrative MS case definition on all subjects above so that we could see if their administrative and clinical diagnosis are concordant or not. Using medical documentation as gold standard, we considered a patient „true positive" when both clinical and administrative diagnoses were MS; „true negative" if administrative criteria were not fulfilled and clinical diagnosis was other than MS or MS could not be

confirmed; „false negative" if clinical diagnosis was MS but administrative case definition was not fulfilled; and „false positive" if final clinical diagnosis was other than MS but administrative case definition was fulfilled. The sensitivity and positive predictive value of the administrative case definition were defined with the help of the groups above.

On the other hand, the calculation of specificity of our case-definition needed a different approach, given the low proportion of non-MS patients. This latter feature is explained by the fact that we were examining those consecutive patients, who had received at least once the diagnosis of G35 in a given period, and thus are at risk of having MS. We had planned to make a second validation on 300 consecutive patients without the restriction of having or not having received the code of G35, but it would have been impossible to state firmly on the absence of MS in their case, as we do not have access to the medical documentation of other institutions where they could have been followed for MS. Thus, in case of those patients, who appear in the anonymous database with G35 code in one or two occasions, but not fulfilling our administrative case definition and not seen in our department for this condition, we could not decide if they are true positive or true negative cases. To solve this problem, we have applied the administrative method used by Bezzini et al. [20] after making some necessary modifications on it. For the test of specificity, we first created a new administrative cohort of individuals (referred as „true negative reference") who were presumably not affected by MS. This cohort was derived from the full NEUROHUN database including 4.29 million subjects and defined by: never undergone cranial nor spinal cord MRI, and never received prescription of any drug with the code of G35 between 2004-2016. Then, we linked this „true negative reference" cohort with those subjects who fulfilled our administrative case definition of MS (14.437 individuals) and analyzed the number and proportion of overlapping subjects who are considered as being false positive. Worth of note, that this method is not applicable for calculation of sensitivity, because the number of false negative patients cannot be determined. It is also important to mention that calculation of specificity and sensitivity was performed on different populations due to the above discussed feasibility issues.

3.5 Search in pharmacy database

Pharmacy dispension data are available between 2010-2016. Two queries were performed: first, all subjects were identified each year who have at least once received any pharmacy refill prescribed with a diagnosis code of G35. A second search in the database identified those subjects who had at least one pharmacy refill for any of the DMDs available

in those years in Hungary: intramuscular interferon-beta-1a (Avonex), subcutaneous interferon-beta-1a (Rebif), interferon-beta-1b (Betaferon, Extavia) and glatiramer-acetate (Copaxone), oral dimethyl-fumarate (Tecfidera), fingolimod (Gilenya) and teriflunomide (Aubagio), intravenous natalizumab (Tysabri) and alemtuzumab (Lemtrada). Finally, with the help of the same encrypted identifier, pharmacy refill records were linked to claims of medical service providers.

3.6 Incidence, prevalence, age-distribution

The date of the first medical inpatient or outpatient contact when ICD-10 code G35 was assigned as primary or secondary diagnosis was considered to be the date of establishing diagnosis of MS. Patients were counted as incident cases for that year and prevalence was calculated as incident cases added to prevalent cases from the previous year, after subtracting patients who died during the year.

As a consequence of the setting of our database, those patients who had been diagnosed with MS before 2004 would also – wrongly – appear as incident cases at the time of their first medical encounter for MS between 2004-2016. In order to reduce this bias, we allowed a 6-year „run-in" period when incidence data (and prevalence data derived from it) were not taken into account for final analysis, and assumed that all people already living with MS before 2004 would use a medical service at least once during these years. Thus, incidence data beginning from 2010 would be considered precise and include only „real" new patients and could be compared with available pharmacy refill data.

It also has to be noticed, that our 3rd administrative criteria of MS requires claims in 2 separate calendar years. Therefore, those patients who first received G35 code in the last year of observation (2016) administratively would not appear as MS patients, even if they turn to be „real" MS patients in subsequent years. Thus, incidence rate is not applicable for 2016 and might be underestimated in the last 2-3 years of the observational period, so for statistical analysis of incidence and prevalence, we have used only data between 2010-2015.

When we estimated changes in average age of people living with MS and their age-distribution, the correlation with pharmacy refill data was not used and we had supposed that subtle changes would manifest during longer observation period. Therefore we were more permissive with the „run-in" period and ignored only the first 3 years' incidence data, so calculations of trends of age of incident patients were made on data between 2007-2015. As the number of prevalent subjects outnumber that of incident cases by 15-20-fold, and

prevalence data are more reliable in our setting of database than incidence data, the age and age-distribution of prevalent patients were analyzed for the whole observational period.

However, even with the possible methodological bias discussed above, we are persuaded that our calculations are meaningful and important. To present the whole picture, the number of incident and prevalent patients, crude incidence and prevalence rates of 2004-2009 and 2016 are available as well in APPENDIX 2. and age-distribution of prevalent patients will be also discussed below between 2004-2016.

We estimated the annual crude incidence and prevalence per 100,000 inhabitants (for women, men and both sexes), with the help of corresponding data of the latest nationwide census in 2011 [21] as denominators. Using the direct standardization method, these results were also age-adjusted to the European Standard Population of 2013 [22; 23] in order to present standardized incidence and prevalence rates.

3.7 Statistical analysis

When calculating confidence intervals for the prevalence and incidence rates we used the gamma distribution [24; 25]. The significance of the trends of changes of incidence, prevalence and DMD-utilisation rates was tested with linear regression. When analyzing changes of average age of prevalent and incident MS-patients, we used multiple linear regression modell to test what impact have the passing years and male/female gender in interaction on these values.

In each modell, *p*-value was considered significant if ≤ 0.05. The goodness of fit of all linear regression models was tested with the Shapiro-Wilks test of normality. The calculations were conducted with the R programming language (version 3.6.2 and 4.0.2) using packages “epitools” and “asht”.

DOI:10.14753/SE.2022.2680

4. Results

4.1 Validation of administrative case definition

With a computed search in the hospital IT-system (MedSol) we have identified 42 cases of inpatients (25 cases in 2011 May-June and 17 in 2014 May-June, altogether 40 individuals) and 517 cases of outpatients (231 cases of 166 subjects in 2011 May-June and 286 cases of 204 subjects in 2014 May-June, representing 291 individuals) who had received at least once the billing code of G35 in primary or secondary position. We found one inpatient in MedSol and one subject in the NEUROHUN who could not been perfectly matched with any individuals of the other database. We still suspect that these two are the same person, only the year of birth was mistaped in MedSol, as all other parameters including dates of medical encounters are matching. Of note, the subject in NEUROHUN is not fulfilling our case-definition of MS and the medical documentation of the subject of MedSol reveals seronegative neuromyelitis optica spectrum disease (NMOSD) as diagnosis. We excluded these patient(s) from validation analysis.

As there is an overlapping between in- and outpatients, altogether we have identified 309 individuals who had received the billing code of G35, summarized in **Table 1**. (published also in paper by Iljicsov et al [14]). The ratio of concordance between administrative and medical diagnosis is as follows: 275 MS-patients (89%) correctly fulfil our case definition; 15 patients having other medical conditions correctly do not fulfil our case definition. Interestingly, one of them had a second neurological attack in 2017 with fulfilling „McDonald criteria 2005" and becoming MS-patient after observational period. One MS-patient did not fulfil our third administrative criterion in NEUROHUN as he received the code G35 more than 3 times only in one single calendar year, which indicates that he discontinued medical follow-up for his condition not only in our center but in the whole public health care. He can be considered as "false-negative". Eighteen subjects (5,8%) were identified who were administratively classed as MS ("false-positive" cases) but medical documentation revealed an other illness (usually after initially considered as MS) or examinations are not completed or missing in the records that makes diagnosis of MS impossible to determine for us. Altogether, the sensitivity of our administrative case definition (true positives / [false negatives + true positives]) is 99%. Its positive predictive value (true positive / [true positive+false positive]) is 94%.

Table 1. Summary of patients managed in our department and received G35 in any diagnosis position during May-June 2011 and May-June 2014 – published originally in [14].

ALL: 309 patients	**medical documentation states MS (*percentage*)**	**medical documentation is not decisive or states another diagnosis (*percentage*)**
administrative case definition of MS is fulfilled	275 (*89%*)	18 (*5.8%*) (5 NMOSD, 1 neurodegeneration with brain iron accumulation, 2 small vessel disease, 1 leukodystrophy, 2 not organic symptoms, 1 PSP, 1 polyneuropathy, 1 Pompe-disease, 1 unknown white matter disease with epilepsy, 3 patients not completing examinations)
administrative case definition of MS is NOT fulfilled	1 (*0.3%*)	15 (*4.9%*) (1 CIS who will be MS in 2017, 1 BPPV, 1 unilateral abducent nerve palsy, 1 Leber's optic neuropathy, 1 partial epilepsy, 2 not organic symptoms, 1 cerebral vasculitis, 1 Bell's palsy, 1 myelitis transversa, 1 cervical disc herniation, 1 paraesthesia of lower limbs, and 3 patients not completing examinations)

BPPV: benign paroxysmal positional vertigo; MS: multiple sclerosis; NMOSD: neuromyelitis optica spectrum disease; PSP: progressive supranuclear palsy.

In this sample of 309 subjects – due to the criteria of the selection – the number of „true and false negative" patients is certainly low (5%), therefore the calculation of specificity with the help of these groups would have been misleading. Instead, we have created an administrative „true negative reference cohort" as discussed above in Methods. The number of individuals, who have never undergone cranial nor spinal MRI and have never had prescription of any drugs for MS between 2004-2016 turned out to be 3,223,001. This cohort was then linked to the cohort of administrative MS-patients: of 14437 subjects 1023 (7%) were overlapping and thus regarded as false positive. Thus, the specificity of the case definition (true negative / [true negative + false positive]) is >99%.

4.2 Crude and standardized prevalence between 2010-2015

Altogether 14,437 people met our administrative case definition of MS between 2004 and 2016. As discussed above, when calculating prevalence and incidence, for methodological reasons we allowed a 6-year-long "run in" period and not considered data until 2010 and those of 2016. The number and gender distribution of incident and prevalent cases between 2010 and 2015 are shown in **Table 2**., as well as crude and adjusted prevalence rates for men, women and in total. During that period, the annual crude prevalence of MS has increased continuously from 109.3/100,000 to 130.8/100,000, mirroring a rise from 150.8/100,000 to 179.5/100,000 among women and from 63.3/100,000 to 76.8/100,000 among men. These growing trends were significant (*p*-value of linear regression model <0.05 for all the three datasets). The ratio between women and men living with MS remained invariably 2.6 during these years.

Using the EU2013 standard European population as reference, age adjusted standardized prevalence of MS in Hungary has gradually increased from 105.2/100,000 (147.3 for women and 60.3/100,000 for men) in 2010 to 127.2/100,000 (175.6 for women and 74.7/100,000 for men) in 2015. These positive trends were significant (*p*-value <0.05).

