Universidade Nova de Lisboa
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CLINICAL RESEARCH MASTER

CONCEPTION AND FIRST RESULTS OF A CROSS-SECTIONAL NATIONAL STUDY ON THE DEMOGRAPHY, DISEASE CHARACTERISTICS AND SOCIOECONOMIC STATUS OF THE PORTUGUESE PATIENTS WITH MULTIPLE SCLEROSIS – THE PORT-MS STUDY

Master's Dissertation | *Dissertação de Mestrado*

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Under the guidance of | *Sob orientação de*

Professor Doutor Armando Sena

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Abbreviations list

Abbreviation	English	Portuguese
CRF	Case Report Form	
DMT	Disease Modifying Treatment	
EDSS	Expanded Disability Status Scale	
EM	[Multiple Sclerosis]	Esclerose Múltipla
EMSP	[Secondary Progressive Multiple Sclerosis]	Esclerose Múltipla Secundária Progressiva
EMSR	[Relapsing Remitting Multiple Sclerosis]	Esclerose Múltipla Surto Remissão
GA	Glatiramer Acetate	
ISCE-93	International Classification by Status in Employment (ICSE) 1993	
MMF	Mycophenolate mofetil	
MS	Multiple Sclerosis	
PP	Primary Progressive	Primária Progressiva
PPMS	Primary Progressive Multiple Sclerosis	
PRMS	Progressive Relapsing Multiple Sclerosis (PPMS with relapses)	
RR	Relapsing Remitting	
RRMS	Relapsing Remitting	
SP	Secondary Progressive	Secundária Progressiva
SPMS	Secondary Progressive Multiple Sclerosis	
SR	[Relapse Remitting]	Surto Remissão

Acknowledgements

I thank Dr José Vale and Professor Maria José Sá for the stimulus and valuable help in the conception and implementation of this study.

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I thank the heads of the Multiple Sclerosis outpatient clinics of the 7 centers for having permitted the recruitment of their patients and use of their data (Dr José Vale and Professor Maria José Sá already mentioned, and also Professor João Cerqueira, Professor Ana Martins da Silva, Dr Livia Sousa, Professor João de Sá, Dr Rui Pedrosa).

I thank all the co-investigators mentioned in the Appendices section of this dissertation.

I very especially thank Professor Armando Sena for having accepted to review this work and guide me in this dissertation. He was, until recently, the neurologist of many of the patients coming from one of the centers.

Abstract | *Resumo*

Background/aims: In Portugal, there wasn't a multicentric study on the general characteristics (demography, disease milestones, DMT, socioeconomic status) of Multiple Sclerosis patients.

Methods: Patients fulfilling McDonald 2010 criteria were sequentially recruited from May to November 2014 in 7 centers and data was systematically collected.

Results: 561 patients included. First symptoms occurred at 30,2±10,5 years-old (RRMS 29,2±10, PPMS 39,4±11,7, p<0,001); diagnosis 3,2±5,3 years later (RRMS 3,0±5,1, PPMS 4,9±2,5, p=0,002); 9,4±7,2 years elapsed since diagnosis (similar for those is RRMS at diagnosis and PPMS); current age 42,9±12,4 years-old (group RRMS at diagnosis 42,0±12,1, PPMS 52,5±11,3, p<0,001); current EDSS 2,5 (RRMS 2.0, PPMS 6.0); females to males 2,5:1 (RRMS similar, PPMS 1,1:1, p<0,05); at diagnosis RRMS 90,6%, SPMS 0,9%, PPMS 8,6%; 9,5% of RRMS reached SP at inclusion (those older at diagnosis, in actuality, or with longer follow-up). PPMS more frequent in patients diagnosed at older ages (p<0,001), also slight increase in females. Along the last decades: new cases have showed stable proportions of gender and disease types; age at first symptoms and diagnosis slightly increased, time between them slightly decreased. Proportion on DMT (May 2014): 84,5% of all; 90,4% of currently in RRMS; 70,8% of SPMS; 36,8% of PPMS; 48% of progressive forms together. Type of DMT, all patients: interferons 56,5%, Glatiramer Acetate 18,4%, Natalizumab 11,6%, Fingolimod 9,7%. Economically active 61,5% of all, unemployment 13,5%, 74,1% of non-active are retired due to disease. Females pregnant after diagnosis 15%. Positive family cases in 7,8%.

Discussion/Conclusions: 10% of the national MS population collected. Data generally consistent with international reports. Proportion under DMT relatively high in all disease types, but second line therapies underrepresented. Young patients with mild disease have an active economic life. Those not active are essentially retired due to disease.

Introdução e objetivos: Não existia um estudo multicêntrico que descrevesse as características dos doentes com EM, da doença em si, ou do seu tratamento, em Portugal.

<u>Métodos</u>: Doentes McDonald 2010 positivos foram sequencialmente recrutados em 7 centros entre Maio e Novembro 2014. Aplicou-se um Caderno de Recolha de Dados incidindo na demografia, doença, educação e emprego (estudo PORT-MS).

<u>Resultados</u>: 561 doentes incluídos. Primeiros sintomas aos 30,2±10,5 anos (RRMS 29,2±10, PPMS 39,4±11,7, p<0,001); diagnóstico 3,2±5,3 anos depois (RRMS 3,0±5,1, PPMS 4,9±2,5, p=0,002); tempo de doença após diagnóstico 9,4±7,2 anos (semelhante RRMS no diagnóstico e PPMS); idade atual 42,9±12,4 anos (grupo RRMS no diagnóstico 42,0±12,1, PPMS 52,5±11,3, p<0,001); EDSS atual 2,5 (RRMS 2.0, PPMS 6.0); proporção feminino:masculino é 2,5:1 (RRMS semelhante, PPMS 1,1:1, p<0,05); no diagnóstico RRMS 90,6%, SPMS 0,9%, PPMS 8,6%; 9,5% dos RRMS encontravam-se em SP na inclusão (nomeadamente os com mais idade no diagnóstico e/ou atualidade ou tempo de doença mais prolongado). PPMS mais frequente em doentes diagnosticados mais tardiamente (p<0,001), onde aumenta também ligeiramente a proporção de mulheres na PPMS. Nas últimas décadas: novos casos mostram estabilidade na proporção de géneros e tipos de doença; idade nos primeiros sintomas e no diagnóstico aumentou ligeiramente, tempo entre eles diminuiu ligeiramente. Proporção sob DMT (Maio 2014): global 84,5%; atualmente RRMS 90,4%; SPMS 70,8%; PPMS 36,8%; progressivas agregadas 48%. Tipo de DMT, amostra global: interferões 56,5%, GA 18,4%, Natalizumab 11,6%, Fingolimod 9,7%. Global: economicamente ativos 61,5%, desemprego 13,5%, 74,1% dos não activos estão reformados por doença. Gravidezes após diagnóstico em 15% mulheres. Casos com história familiar positiva 7,8%.

<u>Discussão e conclusões</u>: Incluída cerca de 10% da população portuguesa. Resultados congruentes com dados internacionais. Elevada proporção sob DMT, mesmo EDSS alto e formas progressivas. Terapêuticas de segunda linha sub representadas. Doentes jovens e com doença ligeira com vida económica ativa; restantes essencialmente reformados por doença.

Introduction and background

Surveys and registries are essential instruments to gather data on multiple aspects of a disease, including: its epidemiology; its clinical course (especially in the long-term); the provision of treatments, services and supplies for it within a given region; the effectiveness, efficiency (cost-effectiveness) and safety of treatments or other interventions (namely in the long-term); the implementation of guidelines relating to care and treatment; and its quality of life, burden of symptoms and socioeconomic aspects from the patient's perspective, just to name a few (Flachenecker 2008, Flachenecker 2014). The information provided by these studies is useful not only to ameliorate the quality of care of patients, but also for society in more general terms, by increasing the understanding and knowledge about diseases and allowing authorities and relevant parties to make better informed, more effective, decisions about them. Surveys and registries are also especially important when rare, complex and/or costly diseases, Multiple Sclerosis (MS) belonging to the group that satisfies these three conditions, are concerned.

In MS, a number of well-known registries exists in the developed world. Many of them, or all of them if we consider them globally, have been extremely important to understand this complex disease in many ways. They clarified many aspects of the natural history, certain long-term effects of treatments, and also the standards of care. In this, as in other diseases, registries are also increasingly becoming instruments that health authorities use (at the same time as investigators) to plan and control many aspects of the health care. In certain countries, authorities determine the obligatory introduction of patients in registries for certain diseases (one example is the Danish MS Treatment Registry) (Flachenecker 2014).

As it would be expectable, the majority of existing registries on MS, including the most important ones, are based on healthcare services, namely MS centers, although some of them also cross their data with information coming from other sources. This last strategy permits to attain a high level of ascertainment of cases at the national level (Danish MS Registry and New Zealand's cross-sectional national prevalence study of 2006). Other studies such as NARCOMS (North American Research Committee on MS) registry, initiated in 1996 by the North-American Consortium of MS Centers, are patient-based. NARCOMS is a long-term project to promote and facilitate clinical and epidemiological research in MS. After informed consent, patients are enrolled into the registry and report subsequent updates or any changes in health state or treatment. These data include demographics, healthcare insurance, therapies, healthcare services used, disability, handicap and quality of life. Since the diagnoses of MS are unverified,

self-reported diagnoses of registry participants are compared to physician-reported diagnoses and with those based on reviews of medical records. Apart from the NARCOMS Registry, several small and uncoordinated MS registries and databases are available within the United States, but one national harmonized data collection system does not exist (Flachenecker 2008, Hurwitz 2010).

Some studies constitute international collaborations (like EDMUS and MS-base), but the majority has a national dimension, with various levels of ascertainment (Danish MS Registry; Danish MS Treatment Registry; Swedish MS Registry; Norwegian MS Registry and biobank; Italian MS Database Network and German MS Registry). The Danish MS Registry is considered de gold standard of MS registries. It has, since January 1, 1949, been continuously updated with collected data on virtually all known new cases of MS in Denmark. The sources of notification are all 22 neurological departments in Denmark, private neurology and general practitioners, rehabilitation hospitals, the Danish MS Society, neuropathological departments, the National Patient Registry and the National Registry of Causes and Death (Flachenecker 2008). Only three neurologists have been involved in classification, ensuring a certain degree of homogeneity (Koch-Henriksen 2012). With the introduction of immunomodulatory therapy in Denmark in 1996, all patients starting treatment were also registered mandatorily in a Danish MS Treatment Registry and followed prospectively. The Danish registries include clinical data, neurological examination and standard laboratory tests that are regularly updated (Flachenecker 2008). They allow analysis of trends in incidence, prevalence, survival and cause-specific mortality and provide samples of patients for research, case-control studies and prospective studies (Bronnum-Hansen 2011). The Swedish Registry was introduced in 1997 and is widely used in neurology clinics all over the country by neurologists when counselling patients. It includes variables such as age at onset, gender and clinical parameters. (Westerlind 2014). The Norwegian MS Registry and Biobank besides gathering clinical and epidemiological data also collects biological samples, including blood, CSF and brain tissue. This registry has a key component in recruiting patients into the large international case–control study to investigate environmental risk factors in MS (Myhr 2012). The Italian MS Database Network is the first Italian MS registry that is based on a user-friendly, electronic MS patient monitoring system. Several specialised MS centres were selected and agreed on a standardized protocol. Each study site has a neurologist responsible for the quality and consistency of data and then a Scientific Advisory Board is responsible for the analysis, approval and validation of the database (Flachenecker 2008). In Germany, there was a study with a 2-year pilot phase and based on experience gained during that phase, some parameters were modified. The survey was not population-based, relying mainly on data provided by health institutions (Flachenecker 2008).

Some studies follow local cohorts prospectively with a high level of detail in information collected (London, Ontario database; British Columbia MS database; New York State MS Consortium database; Department of Veterans Affairs registry; North American Research Committee on MS) (Hurwitz 2010). The majority of the databases have a prospective follow-up, although some important studies were transversal studies (New Zealand's cross-sectional national prevalence study of 2006).

In the European Union, healthcare for, as well as the socioeconomic conditions of, MS patients differs greatly across countries. Different registries and databases also differ in terms of objectives, time, and resources spent for registration and analytical preferences, and they are not available everywhere. In the intent to tackle those disparities, the European Commission financed a project of the international consortium *European MS Platform* (EMSP). This project, called EUReMS (European Register for MS), was set up in 2010 and its general aim is to establish a European-wide platform for systematic analysis and comparison of longitudinally collected MS data in Europe. It involves both scientists and patient organizations. One of EUReMS' principles is that it should be built on already existing national or regional MS registries and databases, harmonizing and merging them. In a systematic survey of the MS registries in Europe in 2012, 20 registries were identified (Table 1). As the authors of the survey stated, these registries differed widely for objectives, structure, collected data, and for patients and centers included. Despite this heterogeneity, common objectives of the registries were epidemiology (n=10), long-term therapy outcome (n=8), healthcare research (n=9) and support/basis for clinical trials (n=8). Less frequent registry aims were cost and cost-effectiveness of treatment (n=5), quality management of healthcare (n=5), and gathering data (n=1). All registries included patients with MS according to the McDonald criteria. In addition, six registries applied Poser criteria, and eight registries also collected data on patients with clinically isolated syndromes (CIS). A Catalan registry was specifically designed for CIS patients. The majority of registries was hospital-based (n=10, 77%), and five (38%) population-based, with three registries being hospital- and population-based together. In three registries, patient lists from MS societies were used either exclusively (n=1) or in combination with the above-mentioned sources of data collection. Most registries (n=9, 69%) intended to capture all MS patients in the country, whereas four registries (31%) attempted to collect data on representative subsets (regions) of patients (Croatia, Italy, Switzerland and United Kingdom). According to EUReMS, a pan European database should focus on four missions: MS epidemiological and clinical surveillance; long-term efficacy, safety and cost-effectiveness of MS disease-modifying and symptomatic treatments; provision and quality

of healthcare services; and quality of life, the burden of symptoms and socioeconomic aspects from the patient's perspective.