Table 2. Crude and age-adjusted standardized prevalence of MS in Hungary between 2010 and 2015. Data originally published in [14] but in other format.

	Number of incident cases (women / men)	Nr. of preva-lent cases (women / men)	Woman /man ratio of preva-lent cases	Total crude preval *(95% CI)*	Crude preval. among women *(95% CI)*	Crude preval. among men *(95% CI)*	Age-adjusted standar-dized preval., total *(95% CI)*	Age-adjusted standardized prevalence, women /men *(95% CI)*
2010	703 (500/ 203)	10859 (7872/ 2987)	2.6	109.3 *(107.2-111.4)*	150.8 *(147.5-154.2)*	63.3 *(61.1-65.6)*	105.2 *(103.2-107.3)*	147.3 / 60.3 *(144.0-150.6) / (58.1-62.5)*
2011	616 (429/ 187)	11338 (8206/ 3132)	2.6	114.1 *(112.0-116.2)*	157.2 *(153.9-160.7)*	66.4 *(64.1-68.7)*	109.9 *(107.9-112.0)*	153.3 / 63.4 *(150.0-156.7) / (61.1-65.7)*
2012	653 (446/ 207)	11809 (8543/ 3266)	2.6	118.8 *(116.7-121.0)*	163.7 *(160.2-167.2)*	69.2 *(66.9-71.6)*	114.6 *(112.5-116.7)*	159.6 / 66.3 *(156.2-163.0) / (64.0-68.7)*
2013	625 (434/ 191)	12234 (8857/ 3377)	2.6	123.1 *(120.9-125.3)*	169.7 *(166.2-173.3)*	71.6 *(69.2-74.0)*	119 *(116.9-121.2)*	165.6 / 68.9 *(162.2-169.1) / (66.5-71.3)*
2014	592 (389/ 203)	12634 (9113/ 3521)	2.6	127.1 *(124.9-129.4)*	174.6 *(171-178.2)*	74.6 *(72.2-77.1)*	123.4 *(121.2-125.6)*	170.7 / 72.2 *(167.2-174.3) / (69.8-74.3)*
2015	538 (375/ 163)	12993 (9369/ 3624)	2.6	130.8 *(128.5-133.0)*	179.5 *(175.9-183.2)*	76.8 *(74.3-79.4)*	127.2 *(125.0-129.4)*	175.6 / 74.7 *(172.0-179.2) / (72.2-77.2)*
[a]*p*-value	N.A.	N.A.	N.A.	<0.001*	<0.001*	<0.001*	<0.001*	<0.001* / <0.001*

Crude prevalence: number of living patients/100,000 inhabitants. Age standardization was performed using the 2013 European standard population and expressed as rate/100.000 population.

*[a]p-value: p-value of trend significance test using linear regression. The p-value ≤0.05 was considered significant and is marked with asterisks**

N.A.: not applicable; Nr: number; CI: confidence interval; preval: prevalence.

Gamma confidence intervals were created using R version 3.6.2 with package "epitools". The method for crude rates is based on Daly [24] and for standardized rates is based on Fay & Feuer [25].

4.3 Crude and standardized incidence between 2010-2015

On the other hand, the number of incident cases as well as crude total incidence has declined (the latter from 7.1/100,000 in 2010 to 5.4/100,000 in 2015, *p*-value=0.018) with a smaller rise in 2012. The Shapiro-Wilks test indicated that linear models for the total crude incidence trend analysis may be inappropriate (*p*-value <0.05), thus results related to this model should be interpreted with caution. The crude incidence for women has also diminished from 9.6/100,000 to 7.2/100,000, showing a negative significant trend (*p*-value <0.05) together with the crude total incidence. The incidence among men has changed from 4.3/100,000 to 3.5/100,000, but the trend was not significant. Yearly data are shown in **Table 3**.

As for age adjusted standardized annual incidence of MS, it remained quite stable among men between 2010 and 2014 (3.7-3.9/100,000) and slightly diminished only in 2015 (3.1/100,000), without showing a significant trend. For age-adjusted standardized incidence among women we could observe a significant negative trend (*p*-value=0.0125) with a slow decline from 9.5/100,000 in 2010 to 7.1/100,000 in 2015. The standardized incidence for both sexes was 6.7/100,000 in 2010, then decreased in 2011, followed by a rise in 2012 and a gradual diminution afterwards to reach 5.1/100,000, altogether representing a significant negative trend (*p*-value=0.016). However, the Shapiro-Wilks test indicated that linear models for the total age-adjusted standardized incidence trend analysis may be inappropriate (p<0.05), thus results related to this model should be interpreted with caution.

Table 3. Crude and age-adjusted standardized incidence of MS in Hungary. Data originally published in [14] but in other format.

	Number of incident cases (women/ men)	Woman/ man ratio of incident cases	Total crude incidence *(95%CI)*	Crude incidence among women *(95% CI)*	Crude incidence among men *(95% CI)*	Age-adjusted stand. incidence, total *(95% CI)*	Age-adjusted stand. incidence, women / men *(95% CI)*
2010	703 (500/203)	2.5	7.1 *(6.6-7.6)*	9.6 *(8.8-10.5)*	4.3 *(3.7-4.9)*	6.7 *(6.2-7.2)*	9.5 / 3.9 *(8.7-10.4) / (3.4-4.4)*
2011	616 (429/187)	2.3	6.2 *(5.7-6.7)*	8.2 *(7.5-9)*	4.0 *(3.4-4.6)*	5.9 *(5.4-6.4)*	8.1 / 3.7 *(7.4-8.9) / (3.2-4.3)*
2012	653 (446/207)	2.3	6.6 *(6.1-7.1)*	8.6 *(7.8-9.4)*	4.4 *(3.8-5.0)*	6.2 *(5.7-6.7)*	8.5 / 3.9 *(7.7-9.3) / (3.4-4.5)*
2013	625 (434/191)	2.3	6.3 *(5.8-6.8)*	8.3 *(7.6-9.1)*	4.0 *(3.5-4.7)*	6 *(5.5-6.5)*	8.2 / 3.7 *(7.5-9) / (3.2-4.3)*
2014	592 (389/203)	1.9	6.0 *(5.5-6.5)*	7.5 *(6.7-8.2)*	4.3 *(3.7-4.9)*	5.7 *(5.2-6.2)*	7.4 / 3.9 *(6.7-8.2) / (3.4-4.5)*
2015	538 (375/163)	2.3	5.4 *(5.0-5.9)*	7.2 *(6.5-8.0)*	3.5 *(2.9-4.0)*	5.1 *(4.7-5.6)*	7.1 / 3.1 *(6.4-7.9) / (2.7-3.7)*
p-value[a]	N.A.	N.A.	0.018276*	0.011609*	0.258283	0.015974*	0.012586* / 0.222197

Crude incidence: new patients/100,000 inhabitants/year. Age standardization was performed using the 2013 European standard population and standardized incidence is expressed as rate/100,000 population.

*[a]p-value: p-value of trend significance test using linear regression. The p-value ≤0.05 was considered significant and is marked with asterisks**

CI: confidence interval; stand: standardized.. Gamma confidence intervals were created using R version 3.6.2 with package "asht". The method for crude rates is based on Daly [24] and for standardized rates is based on Fay & Feuer [25].

4.4 Age distribution of MS patients between 2004-2016

We have examined the average age and age-distribution of prevalent and incident patients in each calendar year. During the calculations of trends of changes, we have ignored the first three years' incidence results because of methodological reasons, as discussed above in Methods.

We used multiple linear regression model to analyze the effect of calendar years and gender in interaction on the age of prevalent patients, shown in **Table 4**. We found that each year, female prevalent subjects are older compared to male patients, by 6 months on average (this difference is significant with *p*-value = 0.002). Also, between 2004-2016 the average age of male prevalent subjects increased by 0.22 year, ie. by 2.5 months by calendar year (significant change, *p*-value <0.001), and the average age of female prevalent patients grew even more rapidly, by 0.32 year per calendar year (the difference between the two genders is significant with *p*-value <0.001). The Shapiro-Wilk test did not indicate problems with the goodness of fit of the model (*p*=0,265).

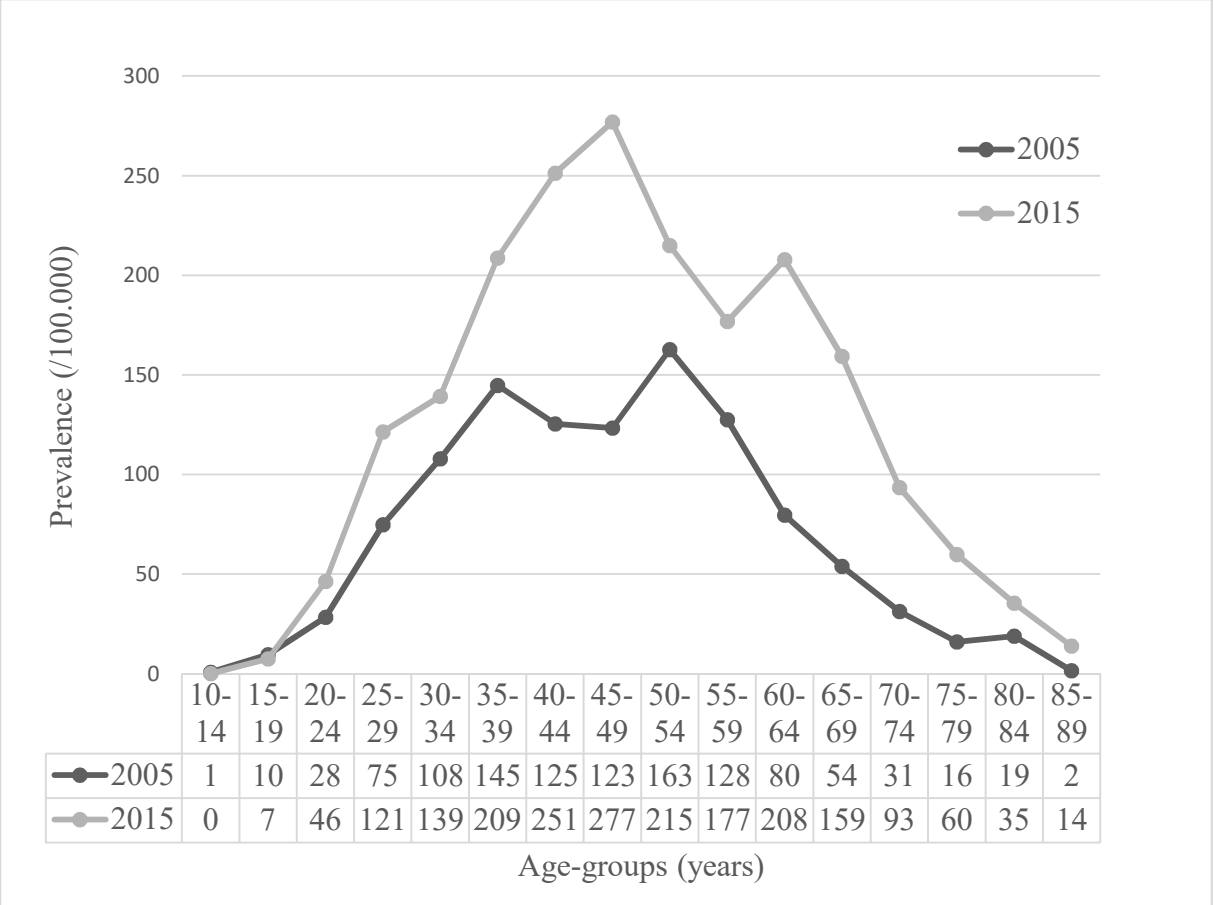
Table 4. Average age of prevalent and incident MS-patients between 2004-2016 – originally published in Hungarian version in [15]

Year	Average age of prevalent cases (year)			Average age of incident cases (year)		
	men	women	total	men	women	total
2004	44,29	45,05	44,84	*44,29*	*45,05*	*44,84*
2005	44,65	45,41	45,20	*42,10*	*42,75*	*42,56*
2006	45,00	45,69	45,50	*41,98*	*41,13*	*41,37*
2007	45,18	45,97	45,75	39,90	40,56	40,37
2008	45,51	46,24	46,04	40,15	39,31	39,54
2009	45,54	46,56	46,28	37,38	39,26	38,68
2010	45,66	46,78	46,47	36,68	37,63	37,35
2011	46,07	47,13	46,83	40,04	38,51	38,98
2012	46,08	47,46	47,05	36,24	38,02	37,46
2013	46,24	47,74	47,33	36,92	38,20	37,80
2014	46,45	48,06	47,61	37,44	37,68	37,60
2015	46,80	48,40	47,95	37,21	37,54	37,44
2016	47,39	49,17	48,68	NA	NA	NA
p-value	Difference between genders: 0,002*		Increase: Men: <0,001* Women compared to men: <0,001* Together: <0.001*	Difference between genders: 0,118		Decrease: Together: <0,001* (no difference between genders)

*NA: not applicable. The p-value ≤0.05 was considered significant and is marked with asterisks**

For trend calculations, incidence data of 2004-2006 (marked in ithalic) were not taken into account for methodological reasons detailed in Methods.

Besides these linear trends, other changes of age-distribution can also be observed: when divided into five-year age groups, an increase of prevalence rate is found in each group, except for childhood intervals, see **Figure 2**. Age-specific prevalence rate used to be the highest among persons aged 50-54 in 2005, while peak prevalence is reached in the group of 45-49 aged subjects in 2015. Our data also suggest that at the same time the most populous age groups shift towards the younger intervals: after 2010, those below 44 years have the most subjects, instead of 50-54 year-old prevalent patients seen between 2004-2009 (data not illustrated separately).



	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85-89
2005	1	10	28	75	108	145	125	123	163	128	80	54	31	16	19	2
2015	0	7	46	121	139	209	251	277	215	177	208	159	93	60	35	14

Figure 2. Prevalence rates in different age-groups in 2005 and in 2015

Note: prevalence rates of 2005 were calculated using population data of 2001 census, while prevalence rates of 2015 were calculated using population data of 2011 census.

The density (relative frequency) of the female and male populations of all ages (in years) between 2004-2016 is illustrated in **Figure 3**. It shows that at the same time, the proportion of elder patients has grown as well: for example in 2004, the rate of 70-year-old subjects was around 0.5%-0.5% among prevalent female and male patients, respectively, while it increased to around 1%-1% by 2016. Also, while in 2004 we could identify 336 persons living with MS above age of 65 years (5.7% of prevalent cases), later in 2010 they were 945 (8.7% of prevalent cases), and in 2015 their number was 1537, accounting for 11.8% of prevalent patients in Hungary. This rise of proportion is significant (p-value of linear regression model is <0.001).

Concerning the average age of incident patients, between 2007 and 2015 we have observed a significant decrease of 4 months/year (p-value <0.001) without difference between male and female subjects.

DOI:10.14753/SE.2022.2680

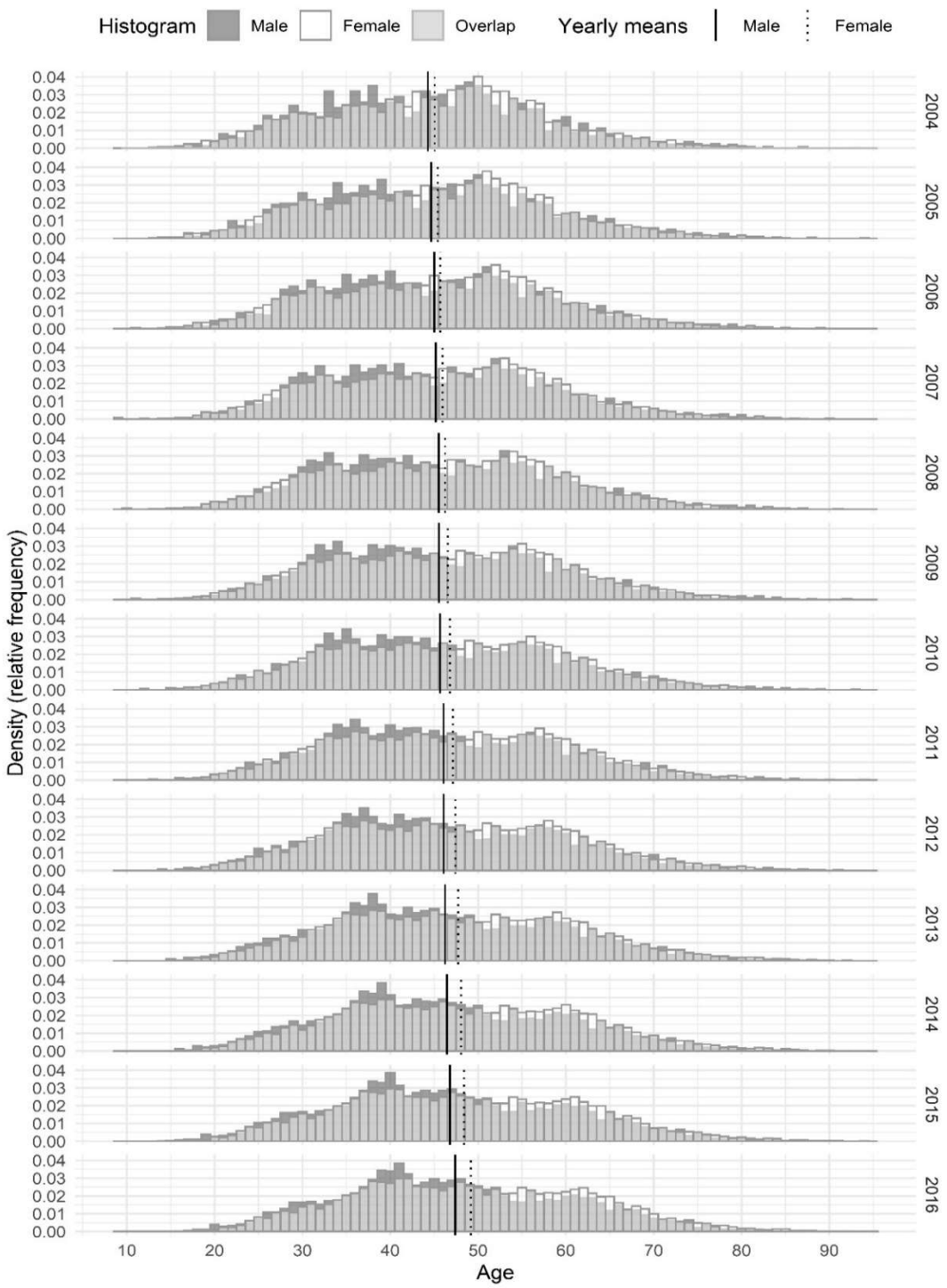


Figure 3. Mean age and prevalence-density of MS-patients, per calendar year and sex - originally published in Hungarian version in [15]

Explanation: X-axis: ages of prevalent patients in years; Y-axis: density (relative frequency) of prevalent patients per calendar year and sex. The average age in years of male and female prevalent patients per calendar year are indicated by solid and dotted lines, respectively.

4.5 Drug dispension data between 2010-2015

Pharmacy dispension data are not containing over-the-counter drugs and were available from 2010 to 2016, but since in the last year the number of incident (and probably also of prevalent) patients is biased due to our administrative case definition, we merged and analyzed only data between 2010-2015, see **Table 5**. During these years, the number of patients who refilled any medication with an indication for MS – i.e. with a diagnosis code of G35 on the prescription – has increased markedly (from 6162 to 7399). Of them, the number of those individuals who do not fulfil our case definition of MS stays quite stable (around 800) in these 6 years. It should be noted that family doctors and any specialist can prescribe drugs with the diagnosis code of G35, but some of these medicines are only reimbursed when prescribed by a neurologist (disease modifying drugs) or a family doctor on the recommendation of a neurologist.

We investigated for each year between 2010 and 2015 the number of those subjects who have at least once refilled any of the 11 DMDs listed earlier (second coloumn of **Table 5.**). These drugs being specifically used for MS, these individuals were therefore considered as MS patients by the prescribing neurologist. The number of DMD-treated patients has nearly doubled from 2010 until 2015 (from 2089 to 3808). We also considered the number of previously treatment-naive, newly DMD-treated patients: those who first refilled DMD in the observed year (**Table 5. fourth column**). For methodological reasons detailed below Table 5., in 2010 all treated subject will appear as new so this number is not valid. In further years, after a high number in 2011 we observe a drop in 2012 and 2013, followed by a rise in 2014. These changes are paralell with the launch date of some DMDs on Hungarian market (natalizumab in 2010; fingolimod, dimethyl-fumarate and teriflunomide in 2014).

Table 5. Yearly Drug Dispension Data – originally published in [14].

	Nr of patients refilling ANY drug with G35 diagnosis in that year (those who fulfil our case definition / those who do not)*	Nr of patients refilling any of the 11 DMD in that year and fulfilling our case definition of MS / Nr of patients refilling any of the 11 DMD and NOT fulfilling our case definition of MS*	Nr of patients refilling any DMD for the first time and fulfilling our case definition of MS / Nr of patients refilling any DMD for the first time and NOT fulfilling our case definition of MS	Ratio of MS patients who received DMD that year
2010	6162 (5358/804)	2089 / 23	2089[a] / 23[a]	0.19
2011	6326 (5535/791)	2746 / 34	828 / 33	0.24
2012	6539 (5758/781)	2969 / 42	392 / 38	0.25
2013	6671 (5920/751)	3108 / 52	357 / 48	0.25
2014	7130 (6314/816)	3482 / 60	500 / 56	0.28
2015	7399 (6573/826)	3808 / 70	466 / 63	0.29

**One patient can appear in more than one year.*

[a]Drug dispension data are available only from 2010 therefore all patients will appear as "first time refill" this year.