No reference is made to Portugal in this study. There is not, in our country, at least at a multicentric level, a registry or even a wide cross-sectional characterizations of the state of this disease, these patients and their treatment. In fact, demographic, epidemiological or clinical data about MS at a regional or national level is scarce in Portugal. A population-based prospective study conducted over a period of five years and published in 2006 revealed a prevalence of 46.3/100 000 in the district of Santarém (De Sá 2006, De Sá 2010), and in 2010 a national transversal study using a survey determined a self-reported MS prevalence in continental-Portugal, among adults of 54/100 000 and an estimated number of patients of 4287 (varying between 2700 and 5875) (EMCode, DGS). We did not find other relevant publications of national level about general aspects of the disease in our country.

Having this in mind, the author of this dissertation, coordinating a group of other investigators, set up the here presented PORT-MS study with the primary objective of knowing the characteristics of the Portuguese MS population in terms of demography, main disease milestones, present clinical state, general aspects of treatment and socioeconomic status, including education and employment data. Secondary objectives of this study were: to identify any eventual focus of high or low prevalence in the Portuguese territory; to collect data on pregnancy in female MS patients; to collect data on familial cases of MS; to know the proportion of patients that has participated in interventional trials; to identify any possible asymmetries in demography, clinical characteristics, milestones of the disease or standards of diagnosis and care between Portugal and other countries and contribute to the explanation or correction of these asymmetries; to foster the development of a prospective national registry and eventually contribute to a European database.

Due the extension of this study and the limit date for the presentation of this dissertation, here I present the design and implementation of the PORT-MS study and also the first results. The analysis of all the data gathered will continue throughout the next few months and sometimes it may be visible in this dissertation that the analysis of some results seems somewhat incomplete. Also, in view of the bilingual nature of this study, sometimes there is some Portuguese phrasing that I was unable to translate.

Country	Survey	Interview	Website
Literature/MS Barometer			
Austria	no[a]	-	
Bosnia-Herzegovina	no response	-	
Croatia	yes	yes	www.sdmsh.hr/baza
Czech Republic	no response	-	
Denmark	yes	yes	www.ms.research.dk
France	yes	-	www.edmus.org
Germany	yes	yes	www.dmsg.de/msregister/
Greece	yes	-	www.gmss.gr
Iceland	no[b]	-	
Italy	yes	yes	www.imedweb.it
Malta	no response	-	
Netherlands	no response	-	
Norway	yes	yes	www.ms-kompetansesenter.no
Slovenia	no response	-	
Spain (Catalonia)	yes	yes	www.epidemcat.cat/index.php/en/epidemcat—registro
Sweden	yes	-	www.msreg.net
United Kingdom	yes	yes	www.ukmsregister.org www.mssociety.org.uk
MS societies			
Russia	yes	-	
Serbia	yes	-	
Switzerland	yes	-	

Overview of the responses of MS registries as identified by literature search and the MS Barometer (above) and by asking MS societies (below). Indicated is whether the registries responded to the survey (2nd column), and whether interviews could be performed (3rd column).
[a]only treatment registries for natalizumab and fingolimod.
[b]no access to data.

Table 1. MS registries in Europe. (Adapted from: Multiple Sclerosis Journal 2014, Vol. 20(11) 1523– 1532.)

Methods

The complete protocol of this study is presented in the Appendices section of this document. Study rationale and objectives, design and procedures, population and sample, informed consent and regulatory aspects, CRF and publication policy are detailed there. Here I present only a brief summary and documentation or data produced after protocol submission (authorizations from competent parties).

Participants

MS patients fulfilling McDonald 2010 criteria in seven participating centers (Table 2 and Figure 1) were sequentially recruited in the outpatient clinics, day-hospital and Neurology wards, from May 2014 until November 2014 (this constitutes the "phase 1" of this project). In order to avoid selection bias, participating physicians were encouraged to include all patients with MS seen in their practice.

- Serviço de Neurologia, Hospital de Braga, Braga, Portugal
- Serviço de Neurologia, Centro Hospitalar de São João, Porto, Portugal
- Serviço de Neurologia, Centro Hospitalar do Porto – Hospital de Santo António, Porto, Portugal
- Serviço de Neurologia, Centro Hospitalar Universitário de Coimbra, Coimbra, Portugal
- Serviço de Neurologia, Hospital Beatriz Ângelo, Loures, Portugal
- Serviço de Neurologia, Centro Hospitalar de Lisboa Norte – Hospital de Santa Maria, Lisboa, Portugal
- Serviço de Neurologia, Centro Hospitalar de Lisboa Central – Hospital de Santo António dos Capuchos, Lisboa, Portugal

Table 2. Identification of the MS Centers that participated in the PORT-MS study (phase 1).

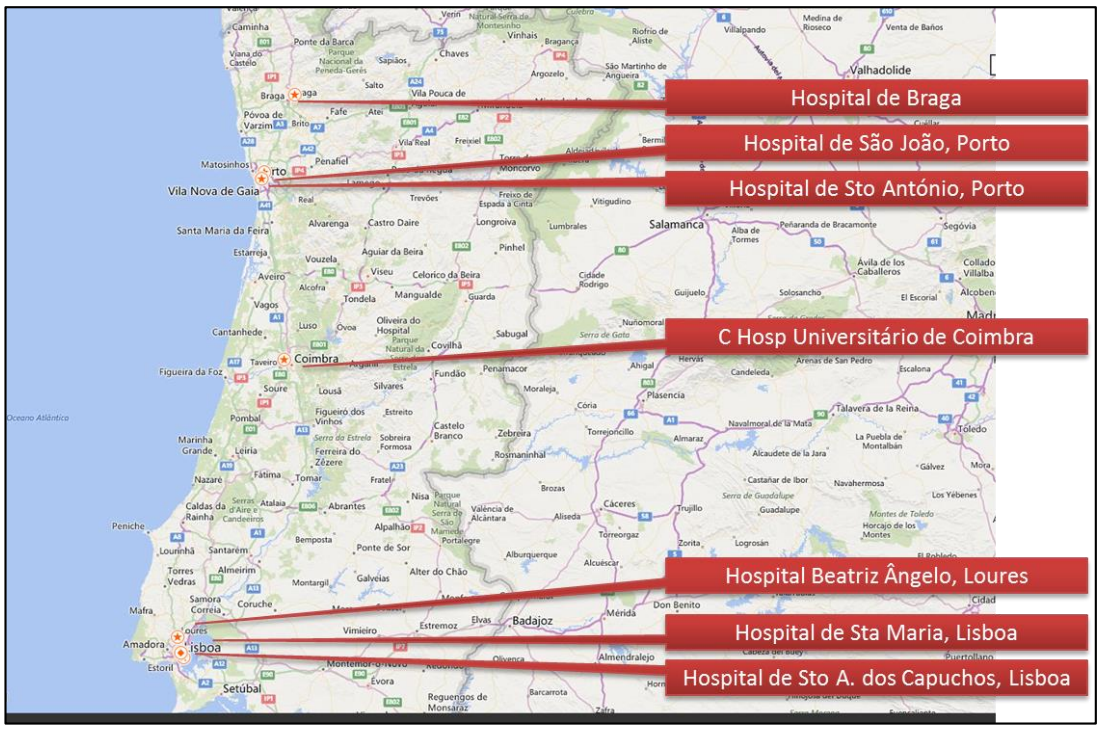


Figure 1. Geographical localization of the 7 participating centers in phase 1 of the PORT-MS study.

Collected Data

A systematized Case Report Form (CRF) collecting retrospective and present data directly from the clinical file, the patient and the patient's physician was applied (cross-sectional study). Date and place of residency at birth, at first symptoms and at diagnosis of MS, gender, migrations abroad during life, disease clinical course, current (May 2014) treatment and EDSS, education (International Standard Classification of Education - ISCED 2011), status of employment in the week preceding the CRF filling (International Classification of Status of Employment - ICSE 1993), need for a caregiver, involvement in clinical trials, familial MS and pregnancy.

Data sets were coded using a unique key designed to allow us to identify repeated cases due to simultaneous follow-up in different hospitals.

Statistical analysis

Phase 1 of this study, which occurred between the mentioned dates, was expected to include 500 patients, which was accomplished.

We used SPSS software for Windows, version 20 (SPSS Inc., Chicago, IL, USA) to calculate descriptive and inferential statistics. Parametric and Non-Parametric tests were used. Comparisons were labeled as statistically significant at the conventional p-value of less than 0.05.

Ethics and other approvals

According to the Portuguese law concerning the treatment of healthcare data and clinical investigation, this study was submitted to the [National Committee for Data Protection] (CNPD, Comissão Nacional de Proteção de Dados) and approved by this organization. The corresponding file number is 5288/2014 and the approval number is the 6761/2014. This data is public and available at the CNPD's internet site.

Although this study is not a Clinical Trial, according to the Portuguese law on clinical investigation (Law number 21/2014, dated the 16th April 2014), this study was submitted to the local ethics committee of each of the hospitals (CES, Comissão de Ética para a Saúde, in the Portuguese acronym and designation) where this study run (and is still running), and approved by each of them. Figure 2 shows one example of these approvals for the sake of proof.

Our procedures also respected the Declaration of Helsinki and the guidelines on Good Clinical Practice (GCP) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), notably in terms of collection of consent from patients (the respect for these norms is integrated on the Portuguese and European law on Clinical trials).

HOSPITAL BEATRIZ ÂNGELO

Exmo. Senhor

Dr. Paulo Alegria

Serviço de Neurologia

Hospital Beatriz Ângelo

Loures, 26 de junho de 2014

N/Ref. *0034/2014_RMEB*

Estudo HBA N.º 0112

Assunto: Estudo: "PORT-MS (base de Dados PORTuguesa de Esclerose Múltipla) – Um inquérito nacional para descrever as características clínicas e demográficas básicas dos doentes com Esclerose Múltipla em Portugal na actualidade".

Caro Dr. Paulo Alegria,

Temos o prazer de informar V. Exa. de que o estudo em epígrafe foi aprovado pela Comissão de Ética para a Saúde e Comissão de Investigação Clínica do Hospital Beatriz Ângelo.

Com os melhores cumprimentos,

O Presidente das Comissões

Professor Doutor Rui Maio

Figure 2. Example of approval of the PORT-MS study by a local ethic committee (in this case corresponding to the Hospital Beatriz Ângelo).

Results

General aspects of the database

The MS centers of seven hospitals collaborated to this database (Table 2 and Figure 1). These hospitals are distributed throughout the northern, central and southern coastal side of the Portuguese continental territory. Six of them are University hospitals, one of them is not. Five of these University hospitals are classified as “tertiary” or “central” hospitals, and they hold the five biggest MS centers in Portugal. The other two hospitals are considered more like “regional” hospitals. Together, these institutions may follow more than half of the Portuguese MS patients, but the number included until now in this database is partial in each of them, globally equilibrated between institutions but reflecting, at the same time, the total number of patients each of them has on follow-up.

The patients that eventually refused to participate in the study were not registered but we are not aware of any, so they must have been exceptional at most (in view of the number of investigators involved, we theoretically admit that the coordinating investigators of the study might have missed some exceptional cases).

The first CRF was filled in May 2014, the last one in November of the same year. No repeated patients were detected in the 568 patients initially included but seven patients were excluded due to incomplete data in six cases and incongruent data in one case.

561 patients were confirmed as fulfilling the minimum requirements in terms of data available and congruency of data. Considering the estimated total number of 5000 to 6000 patients with MS in Portugal, this database contains around 10% of the Portuguese patients.

General characteristics of the patients and of their disease

The clinical type of disease at disease onset (first symptoms) and at diagnosis was asked in a single question that admitted the hypothesis of start as RRMS and diagnosis still in RRMS or the hypothesis of start as RRMS but already diagnosed in SPMS. Of course, the assumption of a

certain clinical profile at disease onset (first symptoms) is, in the great majority of patients, based in the anamnesis. We didn't ask specifically if a patient that was assumed to start as a progressive relapsing form was still having relapses at diagnosis. We opted for distinguishing progressive relapsing patients from not relapsing ones to more accurately identify a group of progressive patients with less bias.

The clinical type of MS at disease onset and diagnosis is shown in Table 3.

Tipo inicial de EM

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	SR	508	90,6	90,6	90,6
	SR já em SP	5	,9	,9	91,4
	PP	38	6,8	6,8	98,2
	PP com surtos	7	1,2	1,2	99,5
	duvidoso	3	,5	,5	100,0
	Total	561	100,0	100,0	

Table 3. Clinical type of MS onset and diagnosis.

The clinical type of disease at disease onset (first symptoms), derived from the previous table, is shown in Table 4 and Figure 3 (we excluded a few patients that were still not definitively classified at inclusion).

RR	91,9%
PP w/o relapses	6,8%
PP w/ relapses	1,3%

Table 4. Clinical type of MS at disease onset (after excluding cases with still ambiguous profile).

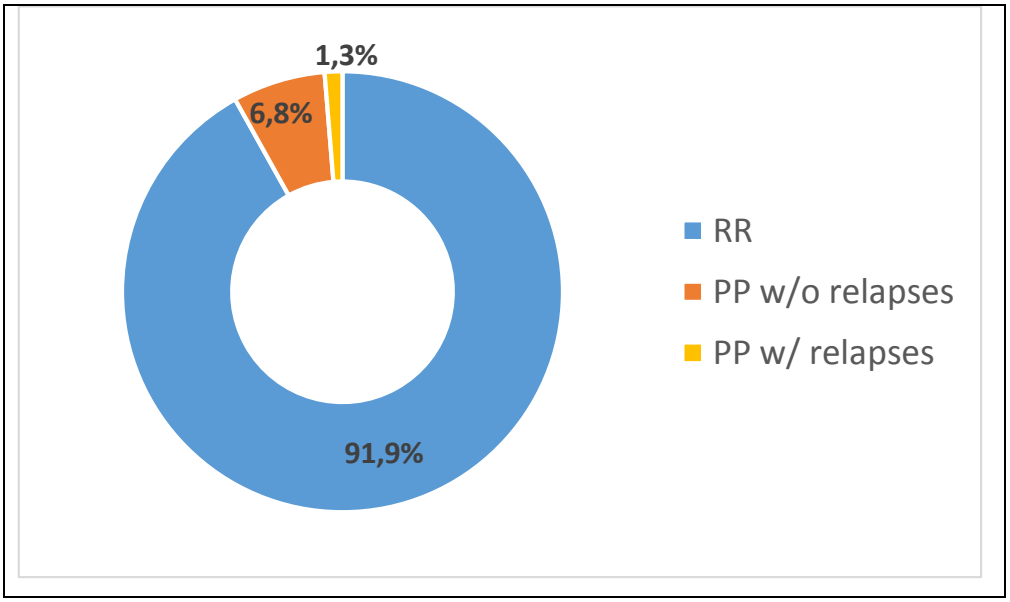


Figure 3. Clinical type of MS at disease onset (after excluding cases with still ambiguous profile).

First symptoms of disease occurred at the age of 30,2±10,5 years-old. (min 5; max 70). The first symptoms were reported to have occurred between November 1964 and May 2014 (median December 200).

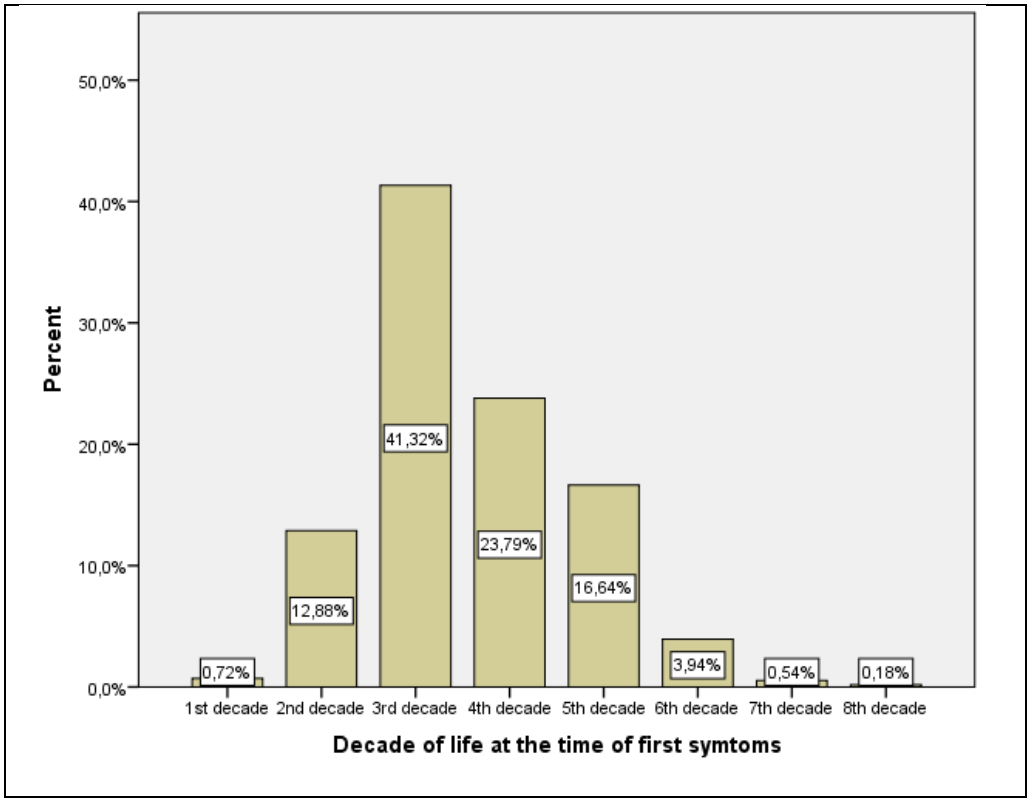


Figure 4. Decade of life at the time of first symptoms.

Time elapsed from first symptoms to diagnosis was 3,2±5,3 years in our sample.

The clinical type of disease at diagnosis is shown in Table 5 and Figure 5 (we excluded a few patients that were still not definitively classified at inclusion).

RR	91,0%
SP	0,9%
PP w/ or w/o relapses	8,1%

Table 5. Clinical type of MS at diagnosis (after excluding cases with still ambiguous profile).

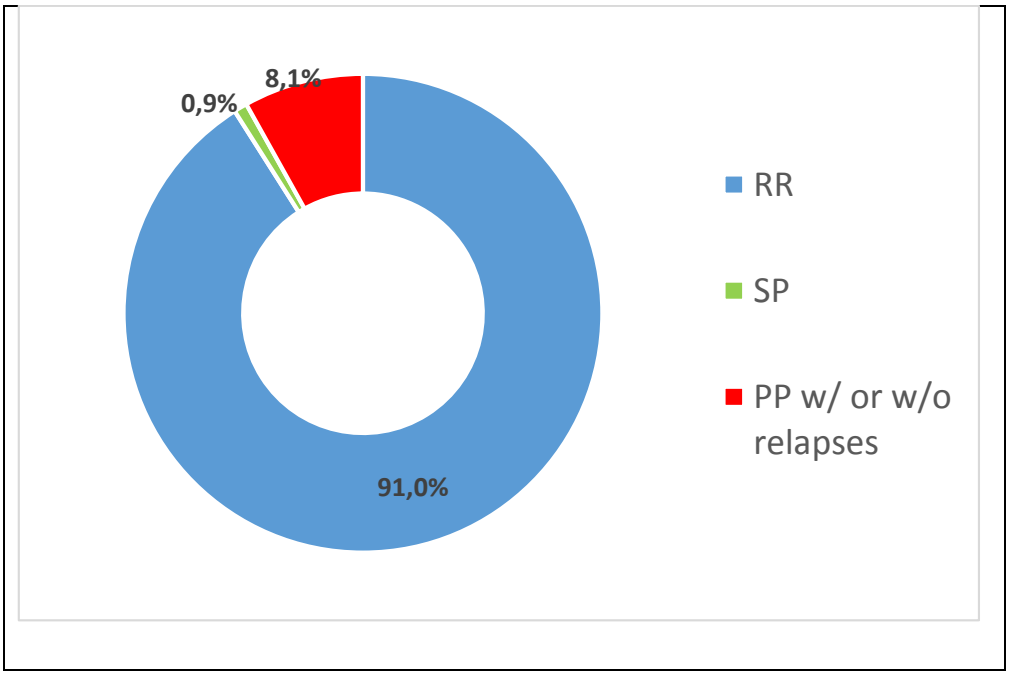


Figure 5. Clinical type of MS at diagnosis (after excluding cases with still ambiguous profile).

Mean age at diagnosis was 33,4±11,1 years-old (min: 5; max: 70). The diagnosis of MS occurred between June 1978 and September 2014 (median February 2007).

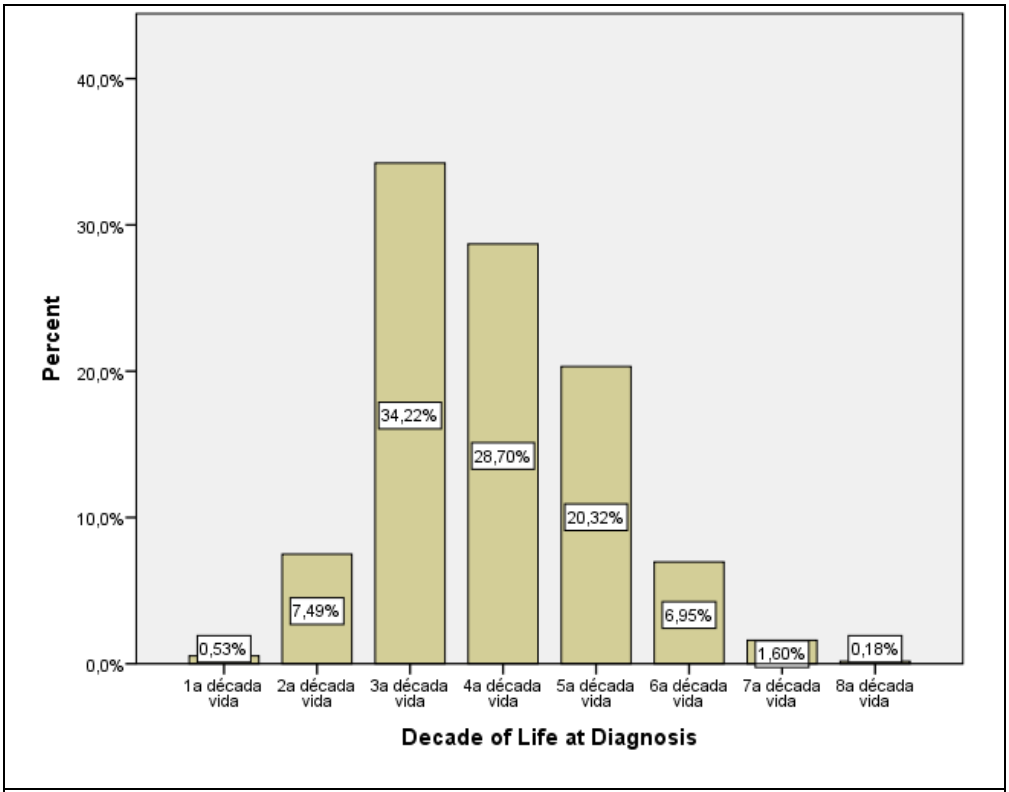


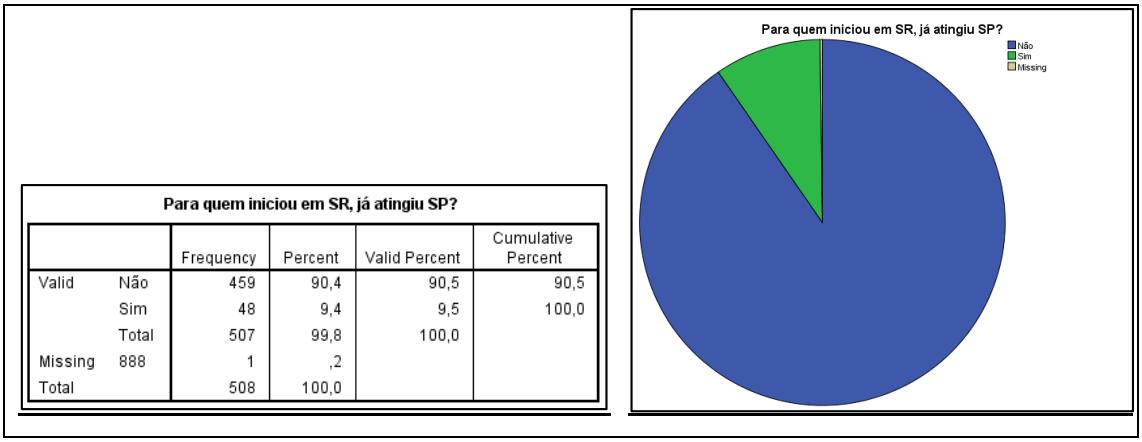
Figure 6. Decade of life of patients at diagnosis.

The time of disease evolution from diagnosis to inclusion for our total sample is 9,4±7,2 years (min: 0; max: 36,2; median: 7,5 years).

Total time of disease evolution from first symptoms to inclusion of patients in our sample is 12,6±9,2 years (min: 0,2; max: 49,8 years).

Time from diagnosis to inclusion of group "RRMS at diagnosis" is 9,6±7,3 years, and of PPMS patients it is 8,1±6,4 years (p=0,2, Independent-samples Mann-Whitney U test).

Of our 508 patients that were in RR phase by the time of diagnosis, 9,5% reached SPMS by inclusion (Figure 7).



Para quem iniciou em SR, já atingiu SP?

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Não	459	90,4	90,5	90,5
	Sim	48	9,4	9,5	100,0
	Total	507	99,8	100,0	
Missing	888	1	,2		
Total		508	100,0		

Figure 7. Patients that reached SPMS by time of CRF filling, having been diagnosed in RRMS phase at diagnosis.

The clinical types of MS at inclusion (or current type of MS or, type of MS at present time) is shown in table Table 6 and Figure 8.

RR	82%
SP started after diagnosis	8,6%
SP already at diagnosis	0,9%
PP w/ or w/o relapses	8,0%
doubtful	0,5%

Table 6. Distribution by clinical type of MS at the day of CRF filling.

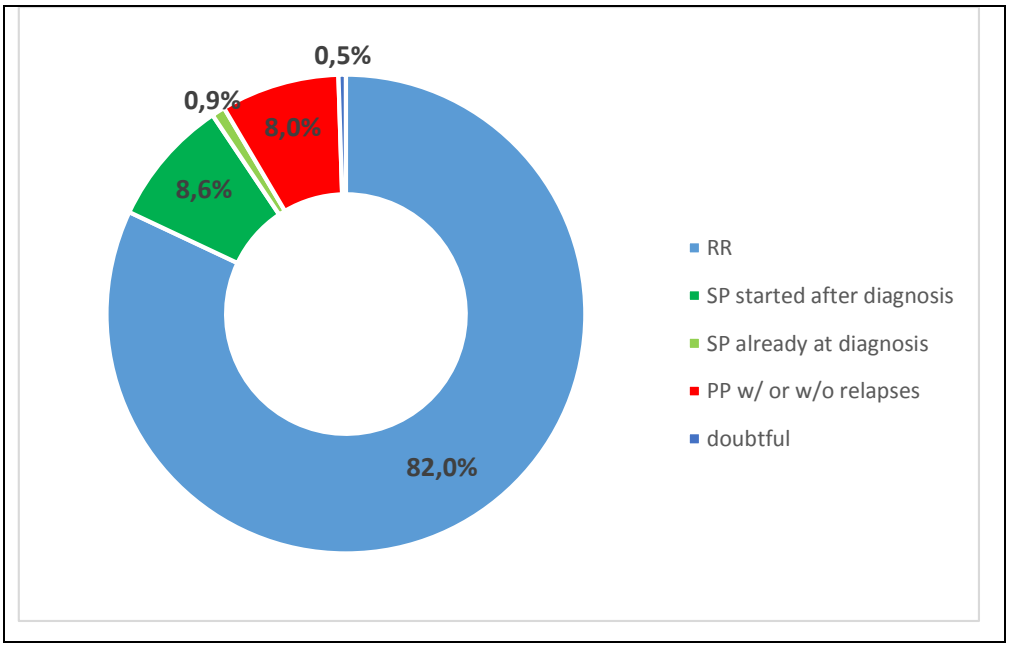


Figure 8. Distribution by clinical type of MS at the day of inclusion in the study.