The proportion of DMD-treated MS-patients can be assessed each year by dividing the number of subjects refilling DMD with that of prevalent MS-cases. This ratio significantly increased between 2010 and 2015 from 0.19 to 0.29 (**Table 5.**), the *p*-value of trend analysis with linear regression is 0.0051.

DOI:10.14753/SE.2022.2680

5. Discussion

In my thesis I present the results of our work on the use of administrative data in the investigation of the epidemiological features of MS in Hungary. First, we developed an administrative case definition of MS, followed by a two-step validation based on a local cohort of patients and an administrative cohort called „true negative reference". Since our case definition showed both high sensitivity and specificity, we used it afterwards for identifying and counting MS-patients.

5.1 Use of administrative data in MS epidemiology

In the past decade, administrative data become widely used for scientific, health-economic and healthcare planning purposes. The analysis of epidemiology of diseases and comorbidities is relevant for all these three points of view. Regarding MS, the first works aiming to determine an administrative MS case definition was carried out by Culpepper et al. investigating the Veterans Health Administration databases in the USA in 2006 [26] and Marrie et al. in Canada [16] using health insurance claims data in the province of Manitoba in 2010. Marrie et al. established and validated the following MS case definition: ≥3 hospital, physician, or prescription claims for MS. Since then, it was applied also to determine prevalence in other Canadian regions [27; 28], and to investigate the epidemiology of comorbidities in MS [29; 30]. In 2015, an other Canadian researcher group developed a different administrative case definition: one hospitalization or at least 5 physician billings for MS over 2 years [31]. These two administrative definitions were validated on medical records and compared to each other in a Canadian county in 2018 [32]. It was found that the Marrie-definition had a sensitivity of 99.5%, a specificity of 98.5%, a positive predictive value of 99.5% and a negative predictive value of 97.5%, altogether presenting a better performance. Recently, the United States Multiple Sclerosis Prevalence Workgroup – in which Culpepper and Marrie both participate – published a summary [33] about the performance of different administrative algorithms for identifying MS cases. Their recommendation for the administrative case definition is as follows: ≥3 MS-related claims in any combination of inpatient, outpatient, or DMD use within a 1 year time period.

Multiple European study groups published their work with administrative data in MS epidemiology, however, the case definitions as well as the calculation and validation methods

are rather heterogenous, largely depending on which healthcare databases are accessible for research. For example, Bezzini et al. [20; 34; 35] from Tuscany used and validated the administrative case definition of meeting at least one of the following 4 criteria: minimum one hospital discharge record with MS diagnosis, or one active payment exemption for MS, or at least 2 prescriptions for MS-specific drugs, or MS diagnosis in home and residential long-term care data. The sensitivity of this definition was 98%, with a specificity of 99%. In their recent paper, Roux et al. [36] studied French nationwide health administrative data between 2010-2015 and used a somewhat similar case definition: at least one reimbursement for a DMD, or an active status of "long-term disease" for MS, or at least one hospitalization with MS among discharge diagnoses. Other examples of administrative MS-definitions include that of Salhofer-Polanyi et al. [37] who analyzed Austrian healthcare data and defined as MS-patient those subjects who had at least 1 prescription for DMD or at least one hospitalisation with discharge diagnosis of MS during the 4-year-long observational period. Two independent studies were driven in Bavaria: Höer et al. considered a subject having MS if he or she had ≥1 ambulantory claims for MS documented by neurologist or psychiatrist, or ≥1 prescription of DMD between 2005-2009 [38]. On the other hand, Daltrozzo et al. used a less strict MS case-definition: diagnosis of MS coded at least in two separate quarterly periods between 2006-2015, given at least once by a neurologist [39]. For comparison, the former method resulted a prevalence rate of 175/100,000 in 2009 (18,176 patients), while the latter definition was fulfilled by 21,720 individuals, meaning a prevalence rate reaching 208.7/100,000 in the same year.

When developing our administrative case definition, we took as basis the works of Marrie et al. [16] as their MS-definition had been validated, compared with another and used in many studies. However, we had to perform some modifications on the „Marrie-definition" as we did not have access to the records of family doctors, and the medication refill database was not available for the entire period of the claim database. We aimed for a high specificity even at the cost of possibly underestimate the number of MS-patients. That is the reason of the temporal restriction among the criteria (G35 occurring in at least 2 calendar years): it was ment to exclude when MS is only the suspected diagnosis of medical attendance and diagnostic workup reveals another illness. „Real" MS-patients are likely to see any kind of physician for their condition more than once during a couple of years, because even non-DMD-treated MS patients are advised to see a neurologist once a year. Indeed, the above mentioned French study [36] found that over 6 years of observation 75.1% of MS-patients had visited a neurologist at least once a year.

In order to minimize false positive MS-diagnosis, we also added the criterion that at least once the coded diagnosis of MS should be given by a neurologist. This specific criterion was true for the 90% of all subjects who ever received the code of G35 (see **Figure 1.**). We may speculate that in case of the more than 10,000 persons who received the diagnosis of MS from a neurologist but do not fulfil the other two criteria, MS was a suspected diagnosis or one of some suspected diagnoses, but ancillary examinations later excluded or could not confirm it. In the latter case some of them may turn out to have MS in years after 2016.

We validated our case definition via case certification with the help of medical records held by our Department. Two 2-month-long time-intervals were randomly selected in our University center. During these time-intervals we identified 309 individuals as possible MS-patients based on the received billing code of G35 in primary or secondary position (**Table 1**). When the administrative case-definition was appplied and then compared with the diagnosis established in medical records (considered as gold standard), it was revealed that the administrative definition performed correctly in 93.9% of the entire cohort of the 309 "MS-suspect" subjects. The administrative MS-diagnosis turned out to be "false-positive" ie. falsely fulfilled in 18 cases (5.8%): in 3 cases it was not possible to firmly determine the diagnosis of MS (evaluation was not finished or the results were not available for our analysis) and 15 subjects had other medical condition (for details see **Table 1**.). Worth of note that of them, 5 patients suffered from NMOSD which both clinically and radiologically can mimic MS. Further 2 subjects had been for years considered as having MS before this diagnosis was revised. We have identified only 1 "false-negative" MS-case who did not fulfil the administrative criterion of having claim for MS in 2 separate calendar years because of refusing medical follow-up. Alltogether, the sensitivity of the administrative case-definition was 99%. The specificity was tested with the help of an administrative "true negative" cohort as discussed above and turned out to be >99%.

5.2 Prevalence of MS in Hungary

In Hungary, national MS patient registry is not functioning yet, although it was already suggested [40] and some preparations have been started. Given this lack of the most responsible source of epidemiological data, it is comprehensible that before 2020 only regional data were published on epidemiology of MS [6-13]. These papers are summarized in chronological order in **Table 6**. (see its original Hungarian version in [15]). Thus, our first aim was to estimate the number of individuals diagnosed and living with MS in Hungary, ie. prevalence and incidence;

secondly, to investigate the patterns of age distribution of patients; and thirdly, to assess the ratio of DMD-treated subjects.

In MS Barometer 2020 [1] the Hungarian MS Society has reported that the estimated population of people living with MS in Hungary was 8500, and in the review of Global Burden of MS [2] this number was estimated to be between 5927 and 7480 in 2016. Both numbers would implicate a lower prevalence than our studies resulted: based on administrative data we found that crude prevalence was 130.8/100,000 in 2015 (179.5 and 76.8 per 100.000 for women and men, respectively, **see Table 2.**) accounting for almost 13,000 patients in the country. This prevalence rate is significantly higher than those reported beforehand (see **Table 6.**).

It is worth to compare our results with the other most recent work in this field. Based on the patient registry of the university MS-center in Szeged, Biernacki et al. [13] reported that standardized prevalence of MS was 101.8/100,000 (53.9 and 144.8/100.000 for men and women, respectively) in 2019. This prevalence rate is lower than that of our study, but still higher than the prevalence rate of 2013 estimated by the same group and based on the same patient registry [12]. The difference between their regional and our administrative nationwide data could be the explained by the use of different methods, implicating that for example chronically disabled or bedridden patients may not visit regional university MS-center and thus are not registered there (recruitment bias), which is plausible regarding the rather low average EDSS score (2.8 points ±2.44) and high percentage of DMD-treated subjects (74.28%) in their center [13]. Other regional factors (number and availability of neurologists, ethnic and age distribution of population) can also play a role.

DOI:10.14753/SE.2022.2680

Table 6. Summary of published papers on the subject of epidemiology of multiple sclerosis in Hungary, in chronological order - originally published in Hungarian version in [15]

Author	Diagn. criteria	Type	Geographi-cally	Date of preva-lence	Crude prev.	Crude preva-lence M/F	M:F ratio of prev. patients	Average age of prev. patients (year)	Average age at diagnosis of prev. patients (year)	Incidence
Lehoczky [6]	N/A	hospital in Budapest	extrapolated to Hungary	1961	20	N/A	N/A	N/A	N/A	N/A
Pálffy [7]	Bauer	university MS Center	Baranya county	31 aug 1981.	37	N/A	1:1.91	N/A	N/A	N/A
Pálffy [8]	Bauer	university MS Center	Pécs	1 oct 1982.	57	N/A	1:1.4	N/A	30	N/A
Guseo [9]	Poser	regional MS Center	Fejér county	31 dec 1992.	78,7	N/A	1:1.5	N/A	male:32.5 female:25.9	1.92 (between 1957-91: 1-8)
Bencsik, 1998 [10]	Poser	university MS Center	Szeged	31 dec 1996.	65	N/A	1:3	N/A	35	7
Bencsik, 2001 [11]	Poser	university MS Center	Csongrád county	1 july 1999.	62	N/A	1:2.75	ben:55, RR:36 SP:59, PP:59	ben:28, RR:28 SP:30, PP:52	In Szeged: 1997: 5 1998: 6
Zsiros [12]	McDonald 2010	university MS Center	Csongrád county	1 jan 2013.	89.8	46.6 / 128.6	1:3.08	N/A	CIS:31.4, RR: 31.7 SP:35.4, PP: 47.3	N/A
Biernacki [13]	McDonald 2017	university MS Center	Csongrád county	1 jan 2019.	105.3	56.5 / 149.3	1:2.925	48.83 (±13.23)	34.15 (±10.64)	4.44
Iljicsov [14; 15]	admin. def.	nationwide healthcare service data	Hungary	2015	130.8	76.8 / 179.5	1:2.6	47.95	average age of incident cases: 37.44	2015: 5.4

Admin.def.: administrative definition; ben: benign MS; CIS: clinically isolated syndrome; diagn.criteria: diagnostic criteria; M: male, F: female; N/A: not available data; PP: primary progressive MS; prev: prevalent; RR: relapsing-remitting MS; MS: multiple sclerosis; SP: secondary progressive multiple sclerosis. Prevalence and incidence rates are displayed as /100.000 person.