The age of the total patients in our sample at inclusion is 42,9±12,4 years-old (min: 17; max: 76 years).

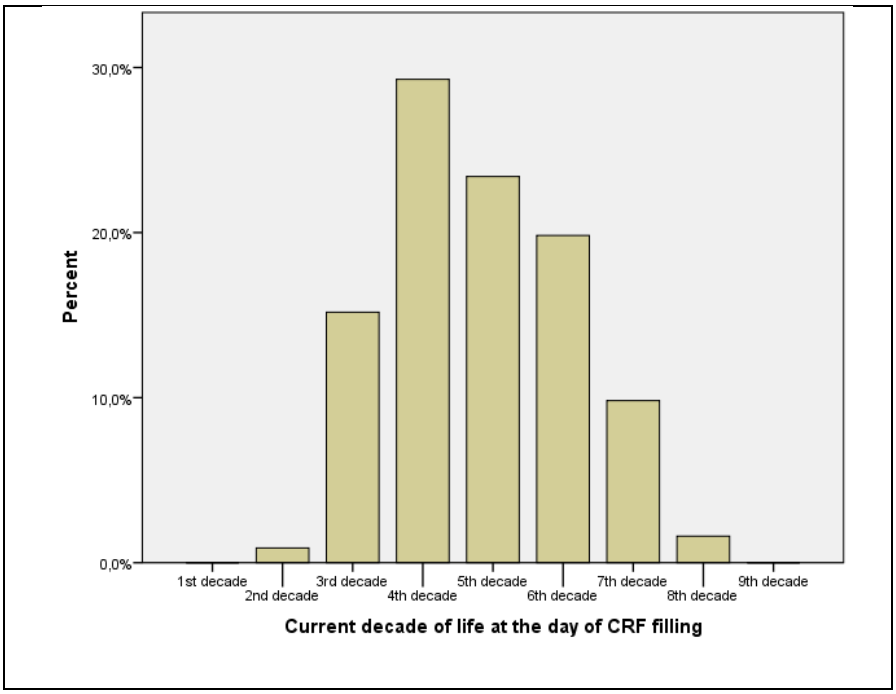


Figure 9. Current decade of life of patients (at inclusion).

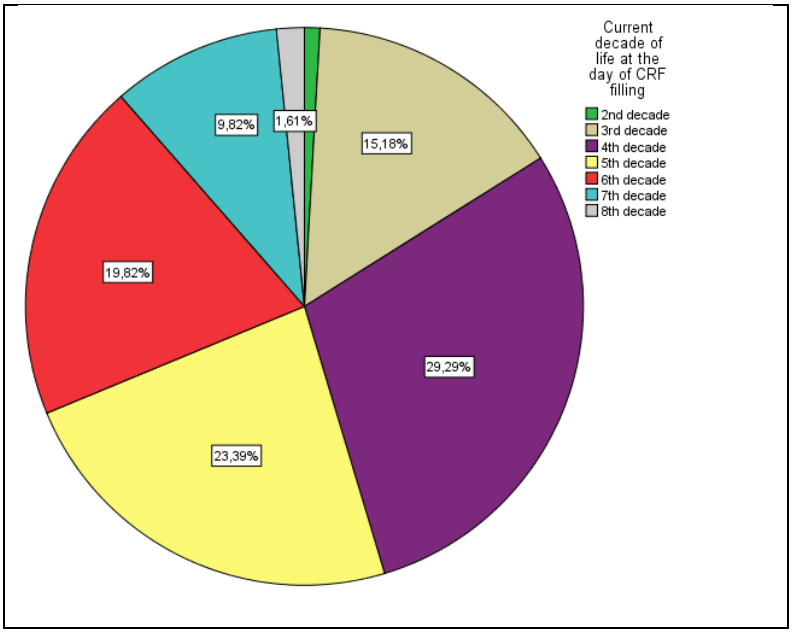


Figure 10. Proportions of current decade of life of patients (at inclusion).

Dates of birth of patients are comprised between June 1938 and September 1997 (median August 1972).

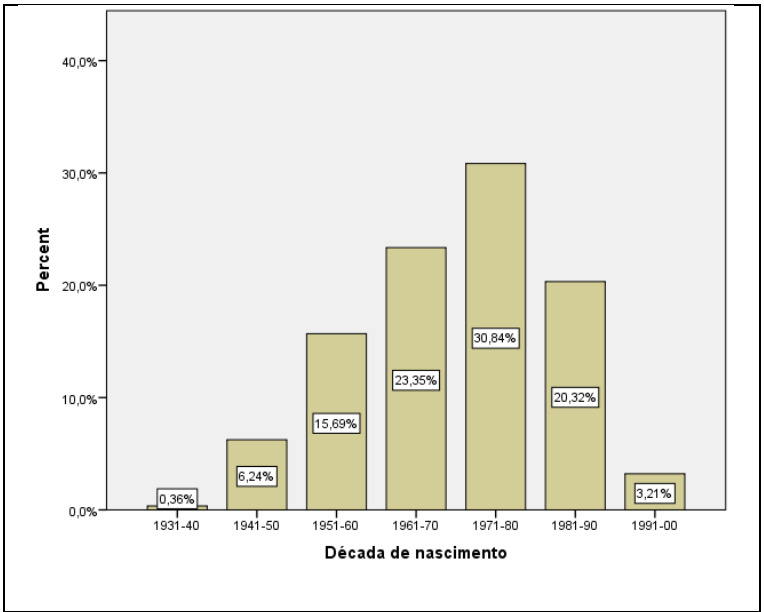


Figure 11. Decade of birth of birth of patients included in the PORT-MS study.

Gender

70,8% (n=397) of patients of our sample are female (29,2% male, n=164), which is equivalent to a proportion of 2,5 females to 1 male.

Place of birth

92,9% of the patients were born in Portugal. Forty patients were born outside de country, essentially in countries belonging to the European Union, in other countries historically associated with Portuguese emigration, or in Portuguese ex-colonies. Around half of these cases correspond to countries of higher latitude or traditionally considered of higher MS prevalence (Table 7). All the patients born in Portugal are of Portuguese nationality, as are 20% (seven cases) of those born abroad.

		Frequency	Percent
Valid	África do Sul	1	,2
	Alemanha	6	1,1
	Angola	6	1,1
	Bielorrússia	1	,2
	Brasil	6	1,1
	Cabo Verde	2	,4
	Canadá	1	,2
	Congo	1	,2
	França	9	1,6
	Guiné-Bissau	1	,2
	Holanda	1	,2
	Itália	1	,2
	Moçambique	2	,4
	Suíça	2	,4
	Total	40	7,1
	PORTUGAL	521	92,9
Total		561	100,0

Table 7. Place of birth of the 40 patients (7,1% of our total patients) that were not born in Portugal.

Ethnicity

98,9% of the patients in the database are white, five patients are black (0,9%), and one case is of south Asian ethnicity (0,2%).

Analysis of age at first symptoms across the last decades, across clinical types of disease and across genders

Age at first symptoms (Figure 12) has slightly increased over the last few decades (p=0,009, Independent-Samples Kruskal-Wallis test).

Report

Age at 1st symptoms

Década de diagnostico	Mean	N	Std. Deviation
1971-80	25,5000	2	6,36396
1981-90	24,1071	28	8,85412
1991-00	28,8525	122	10,36975
2001-10	30,8470	268	10,66071
2011-20	31,5929	140	10,52226
Total	30,2429	560	10,58157

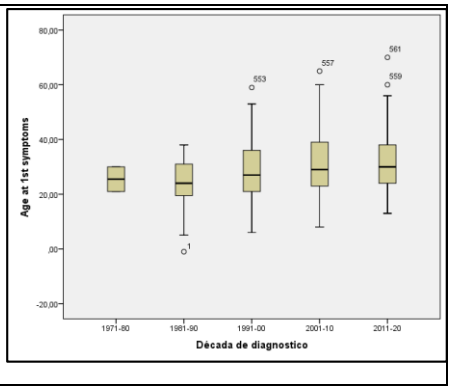


Figure 12. Mean age at first symptoms for diagnosis occurring in each decade in time.

Age at first symptoms of group "RRMS at diagnosis" was 29,3±10 years-old (n=508, CI95%: [28,5;30,2]) versus 39,4±11,7 years-old (n=38, CI95%: [35,6;43,3]) in PPMS patients (p<0,001, Independent-samples Mann-Whitney U test) (Table 8, Figure 13Figure 13. Age at first symptoms by clinical type of MS (RRMS versus PPMS).). From the group of patients RRMS at diagnosis, those that were already in SPMS at inclusion had started the disease at the same age than those that remained in RRMS at inclusion.

	N	Age at first symptoms (years-old)
All	561	30,2±10,5
RRMS at diagnosis	508	29,3±10
PPMS (w/o relapses)	38	39,4±11,7
PPMS w/ relapses	7	42,1±9,7
PPMS together	45	39,9±11,3
SPMS at diagnosis	5	28,6±8,5
SPMS at inclusion (RRMS at diagnosis)	48	30,62±10,6
RRMS at inclusion	458	29,22±9,9
All SPMS at inclusion	53	30,4±10,4

Table 8. Age at first symptoms for each of the clinical subtypes.

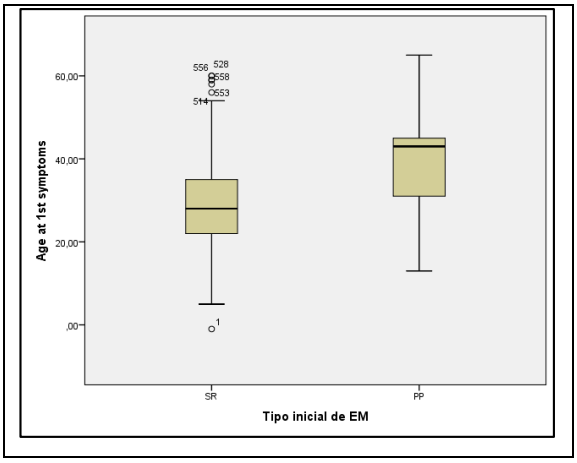


Figure 13. Age at first symptoms by clinical type of MS (RRMS versus PPMS).

Men reported first symptoms at an earlier age than women. Although small, this difference attains statistical significance when we analyze the whole sample or only RRMS at diagnosis. The difference is more marked in PPMS (without relapses), but here statistical significance is not attained, probably due to our small number of patients (Table 9,Figure 14).

	Male (N) age at first symptoms	Female (N) age at first symptoms	p
All	(164) 28,6±9,4	(396) 30,9±10,9	0,021 (Independent-samples Mann-Whitney U test)
RRMS at diagnosis	(144) 27,6±8,9	(363) 30,0±10,3	0,015 (Independent-samples Mann-Whitney U test)
PPMS (w/o relapses)	(18) 35,8±11,2	(20) 42,7±11,3	n.s. (Independent-samples T test)

Table 9. Age at first symptoms for male and female gender in selected clinical subtypes.

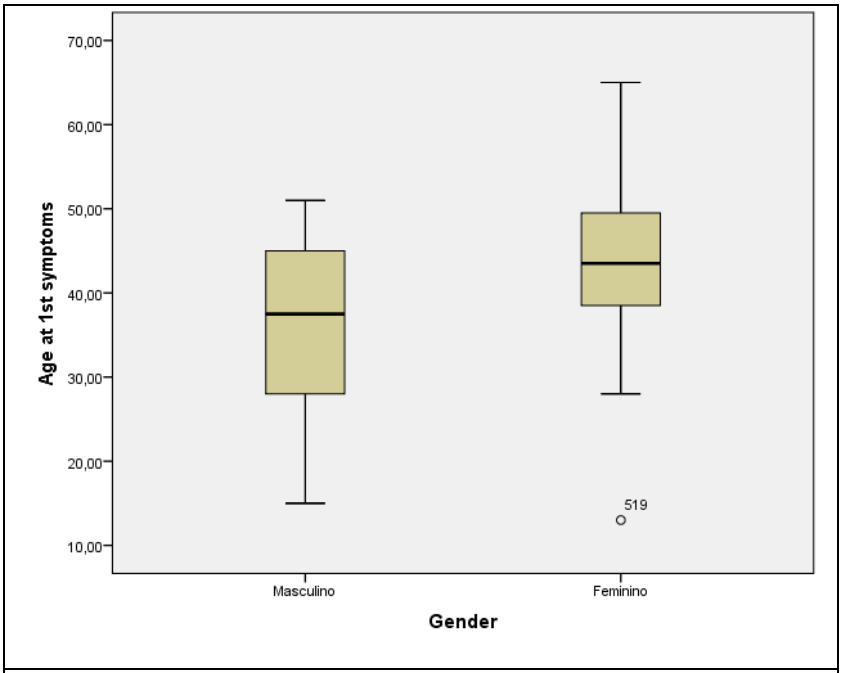


Figure 14. Age at first symptoms of PPMS without relapses, male versus female gender.

Analysis of time from first symptoms to diagnosis across the last decades, across clinical types of disease and across genders

If we only consider from 1991 onwards (we have only 30 patients diagnosed before that date in our database), time from first symptoms to diagnosis seems to has slightly reduced throughout these last decades. There is no significant statistical difference between groups, though (Independent-Samples Kruskal-Wallis test) (Table 10).

Report

Time from 1st sympts to diagn

Década de diagnostico	Mean	N	Std. Deviation
1971-80	2,5000	2	3,53553
1981-90	2,5625	28	2,97716
1991-00	4,2848	122	6,92098
2001-10	2,8703	268	4,66518
2011-20	3,0119	140	5,02635
Total	3,1972	560	5,27600

Table 10. Time elapsed from first symptoms to diagnosis for diagnoses occurring in each decade in time.

Time from first symptoms to diagnosis of "RRMS at diagnosis" cases was 3,0±5,1 years (n=508, CI95%: [2,6;3,5]) versus 4,9±2,5 years (n=38, CI95%: [2,8;7,0]) in PPMS patients. There is a statistically significant difference between these groups (p=0,002, Independent-samples Mann-Whitney U test) (Figure 15).

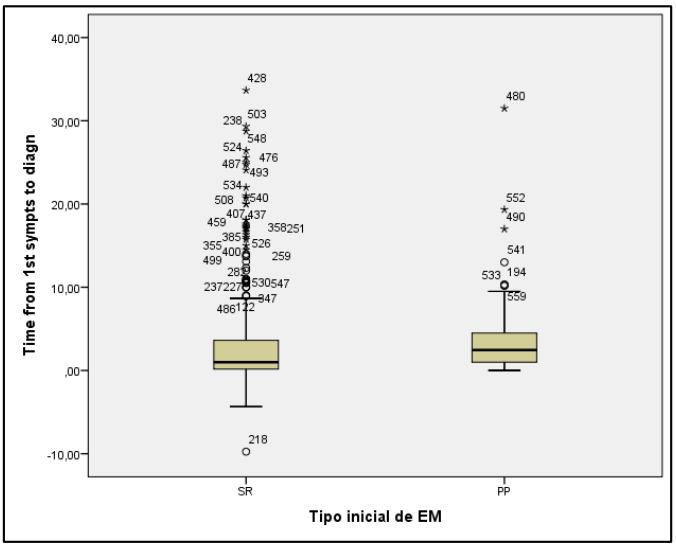


Figure 15. Time elapsed from first symptoms to diagnosis in RRMS versus PPMS cases.

Those that were considered to have started in RRMS form but were already in SPMS at diagnosis reported a much higher lapse of time between first symptoms and diagnosis than patients that were still in RRMS at diagnosis (p=0,03, Independent-samples Mann-Whitney U test).

For patients in RRMS at diagnosis, those that later evolved to SPMS until inclusion also reported an already longer time from first symptoms to diagnosis than those RRMS at diagnosis that remained in RRMS at inclusion (p<0,001, Independent-samples Mann-Whitney U test).

	N	First symptoms to diagnosis (years)
All	561	3,2±5,3
RRMS at diagnosis	508	3,0±5,1
PPMS (w/o relapses)	38	4,9±2,5
PPMS w/ relapses	7	4,3±3,3
PPMS together	45	4,8±6,1
SPMS at diagnosis	5	9,98±6,1
SPMS at inclusion (RRMS at diagnosis)	48	7,3±8,3
RRMS at inclusion	458	2,5±4,4
All SPMS at inclusion	53	7,6±8,1

Table 11. Time from symptoms to diagnosis ion each clinical type of disease.

There are no statistical differences in the elapsed time from first symptoms to diagnosis between genders (Table 12).

	Male (N) from first symptoms to diagnosis (years)	Female (N) from first symptoms to diagnosis (years)	p
All	(164) 3,1±5,1	(396) 3,3±5,4	n.s. (Independent-samples Mann-Whitney U test)
RRMS at diagnosis	(144) 3,0±5,3	(363) 3,0±5,1	n.s. (Independent-samples Mann-Whitney U test)
PPMS (w/o relapses)	(18) 3,4±3,5	(20) 6,3±8,1	n.s. (Independent-samples Mann-Whitney U test)

Table 12. Time from symptoms to diagnosis ion gender for selected clinical types of disease.

Analysis of age at diagnosis across the last decades, across clinical types of disease and across genders

Age at diagnosis (**Erro! A origem da referência não foi encontrada.**) is slightly higher in these last decades (p=0,035, Independent-Samples Kruskal-Wallis test).

Report

Age at diagnosis

Década de diagnostico	Mean	N	Std. Deviation
1971-80	28,00	2	2,828
1981-90	26,61	28	8,543
1991-00	33,11	122	10,699
2001-10	33,75	269	11,186
2011-20	34,59	140	11,483
Total	33,44	561	11,123

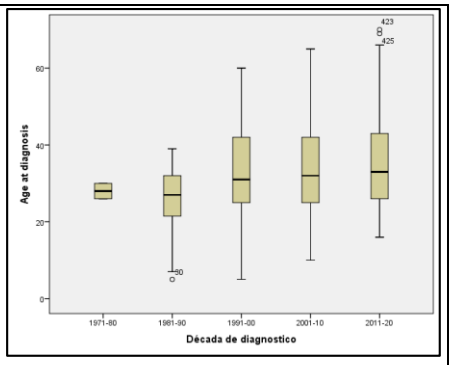


Figure 16. Mean age at diagnosis for diagnosis ocurring in each decade. We have relatively few cases corresponding to the pre CT scan / MRI era.

Age at diagnosis of "RRMS at diagnosis" cases was 32,3±10,4 years-old (n=508, CI95%: [31,4;33,2]) versus 44,2±11,6 years-old (n=38, CI95%: [40,4;48,1]) in PPMS patients (p<0,001, Independent-samples Mann-Whitney U test) (Figure 17).

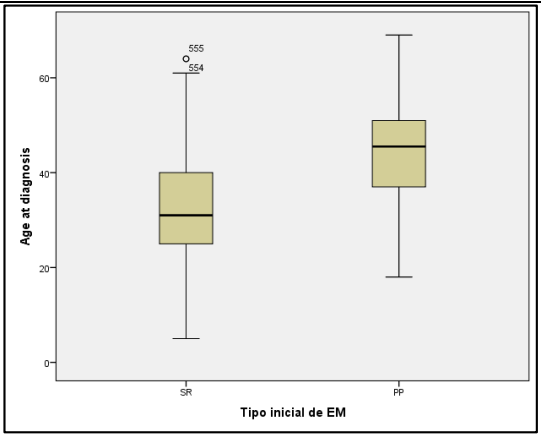


Figure 17. Age at diagnosis of group "RRMS at diagnosis" vs PPMS (without relapses).

Inside patients in “RRMS at diagnosis”, those that later developed SPMS before inclusion were already diagnosed at a later age than the rest of the group “RRMS at diagnosis”, that’s to say, than “RRMS at diagnosis” that remained in RRMS at inclusion (38,0±10,4 vs 31,8±10,3, p<0,001, Independent-samples Mann-Whitney U test) . As a matter of fact, they have been diagnoses at the same age than a small group of patients that have been diagnosed already in the SPMS form.

	N	Age at diagnosis (years-old)
All	561	33,4±11,1
RRMS at diagnosis	508	32,3±10,4
PPMS (w/o relapses)	38	44,2±11,6
PPMS w/ relapses	7	46,4±11,9
PPMS together	45	44,6±11,6
SPMS at diagnosis	5	38,4±9,99
SPMS at inclusion (RRMS at diagnosis)	48	38,0±10,4
RRMS at inclusion	458	31,8±10,3
All SPMS at inclusion	53	38,0±10,3

Table 13. Age at diagnosis for the different clinical groups.

Men are diagnosed at a lower age than women for the whole sample, RRMS at diagnosis and PPMS (Table 14, Figure 18).

	Male (N) Age at diagnosis (years-old)	Female (N) Age at diagnosis (years-old)	p
All	(164) 31,6±10,0	(396) 34,2±11,5	p=0,016 (Independent-samples Mann-Whitney U test)
RRMS at diagnosis	(144) 30,6±9,4	(363) 33,1±10,8	p=0,015 (Independent-samples Mann-Whitney U test)
PPMS (w/o relapses)	(18) 39,2±11,5	(20) 48,9±9,93	p=0,048 (Independent-samples Mann-Whitney U test)

Table 14. Age at diagnosis for each of the genders in each clinical group.

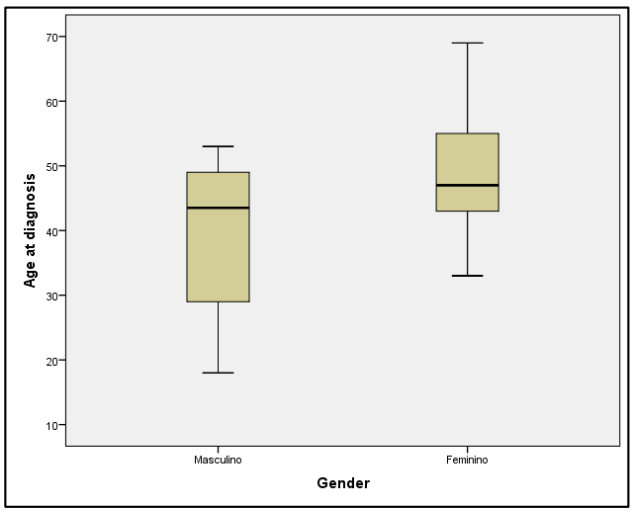


Figure 18. Age at diagnosis by gender for PPMS.

Analysis of total follow-up after first symptoms and after diagnosis across clinical types of disease and across genders (includes progression to SPMS)

Time from diagnosis to inclusion of group "RRMS at diagnosis" is 9,6±7,3 years, similar to that of PPMS patients, which is 8,1±6,4 years (p=0,2, Independent-samples Mann-Whitney U test).

Mean time of evolution from diagnosis to inclusion of patients that evolved to SPMS after diagnosis is the double of those who did not (16,5±7,2 years versus 8,8±6,9 years) (**Erro! A origem da referência não foi encontrada.**). We had seen before that, although these patients had presented the first symptoms at the same age as others "RRMS at diagnosis", they already had more time of interval between first symptoms and diagnosis and had been diagnosed at a later age.

	N	First symptoms to inclusion (years)	Diagnosis to inclusion (years)
All	561	12,6±9,2	9,4±7,2
RRMS at diagnosis	508	12,6±9,3	9,6±7,3
PPMS (w/o relapses)	38	12,98±8,4	8,1±6,4
PPMS w/ relapses	7	13,0±7,4	8,8±8,5
PPMS together	45	12,98±8,2	8,2±6,7
SPMS at diagnosis	5	19,5±8,7	9,5±8,2
SPMS at inclusion (RRMS at diagnosis)	48	23,8±10,98	16,5±7,2
RRMS at inclusion	458	11,3±8,1	8,8±6,9
All SPMS at inclusion	53	23,4±10,8	15,9±7,5

Table 15. Evolution of disease departing from first symptoms and from diagnosis for each clinical course.

As stated above, of our 508 patients that were in RR phase by the time of diagnosis, 9,5% reached SPMS by inclusion (Figure 7) (8,4% of males in RRMS at diagnosis and 9,9% of women).

Table 16 gives us a perspective of the proportion of patients that progresses to SPMS along the evolution time after diagnosis.

Time after diagnosis	Corresponding number of patients we have in our database	Proportion of patients that reached SPMS in the meanwhile
≤5 years	N=171	2,3%
≤7 years	N=237	3%
≤10 years	N=302	3,3%
≤15 years	N=?	5%
≤20 years	N= 458	6,6%
All	N=508	9,5%

Table 16. Proportion of patients in RRMS at diagnosis that evolved to SPMS according to time after diagnosis.

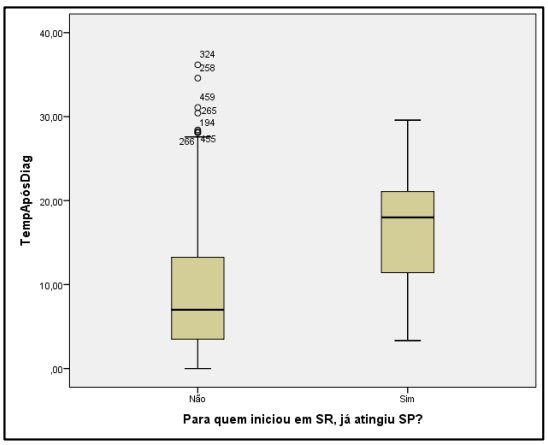


Figure 19. Time of evolution after diagnosis for patients initially diagnosed in RRMS that remained in RRMS at inclusion (left or "Não") versus those that evolved to SPMS in the meanwhile (right or "Sim").

There are no statistical differences in times of follow-up between genders in our sample (Table 17, Table 18).

	Male (N) First symptoms to inclusion (years)	Female (N) First symptoms to inclusion (years)	p
All	(164) 12,8±9,1	(396) 12,6±9,2	n.s. (Independent-samples Mann-Whitney U test)
RRMS at diagnosis	(144) 12,8±9,2	(363) 12,5±9,3	n.s. (Independent-samples Mann-Whitney U test)
PPMS (w/o relapses)	(18) 11,6±7,2	(20) 14,2±9,3	n.s. (Independent-samples T test)

Table 17

	Male (N) Diagnosis to inclusion (years)	Female (N) Diagnosis to inclusion (years)	p
All	(164) 9,7±6,9	(396) 9,3±7,4	n.s. (Independent-samples Mann-Whitney U test)
RRMS at diagnosis	(144) 9,8±6,95	(363) 9,5±7,4	n.s. (Independent-samples Mann-Whitney U test)
PPMS (w/o relapses)	(18) 8,2±6,1	(20) 7,9±6,9	n.s. (Independent-samples Mann-Whitney U test)

Table 18

Analysis of age at inclusion across clinical types of disease and across genders (includes progression to SPMS)

Age at inclusion is considerably higher for PPMS than for group "RRMS at diagnosis" (52,5±11,3 years-old versus 42,0±12,1 years-old, respectively, p<0,001, Independent-samples Mann-Whitney U test) or for group "RRMS at inclusion" (52,5±11,3 years-old versus 40,7±11,6 years-old, respectively, p<0,001, Independent-samples Mann-Whitney U test) (Table 19).