Hungary is part of the Central European region which used to be considered as a medium risk area for MS. However, recent works reveal prevalence rates above 100/100,000 population, which is higher than past values. Those studies from Central Europe include an Austrian calculation using administrative data [37], which found an average crude prevalence at 158.9/100,000 in 2011-2013. In Poland, two researches investigating different geographical sites based on regional MS-registries showed that standardized prevalence was 106.6/100,000 in 2014 in Central Poland [41] and 108.5/100,000 in 2013 [42] when data of two counties were summarized. In Croatia, after merging 3 databases of public health care and that of the MS-patient society, the crude prevalence was found to be 143.8/100,000 in 2015, much higher than previously estimated [43]. Our results are in line with those moderately high prevalence rates in Central Europe, even if direct comparison is hampered by the use of different methods and sometimes lack of standardization. The highest prevalence rates (above 200/100,000) worldwide are reported in Canada, the United Kingdom and Northern Europe [44-46].

Rising prevalence of MS is observed in several countries [47; 48] and also worldwide as summarized in Atlas of MS 2020 [2]. It reported higher prevalence rates in 2020 compared to 2013 in all WHO regions. Considering Europe, the average prevalence rate of 108.25/100,000 in 2013 increased to 142.81/100.000 in 2020. The reason of rising prevalence is multifactorial. Improved ascertainment (for example due to better availability of neurologist and diagnostic tools, also higher awareness of physicians and people in general), a possible rise in incidence and development of methodologies to count MS-patients can all play role in it. Furthermore, the earlier diagnosis [46; 49] (partly supported by modified diagnostic criteria [17-19]) or possible earlier age at onset of the disease, and especially higher age of MS-patients at death with improved survival [44; 50; 51] together result in longer disease duration and therefore higher prevalence.

Our presented results are in line with the above discussed worldwide tendency: the estimated prevalence of MS in Hungary increased severalfold and continuosly from 20/100,000 in 1961 to 130.8/100.000 in 2015 (see **Table 6.**). We could also demonstrate this rise of prevalence during a 6-year-long observational period: between 2010-2015 both crude and standardized prevalence showed significant elevation (in men, women and alltogether as well) as illustrated in **Table 2**. It is not without example to see significant changes in prevalence during only a couple of years, like Höer in Bavaria found an increase during the timeframe of 5 years [38], Campbell in Australia during 8 years [52].

Of note, our study reveals that the ratio of female and male prevalent cases remains 2.6 during the observational period, and the women/men ratio of incident cases varies between 1.9 and 2.5. These results are also in line with the calculations of other groups [27; 49; 53; 54].

5.3 Incidence of MS in Hungary

Previous regional studies revealed an incidence rate between 1.92-7/100,000 during the past three decades, see **Table 6**. The analysis of our data showed results in that range as well: the crude total incidence rate was between 7.1 and 5.4/100,000 from 2010 to 2015, presenting a significant negative trend, in parallel with the changes of crude incidence rate in women (between 9.6 and 7.2/100,000). Interestingly, the crude incidence rate in men remained stable (3.5–4.3 /100,000) during these years. These results, especially trend analysis models should be interpreted with caution as the Shapiro-Wilks test indicated it may be inappropriate ($p<0.05$), and from one year to the next the difference in incident cases is only a couple of dozen subjects.

International studies on the changes of incidence ratios are less unanimous than those about prevalence of MS. Our results are in line with some publications where incidence rates show a plateau or even a decrease in total population or among women: for example in different counties of Canada by Marrie et al [16], Kingwell et al [27], and Rotstein et al [44], furthermore in the United Kingdom by Mackenzie et al [45], in France by Gbaguidi et al [54], and in Italy by Solaro et al [55]. Nevertheless, several studies reveal rise in incidence rates during the last decades (for example in Norway [46], in Wales [56], in Iran [57]) and especially among women (like in Denmark [58] and Finland [59]), the latter reaching rates higher than 10/100.000 in Northern Europe.

These differences in trends of incidence rates are difficult to explain, but environmental, socio-economic and genetic factors might play a role. Some researchers propose different environmental or lifestyle factors to explain the growth of incidence rates with female preponderance, including rise in occurence of obesity and cigarette consumption in women [58], and diminished exposure to sunlight and secondary vitamin D deficiency [60]. Moreover, a causality between the risk of MS and the age of women at first childbirth or number of pregnancies was suspected in different studies [61; 62] but was not confirmed by others [63]. Also, the changes in coding policies, like giving diagnosis of clinically or radiologically isolated syndrome instead of MS until the actual diagnostic criteria are not fulfilled may contribute to the decline in incident administrative cases. Alltogether, the evident rise of MS

prevalence is multifactorial, and is not everywhere and not only driven by significant rise of incidence.

5.4 Age-distribution of MS patients in Hungary

We performed the analysis of age-distribution of prevalent MS-patients between 2004-2016 and found that their average age slowly, but significantly increases year by year, reaching 47.95 years in 2015. This result is concordant with the regional calculations presented by Biernacki et al [13], who published that in 2019 the average age of their prevalent cohort was 48.83. Average age of women subjects increases faster, and therefore the gap between the average age of the two sexes grows (see **Figure 3.**).

At the same time, between 2005-2015 the prevalence rate considerably increased in each age group above 18 years of age (**Figure 2.**). This phenomenon is also described for example by Marrie et al. in Canada [16], Campbell et al. in Australia [52], and Murtonen et al in Finland [48]. Peak prevalence rate used to be 162.6/100,000 in 2005, registered among patients aged 50-54 years, while in 2015, peak prevalence rate was 276.9/100,000 observed among subjects aged 45-49 years. Thus, the peak prevalence range shifted towards younger cohorts, just like the most populous age groups. This age range of peak prevalence was also found by other groups, like Bakirtzis et al in Greece [64],and Murtonen et al in Finland [48], but other studies revealed peak prevalence rates among patients above 50 years of age (Laakso et al in Finland [65], Marrie et al [16] and Rotstein et al [44] in Canada), or even 55 years of age (Campbell et al in Australia [52], Grytten et al in Norway [66]) with a shift towards older ages during the observed years.

As discussed above, a rise in longevity of MS-patients is observed worldwide, resulting a higher prevalence of MS but also a growing proportion of elderly people living with MS. Indeed, our data also show that persons over 65 years are increasingly represented among MS-patients in Hungary: 11.8% in 2015 (see also **Figure 3.**). This rise is in line with the results of other studies [16; 66]. Moreover, other works also suggest that age-adjusted incidence also rises in this population [55; 58], probably in connection with the higher awareness of MS among elderly and better tools for differential diagnosis. The worldwide growing number of MS-patients above 60 years of age is rather neglected so far, but it rises many concerns about their proper management, including unknown efficacy and safety of DMDs, frequent comorbidities, accumulating disabilities, and need of social support, summarized for example by Vaughn et al [67]. Concerning incident subjects, we estimated their average age between

2007-2015 and found a significant decrease from 40.4 to 37.4 years without difference between male and female values. This result is comparable to that of Biernacki et al [13] who described that in Csongrád county the average age of prevalent patients at the time of MS-diagnosis (which is an approximate of age of incident cases) was 34.1 in 2019. This decreasing trend of age of incident patients is at least partly attributable to changing diagnostic criteria and altogether shorter time from first symptoms until definite diagnosis [49; 66].

5.5 Drug dispension data

Since disease-modifying drugs are highly specific for treating MS and their prescription is centralized and regulated in Hungary, our main interest was to analyze their dispension statistics between 2010 and 2015. We also had speculated that the subjects refilling DMD are highly probably MS-patients (mostly with relapsing-remitting and also some with secondary progressive forms), and consequently they would also serve as a validation cohort of our administrative definition. Indeed, of those patients who at least once refilled DMD, each year the maximum proportion of those individuals who do not fulfil our administrative case definition is as low as 2%. At the same time, a continuous rise of the number of DMD-treated patients can be observed with nearly doubling in 5 years. This feature is partly explained by the introduction of new DMDs in the Hungarian market (see above) and the growing number of prevalent MS patients.

Our calculations show that the ratio of DMD-treated prevalent patients was relatively low in 2010 (19%) and significantly increase to reach 29% in 2015. It still can be considered low, but according to MS Barometer 2020 [1] and also pharmaceutical industry estimations [68] considerable differences exist even among European countries: not only reimbursement, but availability of DMDs are highly depending on the country. This is why the proportion of DMD-treated patients could have been as high as 69% in Germany and as low as 13% in Poland in 2013, but in 2018 major differences still existed [1]: treatment rates reach 90% in Lithuania, Malta, and Switzerland, while are around 10% in Bosnia Herzegovina and Serbia. Nevertheless, our data concerning 2015 rates are in line with some other publications: Kingwell et al. [27] reported that 29% of MS patients had received at least once a prescription for a DMD between 1991 and 2010 in British Columbia. According to data of Central Italy [20], 41% of MS-patients received at least 2 prescriptions for DMD in 2011. These important differences between countries regarding the proportion of DMD-treated MS patients are probably multifactorial: national regulations on prescription play a role (for example in Hungary DMDs

are not reimbursed in clinically isolated syndrome), and also genetic and environmental issues could be responsible, for example for affecting the proportion of benign or primary progressive MS.

DOI:10.14753/SE.2022.2680

6. Conclusions

These results discussed above are not only the first to describe the nationwide epidemiologic features of multiple sclerosis in Hungary, but emphasize a rather neglected phenomenon: together with the growing number and prevalence of MS patients, the proportion of elder patients increases. Once MS used to be regarded as a disease of young, but in the era of various effective disease-modifying treatments and rising life-expectancy of the general population as well, neurologists will have to face the challenge of the diagnosis and complex management of elder MS-patients. Not only the neurologic and non-neurologic comorbidities are more frequent among them (raising sometimes difficulties of differential diagnosis, like small vessel diseases, and also of contraindications for DMDs), but the accumulation of physical and cognitive disability as well. Moreover, as the widely used DMDs were not tested in the elder population in pivotal trials, their efficacy and safety is unknown in this setting.

The strengths and possible limitations of our work are also assessed as follows. The strengths of our study include the use of nationwide administrative healthcare data with a 13-year-long observational period, allowing the assessment of temporal trends. We validated our administrative MS case definition on the medical records of 309 consecutive subjects in our neurological department. Furthermore, with the help of an independent database of pharmacy refills we could re-assess the performance of this case definition, that showed an excellent concordance, sensitivity and specificity, see above. The yearly analysis of age of incident and prevalent subjects let us have an insight into the demographical changes of the population living with MS in Hungary.

We have to consider some limitations of our study: the use of administrative health data implicate that clinical details of patients are lacking, for example, there was no information on which diagnostic criteria had been used when establishing and coding diagnosis of MS, neither on clinical subtype, which could help to understand among others the relatively low proportion of DMD-treated individuals. It is also important to keep in mind that the original purpose of diagnosis coding is reimbursement and not scientific.

In our setting, we did not have access to data of health service claims reported by family doctors, that would help to better estimate the proportion of benign and severely handicapped MS-patients who are at higher risk for not meeting a neurologist during the 13 years of

investigation and therefore their number may be underestimated. Indeed, the French study [36] has revealed that 13% of subjects with MS had not been seen by neurologist during the 6-year-long observational period, and these patients were older and had a longer disease duration. In NEUROHUN database we found somewhat similar trends: of more than 30,000 individuals ever receiving G35 diagnostic code, in approximately 90% of cases it was at least once given – in our interpretation: confirmed – by a neurologist (see **Figure 1.**). But, in contrast to the mentioned French study, we didnot considered the remaining 10% as MS-patients in further analysis, as our primary aim was to minimize the risk of including people without MS.