Patients "RRMS at diagnosis" that remain in "RRMS at inclusion" are 40,7±11,6 years-old at inclusion, whereas "RRMS at diagnosis" that evolved to SPMS at inclusion are 54,5± 10,1 (p<0,001) (Figure 20).

	N	Age at inclusion (years-old)
All	561	42,9±12,4
RRMS at diagnosis	508	42,0±12,1
PPMS (w/o relapses)	38	52,5±11,3
PPMS w/ relapses	7	55,1±10,6
PPMS together	45	52,9±11,1
SPMS at diagnosis	5	47,8±9,9
SPMS at inclusion (RRMS at diagnosis)	48	54,5± 10,1
RRMS at inclusion	458	40,7±11,6
All SPMS at inclusion	53	53,9±10,2

Table 19. Age at inclusion for the various clinical courses.

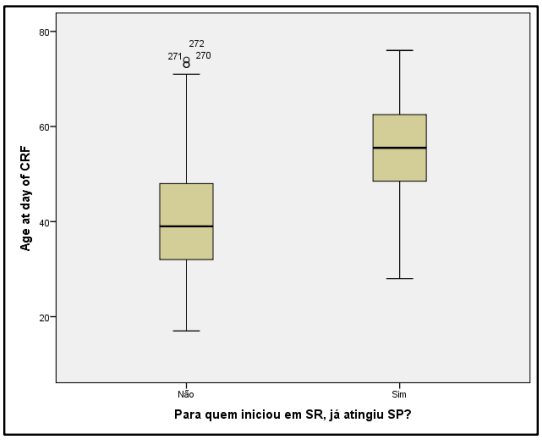


Figure 20. Age at inclusion for patients initially diagnosed in RRMS that remained in RRMS at inclusion (left or "Não") versus those that evolved to SPMS in the meanwhile (right or "Sim").

Men with PPMS (without relapses) included in our sample are younger than women (Table 20). We have seen before that they started first symptoms are a slightly younger age (statistically n.s.) and that they also were diagnosed at an earlier age than their female counterparts. Time from first symptoms to diagnosis and follow-up from diagnosis to inclusion is the same, though (statistically). We have a little number of patients in these categories and this data should be conformed with a larger numbers of patients.

	Male (N) Age at inclusion (years-old)	Female (N) Age at inclusion (years-old)	p
All	(164) 41,5±11,2	(396) 43,6±12,9	n.s. (Independent-samples Mann-Whitney U test)
RRMS at diagnosis	(144) 40,4±10,8	(363) 42,6±12,6	n.s. (Independent-samples Mann-Whitney U test)
PPMS (w/o relapses)	(18) 47,6±11,5	(20) 56,95±9,4	p=0,009 (Independent-samples T-test)

Table 20. Age at inclusion for males and females.

Analysis of the proportions between clinical types of MS across the last decades in time, across different ages at diagnosis and across genders

The number PPMS (without relapses) compared to RRMS (we have very few patients diagnosed in the groups “RR already in SPMS” and “PPMS with relapses”), at diagnosis, is higher in patients born is more distant decades (then, older patients) that in patients born more recently as is shown in Table 21.

Década de nascimento * Tipo inicial de EM Crosstabulation

			Tipo inicial de EM		
			SR	PP	Total
Década de nascimento	1931-40	Count	2	0	2
		% within Década de nascimento	100,0%	0,0%	100,0%
	1941-50	Count	27	6	33
		% within Década de nascimento	81,8%	18,2%	100,0%
	1951-60	Count	67	15	82
		% within Década de nascimento	81,7%	18,3%	100,0%
	1961-70	Count	120	9	129
		% within Década de nascimento	93,0%	7,0%	100,0%
	1971-80	Count	162	7	169
		% within Década de nascimento	95,9%	4,1%	100,0%
	1981-90	Count	112	1	113
		% within Década de nascimento	99,1%	0,9%	100,0%
	1991-00	Count	18	0	18
		% within Década de nascimento	100,0%	0,0%	100,0%
Total		Count	508	38	546
		% within Década de nascimento	93,0%	7,0%	100,0%

Table 21. Proportion of RRMS versus PPMS by decade of birth of the patients.

The proportion of PPMS diagnosed in each decade in time seems, on the other hand, stable in the last few decades (p=0,29, Pearson Chi-Square test, Cochran criteria verified after joining together the decades of 1971-80 and 1981-90) (Figure 21).

Década de diagnostico * Tipo inicial de EM Crosstabulation

			Tipo inicial de EM		
			SR	PP	Total
Década de diagnostico	1971-80	Count	2	0	2
		% within Década de diagnostico	100,0%	0,0%	100,0%
	1981-90	Count	27	0	27
		% within Década de diagnostico	100,0%	0,0%	100,0%
	1991-00	Count	110	11	121
		% within Década de diagnostico	90,9%	9,1%	100,0%
	2001-10	Count	247	16	263
		% within Década de diagnostico	93,9%	6,1%	100,0%
	2011-20	Count	122	11	133
		% within Década de diagnostico	91,7%	8,3%	100,0%
Total		Count	508	38	546
		% within Década de diagnostico	93,0%	7,0%	100,0%

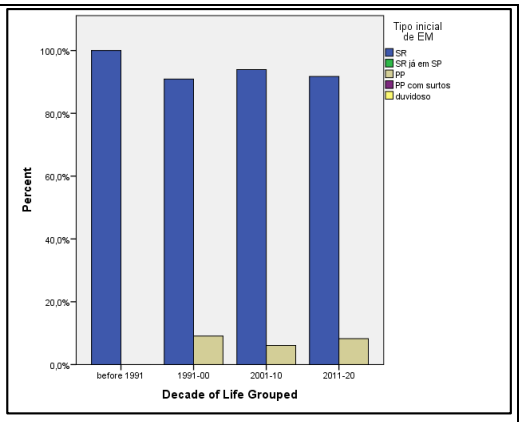


Figure 21. Proportion of RRMS versus PPMS in diagnosis occurring in each decade in time.

The apparent dissociation of the two precedent results is explained by the fact that the proportion of patients with PPMS is higher in patients diagnosed later in life (p<0,001, Pearson Chi-Square test, Cochran criteria verified after joining together the first and second decades of life, and excluding the 7th decade of life, due to low number of patients in those groups) (**Erro! A origem da referência não foi encontrada.**).

Decade of Life at Diagnosis * Tipo inicial de EM Crosstabulation

			Tipo inicial de EM		
			SR	PP	Total
Decade of Life at Diagnosis	1a década vida	Count	3	0	3
		% within Decade of Life at Diagnosis	100,0%	0,0%	100,0%
	2a década vida	Count	40	2	42
		% within Decade of Life at Diagnosis	95,2%	4,8%	100,0%
	3a década vida	Count	188	3	191
		% within Decade of Life at Diagnosis	98,4%	1,6%	100,0%
	4a década vida	Count	149	6	155
		% within Decade of Life at Diagnosis	96,1%	3,9%	100,0%
	5a década vida	Count	94	17	111
		% within Decade of Life at Diagnosis	84,7%	15,3%	100,0%
	6a década vida	Count	29	7	36
		% within Decade of Life at Diagnosis	80,6%	19,4%	100,0%
	7a década vida	Count	5	3	8
		% within Decade of Life at Diagnosis	62,5%	37,5%	100,0%
Total		Count	508	38	546
		% within Decade of Life at Diagnosis	93,0%	7,0%	100,0%

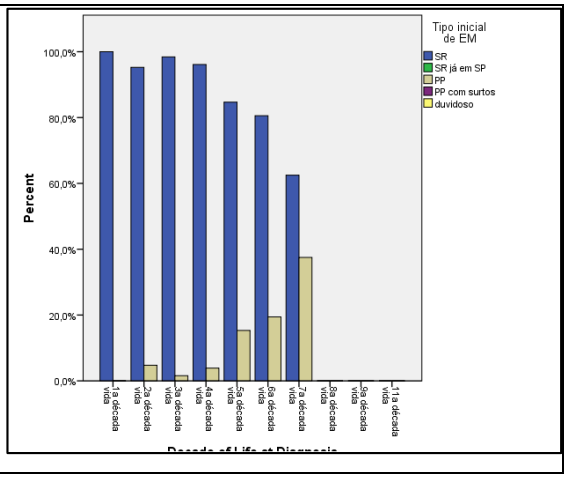


Figure 22. Proportion of patients diagnosed with PPMS versus RRMS in diagnosis occurring in each decade of life.

In Table 22 we present the proportion of each clinical type of disease in each of the genders.

	Males	Females	
Proportion of RMMS at disease onset	88,4%	92,7%	
% of PPMS (w/o relapses) at disease onset	11%	5%	
Proportion of RRMS at diagnosis that had progressed to SPMS at inclusion	8,4%	9,9%	

Table 22. Proportion of each clinical type of disease in each of the genders.

Analysis of gender across the last decades in time, across different ages at diagnosis and across clinical types of disease

The proportion of male to female seems globally stable when we analyze it by decade of birth of patients (p=0,08, Pearson Chi-Square test, Cochran criteria verified after joining together the first 2 decades, where we have relatively few cases) (Figure 23).

It's also stable when we analyze it by decade in time at which the diagnosis occurred (see Figure 24, where we should look essentially to the last 3 decades, where we have a more representative number of patients).

When we analyze this same proportion by decade of life at which the diagnosis occurred (an analysis by age at diagnosis, then), even if apparently, in cases diagnosed later in life, there is an increased proportion of females (Figure 25), this is not statistical significant (p=0,1, Pearson Chi-Square test, Cochran criteria verified after joining together the two decades in both extremes, where we have relatively few cases). In fact, in **Erro! A origem da referência não foi encontrada.**, if we only look to the decades where we have a more significant number of patients, that increase is small. We will need to review this tendency when we have a bigger number of patients in our database.

Década de nascimento * Gender Crosstabulation

			Gender		
			Masculino	Feminino	Total
Década de nascimento	1931-40	Count	0	2	2
		% within Década de nascimento	0,0%	100,0%	100,0%
	1941-50	Count	5	30	35
		% within Década de nascimento	14,3%	85,7%	100,0%
	1951-60	Count	24	64	88
		% within Década de nascimento	27,3%	72,7%	100,0%
	1961-70	Count	36	95	131
		% within Década de nascimento	27,5%	72,5%	100,0%
	1971-80	Count	62	111	173
		% within Década de nascimento	35,8%	64,2%	100,0%
	1981-90	Count	34	80	114
		% within Década de nascimento	29,8%	70,2%	100,0%
	1991-00	Count	3	15	18
		% within Década de nascimento	16,7%	83,3%	100,0%
Total		Count	164	397	561
		% within Década de nascimento	29,2%	70,8%	100,0%

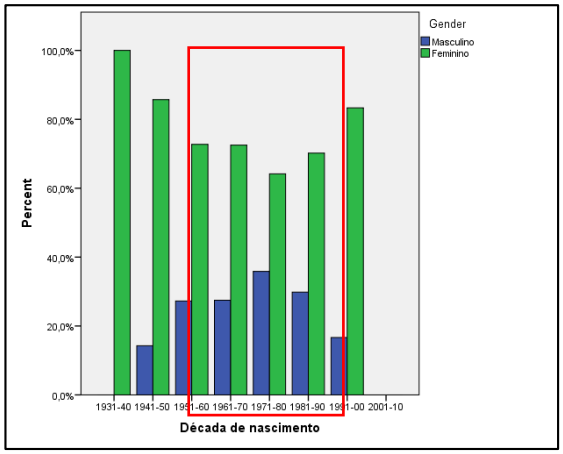


Figure 23. Proportion of male to female by decade of birth of patients (highlighted in red the four decades where we have a more representative number of patients).

Década de diagnostico * Gender Crosstabulation

			Gender		
			Masculino	Feminino	Total
Década de diagnostico	1971-80	Count	0	2	2
		% within Década de diagnostico	0,0%	100,0%	100,0%
	1981-90	Count	5	23	28
		% within Década de diagnostico	17,9%	82,1%	100,0%
	1991-00	Count	41	81	122
		% within Década de diagnostico	33,6%	66,4%	100,0%
	2001-10	Count	82	187	269
		% within Década de diagnostico	30,5%	69,5%	100,0%
	2011-20	Count	36	104	140
		% within Década de diagnostico	25,7%	74,3%	100,0%
Total		Count	164	397	561
		% within Década de diagnostico	29,2%	70,8%	100,0%

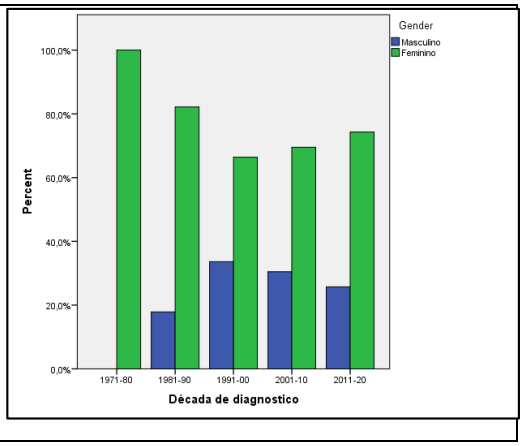


Figure 24.Proportion of male to female by decade in time at which the diagnosis occurred.