Furthermore, the third criterion of our administrative case definition with temporal conditions might seem too restrictive, but we assumed that the majority of MS-patients would have some kind of medical encounter for their condition in at least 2 years of 13. However, we are aware that it can underestimate the incident cases of the last years of the observation period, as the two apparition of G35 required in two different calendar years are not necessarily consecutives. This possible bias is also enhanced by the well-known fact that diagnostic delay in MS can take years, even if recently this time-period shortens in many countries [49; 66].

Further investigation is needed to understand the decreasing trend of incidence. Indeed, we plan to continue our examinations on longer observational period, as soon as raw data will be available. Here it has to be mentioned that the most reliable epidemiologic calculations can be obtained by the analysis of nationwide disease-specific regitries. Regarding MS, this kind of registries are already in use for many years for example in Scandinavian countries [69; 70], and the launch of a Hungarian National MS-registry was also suggested [40; 71] and planned years ago, however, it is still not functioning in 2022. We believe that until a national MS-registry is built up and is available for research, the analysis of nationwide healthcare data gives the best estimation of the epidemiology of MS in Hungary.

DOI:10.14753/SE.2022.2680

7. Summary

In this thesis I presented my work on the epidemiology of MS in Hungary based on analysis of healthcare administrative data covering 13 years. Before, nationwide data were lacking in our country about prevalence, incidence and age-distribution of MS, or proportion of DMD-treated subjects, as only regional studies had been conducted.

First I have established and validated an administrative case-definition of MS, that is proved to have excellent specificity and sensitivity. After applying it on the database of healthcare claims, we could analyze the annual number and age of new and prevalent MS-patients. These findings highlight that MS prevalence shows an increase and is notably higher (crude prevalence being 130.8/100,000 in 2015) than previously reported in Hungary, while crude incidence is relatively low (5.4/100.000 in 2015) and shows a decreasing tendency. While the average age of incident subjects gradually lowers (ie. newly diagnosed patients are younger), the average age of prevalent individuals rises, especially in women. It can be attributable to increased longevity of people living with MS, and has an important consequence: the growing number and proportion of elderly patients.

Concerning drug dispension analysis, the proportion of DMD-treated MS-patients turned out to be rather low (29% in 2015) that may partly be due to special restrictions of their prescription in Hungary.

The above discussed results fit well in the epidemiologic changes of MS described in international and Hungarian scientific literature, that may help to clarify environmental and genetic factors having role in patomechanism of MS. These data also have importance in understanding and estimating the burden of the disease on patients, families, healthcare providers, and society in order to plan future allocation of human and financial resources for complex management of multiple sclerosis.

8. References

1. European Multiple Sclerosis Platform. (2021) MS Barometer 2020. Assessing the gaps in care for people with multiple sclerosis across Europe. [Cited: 04 Febr 2022] In: website of European Multiple Sclerosis Platform [internet]. Brussels. Available from: https://www.emsp.org/wp-content/uploads/2021/03/MS-Barometer2020-Final-Full-Report-Web.pdf
2. Multiple Sclerosis International Federation. (2020) Atlas of MS, 3rd edition. Mapping multiple sclerosis around the world. Part 1: key epidemiologic findings. [Cited: 04 Febr 2022] In: website of MS International Federation [internet]. London: 2000-. Available from: https://www.msif.org/wp-content/uploads/2020/10/Atlas-3rd-Edition-Epidemiology-report-EN-updated-30-9-20.pdf
3. Wallin MT, Culpepper WJ, Nichols E, Bhutta ZA, Gebrehiwot TT, Hay SI, Khalil IA, Krohn KJ, Liang X, Naghavi M, Mokdad AH, Nixon MR, Reiner RC, Sartorius B, Simth M, Topor-Madry R, Werdecker A, Vos T, Feigin VI, Murray CJL. (2019) Global, regional, and national burden of multiple sclerosis 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol, 18(3): 269-285.
4. Péntek M, Gulácsi L, Rózsa C, Simó M, Iljicsov A, Komoly S, Brodszky V. (2012) Health status and costs of ambulatory patients with multiple sclerosis in Hungary. *Ideggyogy Sz, 65*(9–10): 316–324.
5. Paz-Zulueta M , Parás-Bravo P , Cantarero-Prieto D , Blázquez-Fernández C , Agustín Oterino-Durán A. (2020) A literature review of cost-of-illness studies on the economic burden of multiple sclerosis. Mult Scler Relat Disord. 43: 102162. doi: 10.1016/j.msard.2020.102162.
6. Lehoczky T, Halasy-Lehoczky M. (1961) Multiple sclerosis in Hungary. World Neurol, 2: 38-44.
7. Pálffy Gy. (1982) Multiple sclerosis in Hungary, including the Gipsy population. In: Kuroiwa Y, Kurland LT, editors: Multiple Sclerosis East and West, Asian Multiple Sclerosis Workshop, Kyoto, Proceedings, 149-157 doi.org/10.1159/000408037
8. Pálffy Gy. (1983) Prevalence of multiple sclerosis in the city of Pécs. [A sclerosis multiplex prevalenciája Pécsett.] Ideggyogy Sz, 36: 12-17. [Hungarian]
9. Guseo A, Jófejü E, Kocsis A. (1994) Epidemiology of multiple sclerosis in Western Hungary 1957-1992. In: Firnhaber W, Lauer K, editors. Multiple Sclerosis in Europe: an epidemiological update. Darmstadt: Leuchtturm-Verlag/LTV Press, 279-286.

10. Bencsik K, Rajda C, Klivényi P, Járdánházy T, Vécsei L. (1998) The prevalence of multiple sclerosis in the Hungarian city of Szeged. Acta Neurol Scand, 97: 315-319.
11. Bencsik K, Rajda C, Füvesi J, Klivényi P, Járdánházy T, Török M, Vécsei L. (2001) The prevalence of multiple sclerosis, distribution of clinical forms of the disease and functional status of patients in Csongrád County, Hungary. Eur Neurol, 46: 206-209.
12. Zsiros V, Fricska-Nagy Z, Füvesi J, Kincses ZT, Langane E, Paulik E, Vécsei L, Bencsik K. (2014) Prevalence of multiple sclerosis in Csongrád County, Hungary. Acta Neurol Scand, 130: 277–282.
13. Biernacki T, Sandi D, Fricska-Nagy Z, Kincses ZT, Füvesi J, Laczkó R, Kokas Zs, Klivényi P, Vécsei L, Bencsik K. (2020) Epidemiology of multiple sclerosis in Central Europe, update from Hungary. Brain Behav, Mar 20:e01598. doi:10.1002/brb3.1598
14. Iljicsov A, Milanovich D, Ajtay A, Oberfrank F, Bálint M, Dobi B, Bereczki D, Simó M. (2020) Incidence and prevalence of multiple sclerosis in Hungary based on record linkage of nationwide multiple healthcare administrative data. PLoS ONE, 15: e0236432.
15. Iljicsov A, Bereczki D, Dobi B, Oberfrank F, Bálint M, Ajtay A, Milanovich D, Simó M. (2021) Age and gender characteristics of patients affected with multiple sclerosis in Hungary between 2004 and 2016 [A hazai sclerosis multiplex betegpopuláció életkori és nemi megoszlása 2004 és 2016 között.] Orv Hetil, 162(19): 746–753. [Hungarian]
16. Marrie RA, Yu N, Blanchard J, Leung S, Elliot L. (2010) The rising prevalence and changing age distribution of multiple sclerosis in Manitoba. Neurology, 74(6): 465-471. doi: 10.1212/WNL.0b013e3181cf6ec0
17. Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L, Lublin FD, Metz LM, McFarland HF, O'Connor PW, Sandberg-Wollheim M, Thompson AJ, Weinshenker BG, Wolinsky JS. (2005) Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". Ann Neurol, 58(6): 840–846.
18. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, Fujihara K, Havrdova E, Hutchinson M, Kappos L, Lublin FD, Montalban X, O'Connor P, Sandberg-Wollheim M, Thompson AJ, Waubant E, Weinshenker BG, Wolinsky JS. (2011) Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol, 69(2): 292-302.
19. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, Correale J, Fazekas F, Filippi M, Freedman MS, Fujihara K, Galetta SL, Hartung HP, Kappos L, Lublin FD, Marrie RA, Miller AE, Miller DH, Montalban X, Mowry EM, Soelberg

Sorensen P, Tintoré M, Traboulsee AL, Trojano M, Uitdehaag BMJ, Vukusic S, Waubant E, Weinshenker BG, Reingold SC, Cohen JA. (2018) Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol, 17(2): 162-173.

20. Bezzini D, Policardo L, Meucci G, Ulivelli M, Bartalini S, Profili F, Battaglia MA, Francesconi P. (2016) Prevalence of multiple sclerosis in Tuscany (Central Italy): a study based on validated administrative data. Neuroepidemiology, 46: 37-42.
21. Hungarian Population Census 2011. [Internet] Budapest: Központi Statisztikai Hivatal; 1995 - [Cited: 04 February 2022]. Available from: http://www.ksh.hu/nepszamlalas/tables_regional_00
22. Ahmad OB, Boschi-Pinto C, Lopez AD, Murray CJL, Lozano R, Inoue M. (2001) Age standardization of rates: a new WHO standard. GPE Discussion Paper Series: No.31. EIP/GPE/EBD World Health Organization 2001.
23. EUROSTAT (2013) Methodologies and working papers: Revision of the European Standard Population. Report of Eurostat's Task Force. 2013 edition. [Internet] 11 July 2013 [Cited: 04 February 2022] Available from: https://ec.europa.eu/eurostat/documents/3859598/5926869/KS-RA-13-028-EN.PDF/e713fa79-1add-44e8-b23d-5e8fa09b3f8f
24. Daly L. (1992) Simple SAS macros for the calculation of exact binomial and Poisson confidence limits. Comput Biol Med, 22: 351-61.
25. Fay MP, Feuer EJ. (1997) Confidence intervals for directly standardized rates: a method based on the gamma distribution. Stat Med, 16(7): 791-801.
26. Culpepper WJ, Ehrmantraut M, Wallin MT, Flannery K, Bradham DD. (2006) Veterans Health Administration multiple sclerosis surveillance registry: The problem of case-finding from administrative databases. J Rehabil Res Dev, 43: 17-24.
27. Kingwell E, Zhu F, Marrie RA, Fisk JD, Wolfson C, Warren S, Profetto-McGrath J, Svenson LW, Jette N, Bhan V, Yu BN, Elliott L, Tremlett H. (2015) High incidence and increasing prevalence of multiple sclerosis in British Columbia, Canada: Findings from over two decades (1991–2010). J Neurol, 262(10): 2352–2363.
28. Marrie RA, Fisk JD, Stadnyk KJ, Yu BN, Tremlett H, Wolfson C, Warren S, Bhan V. (2013) The incidence and prevalence of multiple sclerosis in Nova Scotia, Canada. Can J Neurol Sci, 40(6):824–31.
29. Marrie RA, Fisk JD, Yu BN, Leung S, Elliott S, Caetano P, Warren S, Evans C, Wolfson C, Svenson LW, Tremlett H, Blanchard JF, Patten SB. (2013) Mental

comorbidity and multiple sclerosis: validating administrative data to support population-based surveillance. BMC Neurol, 13:16. doi: 10.1186/1471-2377-13-16