Decade of Life at Diagnosis * Gender Crosstabulation

			Gender		
			Masculino	Feminino	Total
Decade of Life at Diagnosis	1a década vida	Count	1	2	3
		% within Decade of Life at Diagnosis	33,3%	66,7%	100,0%
	2a década vida	Count	15	27	42
		% within Decade of Life at Diagnosis	35,7%	64,3%	100,0%
	3a década vida	Count	67	125	192
		% within Decade of Life at Diagnosis	34,9%	65,1%	100,0%
	4a década vida	Count	43	118	161
		% within Decade of Life at Diagnosis	26,7%	73,3%	100,0%
	5a década vida	Count	30	84	114
		% within Decade of Life at Diagnosis	26,3%	73,7%	100,0%
	6a década vida	Count	7	32	39
		% within Decade of Life at Diagnosis	17,9%	82,1%	100,0%
	7a década vida	Count	1	8	9
		% within Decade of Life at Diagnosis	11,1%	88,9%	100,0%
	8a década vida	Count	0	1	1
		% within Decade of Life at Diagnosis	0,0%	100,0%	100,0%
Total		Count	164	397	561
		% within Decade of Life at Diagnosis	29,2%	70,8%	100,0%

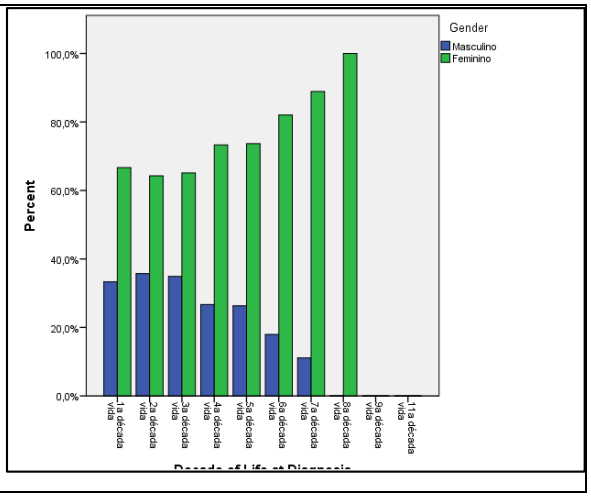


Figure 25.Proportion of male to female by decade of life at which the diagnosis occurred.

The analysis of distribution of gender in each type of disease shows a proportion of 2,5 females to 1 male in “RRMS at diagnosis” and an almost equilibrated representation of both sexes in PPMS (without relapses), with 1,1 females to 1 male ($p<0,05$, Pearson Chi-Square, Cochran criteria verified) (Figure 26).

Tipo inicial de EM * Gender Crosstabulation

			Gender		
			Masculino	Feminino	Total
Tipo inicial de EM	SR	Count	144	364	508
		% within Tipo inicial de EM	28,3%	71,7%	100,0%
	PP	Count	18	20	38
		% within Tipo inicial de EM	47,4%	52,6%	100,0%
Total		Count	162	384	546
		% within Tipo inicial de EM	29,7%	70,3%	100,0%

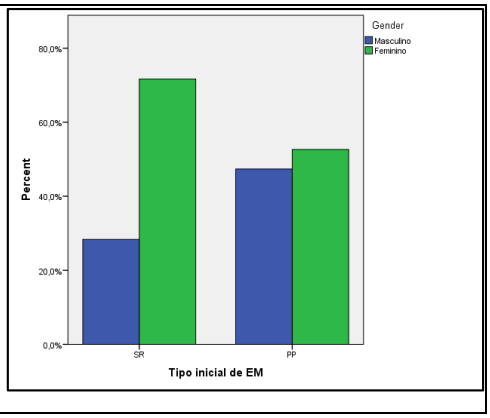


Figure 26. Analysis of distribution of gender in each type of disease.

The proportion of females to males in each clinical group of our sample is shown in Table 23.

	Females:Males
All	2,5:1
RRMS at diagnosis	2,5:1
PPMS (w/o relapses)	1,1:1
PPMS w/ relapses	Low number of patients
PPMS together	1,4:1
SPMS at diagnosis	Low number of patients
SPMS at inclusion (RRMS at diagnosis)	3:1
RRMS at inclusion	2,5:1
All SPMS at inclusion	3,1:1

Table 23.Proportion of females to males in each clinical course.

EDSS

The exact value of EDSS in May 2014 was possible to obtain for 465 patients (83% of the total patients). Median EDSS for the 465 patients with exact EDSS available is 2,5 (P25: 1,0; P75: 5,0). Distribution of patients according to the exact EDSS is shown in Figure 27.

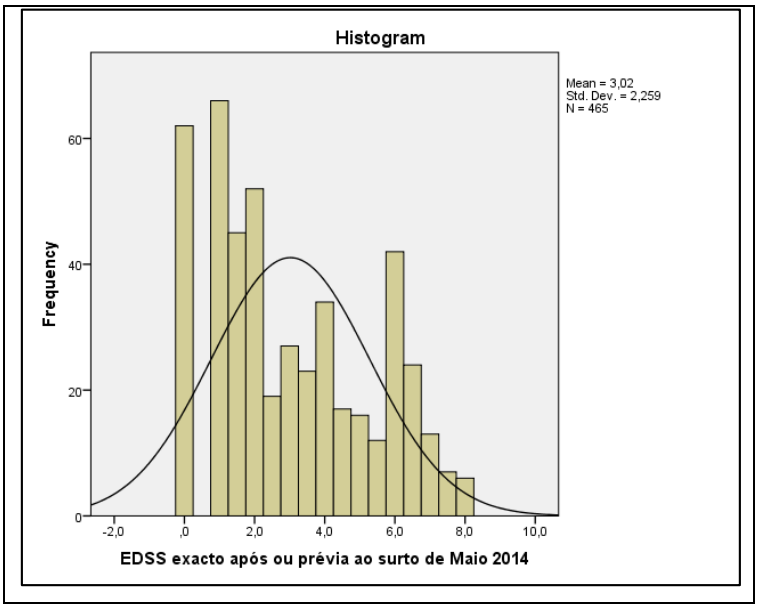


Figure 27. Distribution of 465 cases of our population with exact EDSS available.

The class of EDSS was obtained for all patients as predefined in the CRF and essentially taking ability to walk in consideration. Distribution of patients by these classes of EDSS is shown in Figure 28.

Classes de EDSS

		Frequency	Percent	Cumulative Percent
Valid	0-4.0	404	72,7	72,7
	4.5	18	3,2	75,9
	5.0	16	2,9	78,8
	5.5	12	2,2	80,9
	6.0	49	8,8	89,7
	6.5	25	4,5	94,2
	7.0-7.5	26	4,7	98,9
	8.0-9.5	6	1,1	100,0
	Total	556	100,0	

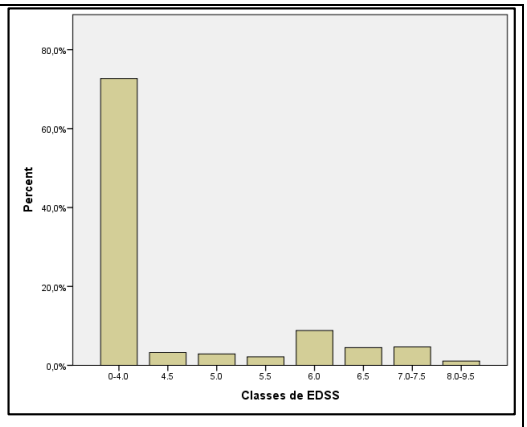


Figure 28. Distribution of patients by classes of EDSS in May 2014.

For the 465 patients for whom we have an exact value of EDSS available, the relation between the current median EDSS and the year of birth (or current age), and between current median EDSS and both time of disease evolution since first symptoms and time of disease evolution since diagnosis, is shown in Figure 29and Figure 30 respectively. Older patients show a tendency to higher EDSS values (rho=0,44, p<0,001, Sperman's correlation), as do patients with longer elapsed times since first symptoms (rho=0,45, p<0,001, Sperman's correlation), or diagnosis (rho=0,40, p<0,001, Sperman's correlation).

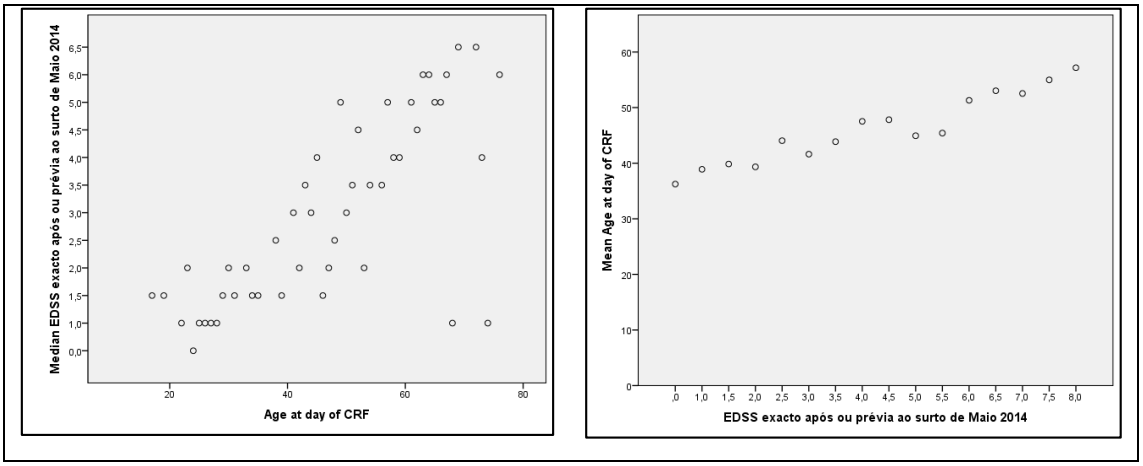


Figure 29. Relation between the median EDSS and age at the day of CRF filling, and mean age of the patients for each EDSS category.

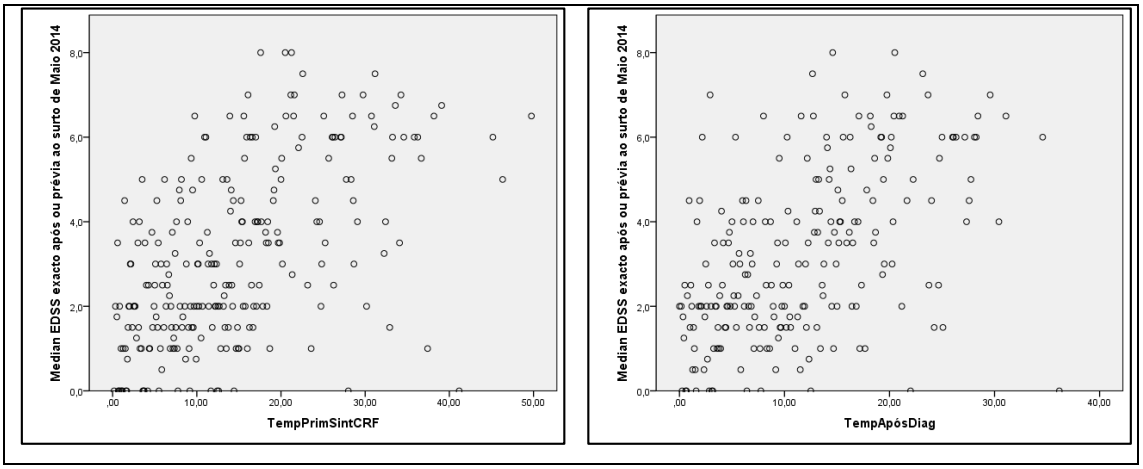
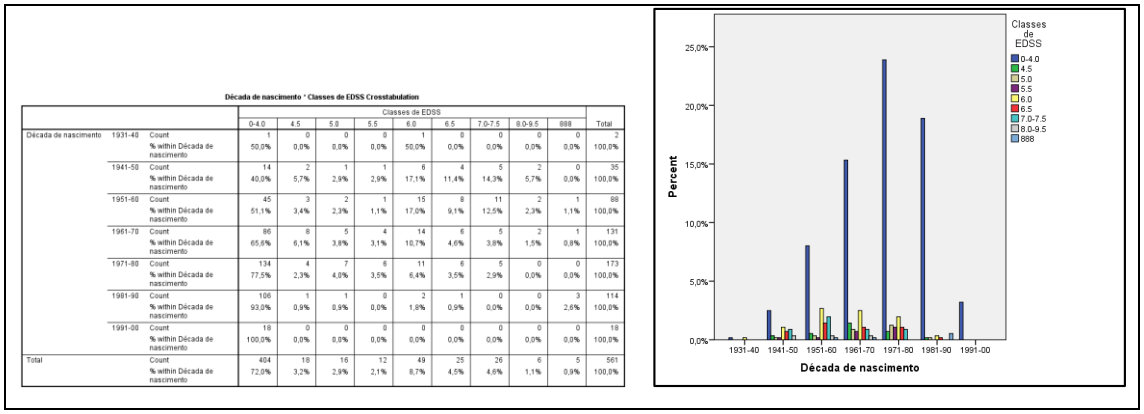


Figure 30. Relation between the median EDSS and the time of evolution since first symptoms and the time of evolution since diagnosis.

For the whole population of our database, the distribution by EDSS classes according to decade of birth renders similar results (Figure 31), as older patients show higher representations of higher EDSS categories.



Década de nascimento * Classes de EDSS Crosstabulation

			Classes de EDSS									
			0-4.0	4.5	5.0	5.5	6.0	6.5	7.0-7.5	8.0-9.5	888	Total
Década de nascimento	1931-40	Count	1	0	0	0	1	0	0	0	0	2
		% within Década de nascimento	50,0%	0,0%	0,0%	0,0%	50,0%	0,0%	0,0%	0,0%	0,0%	100,0%
	1941-50	Count	14	2	1	1	6	4	5	2	0	35
		% within Década de nascimento	40,0%	5,7%	2,9%	2,9%	17,1%	11,4%	14,3%	5,7%	0,0%	100,0%
	1951-60	Count	45	3	2	1	15	8	11	2	1	88
		% within Década de nascimento	51,1%	3,4%	2,3%	1,1%	17,0%	9,1%	12,5%	2,3%	1,1%	100,0%
	1961-70	Count	86	8	5	4	14	6	5	2	1	131
		% within Década de nascimento	65,6%	6,1%	3,8%	3,1%	10,7%	4,6%	3,8%	1,5%	0,8%	100,0%
	1971-80	Count	134	4	7	6	11	6	5	0	0	173
		% within Década de nascimento	77,5%	2,3%	4,0%	3,5%	6,4%	3,5%	2,9%	0,0%	0,0%	100,0%
	1981-90	Count	106	1	1	0	2	1	0	0	3	114
		% within Década de nascimento	93,0%	0,9%	0,9%	0,0%	1,8%	0,9%	0,0%	0,0%	2,6%	100,0%
	1991-00	Count	18	0	0	0	0	0	0	0	0	18
		% within Década de nascimento	100,0%	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	100,0%
Total		Count	404	18	16	12	49	25	26	6	5	561
		% within Década de nascimento	72,0%	3,2%	2,9%	2,1%	8,7%	4,5%	4,6%	1,1%	0,9%	100,0%

Figure 31. Distribution of patients by EDSS classes according to decade of birth. Older patients are more frequently distributed in higher classes of EDSS.