30. Marrie RA, Elliott L, Marriott J, Cossoy M, Blanchard J, Leung S, Yu N. (2015) Effect of comorbidity on mortality in multiple sclerosis. Neurology, 85(3): 240-247.
31. Widdifield J, Ivers NM, Young J, Green D, Jaakkimainen L, Butt DA, O'Connor P, Hollands S, Tu K. (2015) Development and validation of an administrative data algorithm to estimate the disease burden and epidemiology of multiple sclerosis in Ontario, Canada. Mult Scler, 21(8): 1045–54. doi: 10.1177/1352458514556303
32. Al-Sakran LH, Marrie RA, Blackburn DF, Knox KB, Evans CD. (2018) Establishing the incidence and prevalence of multiple sclerosis in Saskatchewan. Can J Neurol Sci, 45(3): 295–303.
33. Culpepper WJ, Marrie RA, Langer-Gould A, Wallin MT, Campbell JD, Nelson LM, Kaye WE, Wagner L, Tremlett H, Chen LH, Leung S, Evans C, Yao S, LaRocca NG. (2019) Validation of an algorithm for identifying MS cases in administrative health claims datasets. Neurology, 92(10): e1016–e1028. doi:10.1212/WNL.0000000000007043
34. Bezzini D, Policardo L, Profili F, Meucci G, Ulivelli M, Bartalini S, Francesconi P, Battaglia MA. (2018) Multiple sclerosis incidence in Tuscany from administrative data. Neurol Sci, 39(11): 1881-1885.
35. Bezzini D, Ulivelli M, Gualdani E, Razzanelli M, Ferretti F, Meucci G, Francesconi P, Battaglia MA. (2020) Increasing prevalence of multiple sclerosis in Tuscany, Italy. Neurol Sci. 41(2): 397-402.
36. Roux J, Guilleux A, Lefort M, Leray E. (2019) Use of healthcare services by patients with multiple sclerosis in France over 2010-2015: a nationwide population-based study using health administrative data. Mult Scler J Exp Transl Clin, 5(4):2055217319896090.
37. Salhofer-Polanyi S, Cetin H, Leutmezer F, Baumgartner A, Blechinger S, Dal-Bianco A, Altmann P, Bajer-Kornek B, Rommer P, Guger M, Leitner-Bohn D, Reichardt B, Alasti F, Temsch W, Stamm T. (2017) Epidemiology of multiple sclerosis in Austria. Neuroepidemiology, 49(1-2):40-44. doi: 10.1159/000479696
38. Höer A, Schiffhorst G, Zimmermann A, Fischaleck J, Gehrmann L, Ahrens H, Carl G, Siegel KO, Osowski U, Klein M, Bleß HH. (2014) Multiple sclerosis in Germany: data analysis of administrative prevalence and healthcare delivery in the statutory health system. BMC Health Serv Res, 14:381. doi: 10.1186/1472-6963-14-381

39. Daltrozzo T, Hapfelmeier A, Donnachie E, Schneider A, Hemmer B. (2018) A systematic assessment of prevalence, incidence and regional distribution of multiple sclerosis in Bavaria from 2006–2015. Front Neurol, 9:871. doi: 10.3389/fneur.2018.00871
40. Bencsik K, Sandi D, Biernacki T, Kincses Z, Füvesi J, Fricska-Nagy Z, Vécsei L. (2017) The Multiple Sclerosis Registry of Szeged. [A Szegedi Sclerosis Multiplex Regiszter], Ideggyogy Sz, 70: 301-306. [Hungarian]
41. Brola W, Sobolewski P, Flaga S, Fudala M, Szczuchniak W, Stoinski J, Rosołowska A, Wójcik J, Kapica-Topczewska, Ryglewicz D. (2016) Prevalence and incidence of multiple sclerosis in central Poland, 2010–2014. BMC Neurol, 16:134. doi: 10.1186/s12883-016-0662-8
42. Kapica-Topczewska K, Brola W, Fudala M, Tarasiuk J, Chorazy M, Snarska K, Kochanowicz J, Kulakowska A. (2018) Prevalence of multiple sclerosis in Poland. Mult Scler Relat Disord, 21: 51-55.
43. Benjak T, Štefančić V, Draušnik Ž, Cerovečki I, Roginić D, Habek M, Mihel S, Stefanović R. (2018) Prevalence of multiple sclerosis in Croatia: data from national and non-governmental organization registries. Croat Med J, 59: 65–70. doi: 10.3325/cmj.2018.59.65
44. Rotstein DL, Chen H, Wilton AS, Kwong JC, Marrie RA, Gozdyra P, Krysko KM, Kopp A, Copes R, Tu K. (2018) Temporal trends in multiple sclerosis prevalence and incidence in a large population. Neurology, 90(16): e1435–e1441.
45. Mackenzie IS, Morant SV, Bloomfield GA, MacDonald TM, O'Riordan J. (2014) Incidence and prevalence of multiple sclerosis in the UK 1990-2010: a descriptive study in the General Practice Research Database. J Neurol Neurosurg Psychiatry, 85: 76–84.
46. Grytten N, Torkildsen Ø, Myhr KM. (2015) Time trends in the incidence and prevalence of multiple sclerosis in Norway during eight decades. Acta Neurol Scand, 132: 29–36.
47. Otero-Romero S, Roura P, Solà J, Altimiras J, Sastre-Garriga J, Nos C, Vaqué J, Montalban X, Bufill E. (2013) Increase in the prevalence of multiple sclerosis over a 17-year period in Osona, Catalonia, Spain. Mult Scler, 19(2): 245–248. doi: 10.1177/1352458512444751
48. Murtonen A, Sumelahti ML. (2020) Multiple sclerosis prevalence in 2000 and 2010 in Western Finland. Acta Neurol Scand, 141(4): 311-318. doi: 10.1111/ane.13203

49. Trojano M, Lucchese G, Graziano G, Taylor BV, Simpson S Jr, Lepore V, Grand'maison F, Duquette P, Izquierdo G, Grammond P, Amato MP, Bergamaschi R, Giuliani G, Boz C, Hupperts R, Van Pesch V, Lechner-Scott J, Cristiano E, Fiol M, Oreja-Guevara C, Saladino ML, Verheul F, Slee M, Paolicelli D, Tortorella C, D'Onghia M, Iaffaldano P, Direnzo V, Butzkueven H. (2012) Geographical variations in sex ratio trends over time in multiple sclerosis. PLoS ONE, 7(10): e48078.
50. Brønnum-Hansen H, Koch-Henriksen N, Stenager E. (2004) Trends in survival and cause of death in Danish patients with multiple sclerosis. Brain, 127(Pt 4): 844-850.
51. Bentzen J, Flachs EM, Stenager E, Bronnum-Hansen H, Koch-Henriksen N. (2010) Prevalence of multiple sclerosis in Denmark 1950–2005. Mult Scler, 16: 520-525. doi: 10.1177/1352458510364197
52. Campbell JA, Simpson S Jr, Ahmad H, Taylor BV, van der Mei I, Palmer AJ. (2020) Change in multiple sclerosis prevalence over time in Australia 2010-2017 utilising disease-modifying therapy prescription data. Mult Scler, 26(11): 1315-1328.
53. Celius EG, Smestad C. (2009) Change in sex ratio, disease course and age at diagnosis in Oslo multiple sclerosis patients through seven decades. Acta Neurol Scand, 120(Suppl 189): 27-29. doi: 10.1111/j.1600-0404.2009.01208.x.
54. Gbaguidi B, Guillemin F, Soudant M, Debouverie M, Mathey G, Epstein J. (2022) Age-period-cohort analysis of the incidence of multiple sclerosis over twenty years in Lorraine, France. Scientific Reports, 12(1): 1001. doi: 10.1038/s41598-022-04836-5.
55. Solaro C, Ponzio M, Moran E, Tanganelli P, Pizio R, Ribizzi G, Venturi S, Mancardi GL, Battaglia MA. (2015) The changing face of multiple sclerosis: Prevalence and incidence in an aging population. Mult Scler, 21(10): 1244-50. doi: 10.1177/1352458514561904.
56. Hirst C, Ingram G, Pickersgill T, Swingler R, Compston DA, Robertson NP. (2009) Increasing prevalence and incidence of multiple sclerosis in South East Wales. J Neurol Neurosurg Psychiatry, 80(4): 386-391.
57. Elhami SR, Mohammad K, Sahraian MA, Eftekhar H. (2011) A 20-year incidence trend (1989–2008) and point prevalence (March 20, 2009) of multiple sclerosis in Tehran, Iran: a population-based study. Neuroepidemiology, 36(3): 141–147. doi: 10.1159/000324708

58. Koch-Henriksen N, Thygesen LC, Stenager E, Laursen B, Magyari M. (2018) Incidence of MS has increased markedly over six decades in Denmark particularly with late onset and in women. Neurology, 90(22): 1954–1963.
59. Krökki O, Bloigu R, Ansakorpi H, Reunanen M, Remes AM. (2011) Increasing incidence of multiple sclerosis in women in Northern Finland. Mult Scler, 17: 133–138.
60. Maghzi AH, Ghazavi H, Ahsan M, Etemadifar M, Mousavi S, Khorvash F, Minagar A. (2010) Increasing female preponderance of multiple sclerosis in Isfahan, Iran: a population-based study. Mult Scler, 16(3): 359-361.
61. Runmarker B, Andersen O. (1995) Pregnancy is associated with a lower risk of onset and a better prognosis in multiple sclerosis. Brain, 118 (Pt 1): 253-61.
62. Ponsonby A-L, Lucas RM, van der Mei IA, Dear K, Valery PC, Pender MP, Taylor BV, Kilpatrick TJ, Coulthard A, Chapman C, Williams D, McMichael AJ, Dwyer T. (2012) Offspring number, pregnancy, and risk of a first clinical demyelinating event: The AusImmune Study. Neurology, 78(12): 867-74.
63. Magyari M, Koch-Henriksen N, Pfleger CC, Sørensen PS. (2013) Reproduction and the risk of multiple sclerosis. Mult Scler, 19(12): 1604-1609.
64. Bakirtzis C, Grigoriadou E, Boziki MK, Kesidou E, Siafis S, Moysiadis T, Tsakona D, Thireos E, Nikolaidis I, Pourzitaki C, Kouvelas D, Papazisis G, Tsalikakis D, Grigoriadis N. (2020) The administrative prevalence of multiple sclerosis in Greece on the basis of a nationwide prescription database. Front Neurol, 11: 1012. doi: 10.3389/fneur.2020.0101
65. Laakso SM, Viitala M, Kuusisto H, Sarasoja T, Hartikainen P, Atula S, Tienari PJ, Soilu-Hänninen M. (2019) Multiple sclerosis in Finland 2018 — Data from the national register. Acta Neurol Scand, 140(5): 303-311. doi: 10.1111/ane.13145
66. Grytten N, Aarseth JH, Lunde HMB, Myhr KM. (2016) A 60-year follow-up of the incidence and prevalence of multiple sclerosis in Hordaland County, Western Norway. J Neurol Neurosurg Psychiatry, 87(1): 100-5. doi: 10.1136/jnnp-2014-309906.
67. Vaughn CB, Jakimovski D, Kavak KS, Ramanathan M, Benedict RHB, Zivadinov R, Weinstock-Guttman B. (2019) Epidemiology and treatment of multiple sclerosis in elderly populations. Nat Rev Neurol, 15(6): 329-342. doi: 10.1038/s41582-019-0183-3.
68. Giovannoni G, Butzkueven H, Dhib-Jalbut S, Hobart J, Kobelt G, Pepper G, Sormani MP, Thalheim C, Traboulsee A, Vollmer T. (2016) Brain health: Time matters in multiple sclerosis. Mult Scler Relat Disord, 9(Suppl 1): S5-S48.

69. Magyari M, Joensen H, Laursen B, Koch-Henriksen N. (2021) The Danish Multiple Sclerosis Registry, Brain and Behavior, 11(1): e01921. doi: 10.1002/brb3.1921.
70. Hillert J, Stawiarz L. (2015) The Swedish MS registry – clinical support tool and scientific resource, Acta Neurol Scand, 132(Suppl 199): 11-19.
71. Iljicsov A, Simó M, Tegze N, Szócska M, Mátyus P, Bereczki D. (2019) Multiple sclerosis in central Hungary: experiences and future possibilities of developing a local database. [Sclerosis multiplex a közép-magyarországi régióban: a helyi adatbázisfejlesztés tapasztalatai és jövőbeli lehetőségei]. Orv Hetil, 160(4): 131-137. [Hungarian]

9. Bibliography of the candidate's publications

Publications related to the subject of the thesis:

Iljicsov A, Milanovich D, Ajtay A, Oberfrank F, Bálint M, Dobi B, Bereczki D, Simó M (2020) Incidence and prevalence of multiple sclerosis in Hungary based on record linkage of nationwide multiple healthcare administrative data. PLoS ONE, 15: e0236432. **IF: 3,24**

Iljicsov A, Bereczki D, Dobi B, Oberfrank F, Bálint M, Ajtay A, Milanovich D, Simó M. (2021) A hazai sclerosis multiplex betegpopuláció életkori és nemi megoszlása 2004 és 2016 között. Orv Hetil, 162(19): 746–753. **IF: 0,54**

Hegedűs K, Kárpáti J, Iljicsov A, Simó M. (2019) Neuropsychological characteristics of benign multiple sclerosis patients: A two-year matched cohort study. Mult Scler Rel Disord. 35: 150–155. IF: 2,889

Iljicsov A, Simó M, Tegze N, Szócska M, Mátyus P, Bereczki D. (2019) Nagy adatbázisok neurológiai kórképekben: nemzetközi áttekintés a sclerosis multiplex példáján. Orv Hetil. 160(4): 123–130. IF: 0,497

Iljicsov A, Simó M, Tegze N, Szócska M, Mátyus P, Bereczki D. (2019) Sclerosis multiplex a közép-magyarországi régióban: a helyi adatbázisfejlesztés tapasztalatai és jövőbeli lehetőségei. Orv Hetil. 160(4): 131–137. IF: 0,497

Gombos B, Iljicsov A, Barsi P, Hegedűs K, Simó M. (2017) Natalizumabkezeléssel szerzett tapasztalataink a Semmelweis Egyetem Neurológiai Klinikáján. Ideggyogy Sz. 70(5-6):185-191. IF: 0,252

Simó M, Iljicsov A. (2017) A pegylált interferon-beta-1A helye a sclerosis multiplex kezelésében. Ideggyogy Sz. 70(11-12):365-368. IF: 0,252

Iljicsov A, Pál Zs, Simó M. (2015) Szájon át szedhető immunmoduláns kezelési lehetőségek sclerosis multiplexben. Neuropsychopharmacol Hung. 17(4): 197-205. IF: 0

Péntek M, Gulácsi L, Rózsa Cs, Simó M, Iljicsov A, Komoly S, Brodszky V. (2012) Health status and cost of ambulatory patients with multiple sclerosis in Hungary. Ideggyogy Szle. 65(9-10): 316-324. IF: 0,348

Other publications:

Tatrai E, Simó M, Iljicsov A, Németh J, Debuc D, Somfai G. (2012) In vivo evaluation of retinal neurodegeneration in patients with multiple sclerosis. PLoS ONE. 7(1):e30922. IF:3,73

Iljicsov A, Barsi P, Várallyay Gy, Tátrai E, Somfai GM, Bereczki D, Rudas G, Simó M. (2010) Devic-szindróma – esetismertetés, valamint a diagnosztika és kezelés aktuális irányelvei. Ideggyogy Sz. 63(9-10): 320-326. IF: 0,236

Papp V, Trones KDP, Magyari M, Koch-Henriksen N, Iljicsov A, Rajda C, Nielsen HH, Petersen T, Lovas G, Rózsa Cs, Kristiansen BH, Stenager E, Frederiksen JL, Komoly S, Sellebjerg F, Petersen T, Illés Zs. (2021) Population-based head-to-head comparison of the clinical characteristics and epidemiology of AQP4antibody-positive NMOSD between two European countries. Mult Scler Relat Disord. 51:102879. IF: 4,339

Papp V, Iljicsov A, Rajda C, Magyari M, Koch-Henriksen N, Petersen T, Jakab G, Deme I, Nagy F, Imre P, Lohner Zs, Kovács K, Jóri Birkás A, Köves Á, Rum G, Nagy Zs, Kerényi L, Vécsei L, Bencsik K, Jobbágy Z, Diószeghy P, Horváth L, Galántai Gy, Kasza J, Molnár G, Simó M, Sátori M, Rózsa Cs, Ács P, Berki T, Lovas G, Komoly S, Illés Zs. (2020) A population-based epidemiological study of neuromyelitis optica spectrum disorder in Hungary. Eur J Neurol, 27: 308-317. IF: 6,089

Mathis S, Pin JC, Pierre F, Ciron J, Iljicsov A, Lamy M, Neau JP. (2015) Anti-NMDA receptor encephalitis during pregnancy. A case report. Medicine, 94(26):e1034. IF: 2,133

Ciron J, Mathis S, Iljicsov A, Boucebci S, Neau JP. (2015) Multiple simultaneous intracranial haemorrhages due to hornet stings. Clin Neur Neurosurg. 128:53-55. IF: 1,198

Mathis S, Neau JP, Pluchon C, Fargeau MN, Karolewicz S, Iljicsov A, Gil R. (2014) Apathy in Pakinson's disease: an electrophysiological study. Neurol Res Int. 2014: 290513. IF: 0

Mathis S, Lamy M, Ciron J, Iljicsov A, Arjmand R, Agius P, Neau JP. (2014) Paroxysmal sneezing at the onset of syncopes and transient ischaemic attack revealing a papillary cardiac fibroelastoma. Case reports in neurological medicine, 881:734849 IF: 0

DOI:10.14753/SE.2022.2680

10. Acknowledgements

Both the research work and the writing of this thesis would have been impossible without the ongoing help of many people.

Of them, I mention first dr Magdolna Simó, who is not only the supervisor of this thesis but also my mentor for long years, and who has transmitted me a lot of her deep knowledge and experience in neurology and neuroimmunology - I wish to thank to her for all support.

I express my gratitude to Professor Dániel Bereczki, who is the head of the neuroepidemiological research group that I could became a participant: his innovative ideas and continuous encouragement were essential.

I owe many thanks to the members of the neuroimmonology team at the Department of Neurology in Semmelweis University, namely Dr Dániel Milanovich, Dr Nárcis Tegze, Dr Zsolt Mezei, Viktória Szórád, Nikoletta Tóth, Judit Kárpáti, Katalin Hegedüs.

I would thank to all my co-authors in different papers, especially Balázs Dobi, for their enthusiasm and excellent work that made possible to share our results.

And of course, the emotional and practical support of my family members were crutial and I am grateful for their endless efforts.

DOI:10.14753/SE.2022.2680

Appendix 1.

List of diagnoses with corresponding ICD-10 codes that were used to set up the NEUROHUN database

- neurological diseases (ICD-10 codes: G00-G99)
- cerebrovascular diseases (I60-I69)
- benign, uncertain or malignant neoplasms of the meninges and the central nervous system (D32-33, D42-43, C69-72)
- unspecified neurological symptoms: headache (R51); pain, unspecified (R52); malaise and fatigue (R53), syncope and collapse (R55); not classified convulsions (R56)

DOI:10.14753/SE.2022.2680

Appendix 2.

Table with number of incident and prevalent cases, crude prevalence and incidence between 2004-2016

	number of living patients (prevalence) - male	number of living patients (prevalence) - female	crude preval. total	crude preval. male / female	number of new patients (incid.)	number of new patients (incid.) male /female	crude incid. total	crude incid. male / female
2004	1593	4252	58.8	33,8 / 81.5	5845	1593 / 4252	58.8	33.8/ 81.5
2005	1994	5272	73.1	42.3 / 101.0	1421	401 / 1020	14.3	8.5 / 19.5
2006	2270	5968	82.9	48.1 / 114.3	1037	302 / 735	10.4	6.4 / 14.1
2007	2487	6541	90.8	52.7 / 125.3	891	257 / 634	9.0	5.4 / 12.1
2008	2662	7044	97.7	56.4 / 135.0	788	219 / 569	7.9	4.6 / 10.9
2009	2829	7460	103.5	60.0 / 142.9	728	224 / 504	7.3	4.7 / 9.7
2010	2987	7872	109.3	63.3 / 150.8	703	203 / 500	7.1	4.3 / 9.6
2011	3132	8206	114.1	66.4 / 157.2	616	187 / 429	6.2	4.0 / 8.2
2012	3266	8543	118.8	69.2 / 163.7	653	207 / 446	6.6	4.4 / 8.5
2013	3377	8857	123.1	71.6 / 169.7	625	191 / 434	6.3	4.0 / 8.3
2014	3521	9113	127.1	74.6 / 174.6	592	203 / 389	6.0	4.3 / 7.5
2015	3624	9369	130.7	76.8 / 179.5	538	163 / 375	5.4	3.5 / 7.2
2016*								

**Health insurance claims data available between 2004-2016, but as MS-definition includes apparition of G35 in ≥2 calendar years, last reliably interpretable year is 2015*
Incid: incidence. Preval: prevalence