Although "RR at diagnosis" and PP types have about the same time of evolution after diagnosis in our database, we verify that EDSS, at present time, is different between the two groups, as shown in Figure 32 and Figure 33 . Analyzing patients in our database for whom we have exact EDSS, we ascertain, for the RRMS group (n= 420), a median EDSS of 2,0 (P25: 1,0; P75: 4,0) and median EDSS for PPMS patients (n= 31) of 6,0 (P25: 5,0; P75: 7,0).

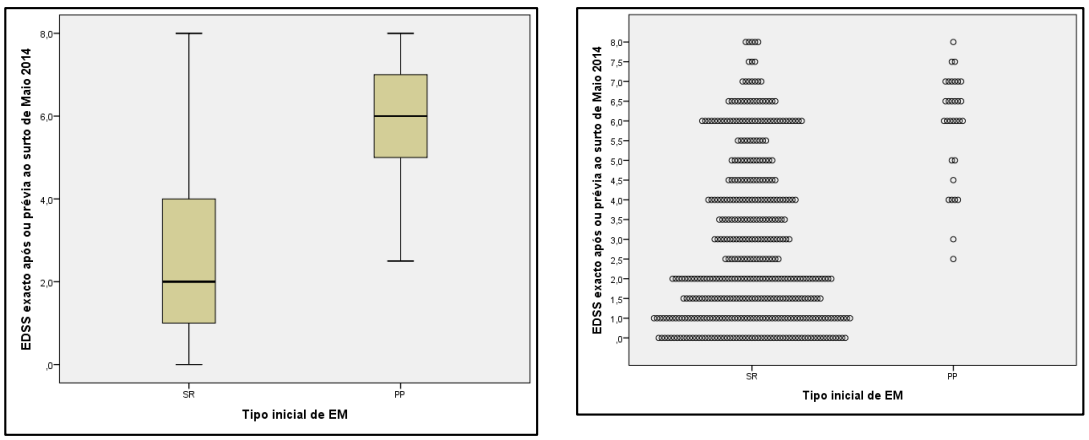


Figure 32. Distribution of RRMS and PPMS cases in terms of EDSS.

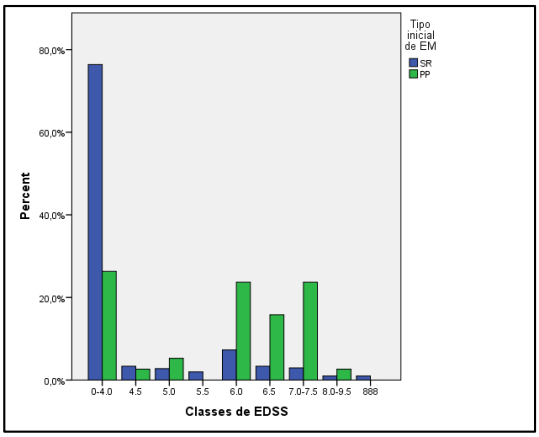


Figure 33. Distribution of RRMS and PPMS through these the (predefined) classes of EDSS (the sum of the bars of each type of MS completes 100% of patients for that type).

Treatment

84,5% of our total population of patients were under Disease Modifying Treatment (DMT) in May 2014 (Table 24). Patients currently in RRMS form are under DMT in 90,4% of cases, as are more than half of patients currently in progressive forms (especially those in SPMS).

Population		N	Under DMT (May 2014)
All patients		561	84,5%
RRMS at diagnosis (independently of current clinical type)		508	88,4%
	Currently in RRMS	459	**90,4%**
	RRMS at diagnosis that evolved to SPMS	48	70,8%
SPMS at diagnosis		5	80%
All currently in SPMS together		53	**71,6%**
PPMS (with or without relapses)		45	44,4%
All progressive forms together		98	**59,2%**

Table 24. Proportion of patients under disease modifying treatment (DMT) in May 2014 for the total population of the database and for each subgroup of clinical type of MS.

Taking all the population of our database together, patients not under treatment differ from those under DMT in that they have been diagnosed at a somewhat older age, they are currently older, their disease is slightly longer, but above all in that half of them have progressive forms (Table 25). This last fact also means that half of the non-treated patients are in RRMS form, which theoretically should be under DMT (see under). Half of the non-treated patients have, been treated before.

	ALL PATIENTS		
	Under DMT (May 2014) N= 474 (**84,5%**)	No DMT (May 2014) N=87 (**15,5%**)	p
Age at diagnosis (years-old)	32,6 (±10,7)	38,3 (±12,0)	p<0,001
Disease evolution time (years)	9,1 (±6,9)	11,3 (±8,5)	n.s.
Current Age (years-old)	41,7 (±11,9)	49,6 (±13,2)	p<0,001
% Females	71,3%	67,8%	n.s.
% Progressive forms	12,2%	**46%**	p<0,001
EDSS (median)	2.0	**4.0 – 4.5**	p<0,001
No DMT = Patient's decision	Not applicable	13,3%	-
Were previously on (other) DMT	51%	**50%**	n.s

Table 25. Comparison of the main characteristics of all patients under disease modifying treatment (DMT) versus all patients that were not under DMT (in May 2014).

The 10% (n=44) of patients currently in RRMS are not under treatment been diagnosed at a slightly older age and they are currently also slightly older than the 90% treated patients, also in part because they have the disease at a longer time, but these differences don't seem too expressive (Table 26). The gender distribution is similar between treated and non-treated patients, and EDSS is not that different either. Almost half of the non-treated patients have been treated before.

15% of the non-treated patients chose not to be treated (n=7). The remaining are not under treatment due to medical decision, then. Our data also shows that another 15% of all non-treated RRMS (n=7) have a very recent diagnosis (2 months or less) which can be an explanation per se. We also know that another situation where a substantial part of RRMS are not on DMT is when the diagnosis has 20 or more years (Table 27). Then, globally, patients with RRMS not treated, in Portugal, they are either in the first 3 months of disease or they have more than 10 years of disease. We have no other data to explain the other cases. Nevertheless, 75,7% of all these non-treated patients were women, men and women have about the same age (45,1±13,8 years-old), they have 11,5±9,2 years of disease evolution after diagnosis and their EDSS is distributed from 0,0 to 8,0 in a relatively equilibrated fashion without significant differences.

	CURRENTLY RRMS (N=459)		
	Under DMT (May 2014) N= 415 (90,4%)	No DMT (May 2014) N=44 (**9,6%**)*	p
Age at diagnosis (years-old)	31,6 (±10,2)	33,5 (±11,1)	n.s.
Disease evolution time (years)	8,7 (±6,6)	10,5 (±8,8)	n.s.
Current Age (years-old)	40,3 (±11,3)	43,9 (±13,4)	n.s.
% Females	71,3%	72,7%	n.s.
EDSS (median)	2.0	2.5	n.s.
No DMT = Patient's decision	Not applicable	15%	-
Were previously on (other) DMT	49%	**47,7%**	n.s.

* Of these, 7 cases (15%) had less than 3 months of diagnosis (none of them coinciding with the 15% that refused treatment).

Table 26. Comparison of the main characteristics of patients currently in RRMS that were under disease modifying treatment (DMT) versus those not under DMT (in May 2014).

Table 27 also shows us that (for patients on DMT) it's between the end of the first year of diagnosis and the start of the 3rd year after diagnosis that many (around 40%) RRMS patients change DMT (for the first time), and that around 40% of the patients with more than 10, 15 and

even 20 years of disease evolution, always stayed of the first DMT. The remaining 20% change DMT somewhere in the middle. As stated before, it's in the second decade of disease evolution that some RRMS patients quit DMT, which is even more pronounced after the 20th year of disease after diagnosis. This table must, of course, be interpreted in the particular context of the availability of therapies. This availability is homogenous in Portugal because almost all patients are treated in public hospital with very similar availability (some discrepancies exist in practice due to different administrative procedures to have access to some (more expensive) therapies). In 2014, in Portugal, despite approval by the EMA of drugs like dimethyl fumarate, teriflunomide and alemtuzumab, none of these is widely available in Portuguese public hospitals.

PATIENTS THAT REMAIN IN RRMS			
Years after diagnosis	N	Under DMT	…of which had been on other DMT before (%)
<=1	35*	80%	0%
1-2	36	88,9%	15,6%
2-3	28	96,4%	44,4%
3-4	29	100%	41,4%
4-5	39	94,9%	51,4%
5-10	125	93,6%	56,4%
10-15	74	86%	60,8%
15-20	50	96%	62,5%
>20	30	63,3%	59,1%

* All the patients not under DMT in this group (7 patients, 20% of the group) had less than 3 months of diagnosis.

Table 27. Percentage of patients currently on DMT and that had (other) DMT before in each interval of disease evolution time.

For what concerns progressive forms, our data are unable to distinguish between patients with progressive forms of the disease under DMT and not on DMT (Table 28). We know that in 10% of the non-treated cases it was the patient's decision that apparently determined that option, at that half of the currently non-treated cases were treated (sometime) before (such is an expected situation, at least in the SP forms).

	CURRENTLY PROGRESSIVE (N=98)		
	Under DMT (May 2014) N= 58 (**59,2%**)	No DMT (May 2014) N=40 (40,8%)	p
Age at diagnosis (years-old)	39,5 (±12)	43,3 (±10,1)	n.s
Disease evolution time (years)	12,2 (±8,3)	12,4 (±7,9)	n.s.
Current Age (years-old)	51,8 (±11,0)	55,8 (±9,5)	n.s.
% Females	70,7%	62,5%	n.s.
EDSS (median)	6.5	6.0	n.s.
No DMT = Patient's decision	Not applicable	10,8%	-
Were previously on (other) DMT	65%	**55%**	n.s.

Table 28. Comparison of the main characteristics of patients currently in progressive forms that were under disease modifying treatment (DMT) versus those not under DMT (in May 2014).

When we analyze de proportion of treated patients by categories of EDSS, we see that all patients with RRMS forms are highly treated (around 90% cases)(Table 29). We'd previously seen that those not treated are above all very recent diagnosis, very long evolution time or patient's refusal. All progressive forms, even with high EDSS, are treated in more than half of cases.

EDSS category	N	On DMT
ALL PATIENTS		
<= 4.0	404	88,9%
4.5-6.0	95	76,8%
>=6.5	62	67,7%
CURRENTLY IN RRMS		
<= 4.0	388	90,5%
4.5-6.0	57	89,5%
>=6.5	14	92,9%
CURRENTLY IN PROGRESSIVE FORMS		
<= 4.0	13	53,8%
4.5-6.0	37	59,5%
>=6.5	48	60,4%

Table 29. Proportion of patients on DMT in each EDSS category for each clinical type of disease.

The proportion of our total population (progressive patients included) in each type of treatment is shown in Figure 34 (not excluding patients not under DMT) and Figure 35 (after excluding patients that where not on DMT in May 2014). 74,9% (approximately) of our treated patients were under first line DMT (interferons and GA), 21,3% were under 2nd line DMT (natalizumab or fingolimod), (around) 3,7% were on "other therapies" (these are explained under, for each clinical type).

Grupo da TMD Maio 14

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	IFN-beta-1a SC	69	12,3	12,3	12,3
	IFN-beta-1a IM	100	17,8	17,8	30,1
	IFN-beta-1b SC	99	17,6	17,6	47,8
	Glatiramer acetate	87	15,5	15,5	63,3
	Natalizumab	55	9,8	9,8	73,1
	Fingolimod	46	8,2	8,2	81,3
	Mitoxantrone	2	,4	,4	81,6
	Alemtuzumab	1	,2	,2	81,8
	Other therapeutics	15	2,7	2,7	84,5
	Not currently treated	87	15,5	15,5	100,0
	Total	561	100,0	100,0	

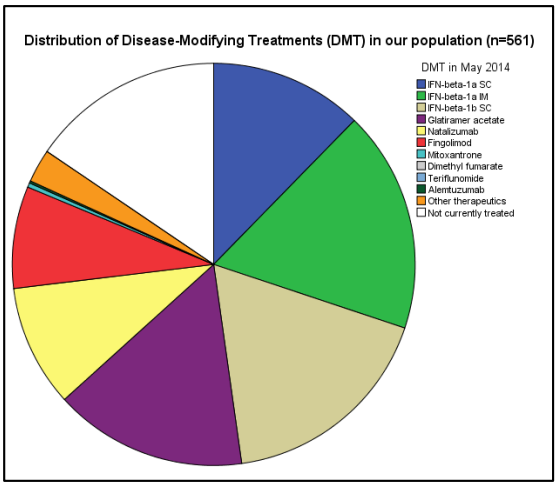


Figure 34. Distribution of types of DMT in our total population, not excluding those not on DMT.

Distribution of total population by type of DMT		
	N	%
IFN-beta 1a SC	69	14.6
IFN-beta 1a IM	100	21.1
IFN-beta 1b SC	99	20.9
Glatiramer acetate	87	18.4
Natalizumab	55	11.6
Fingolimod	46	9.7
Mitoxantrone	2	0.4
Alemtuzumab	1	0.2
Other therapeutics	15	3.2
Total	474	100.0

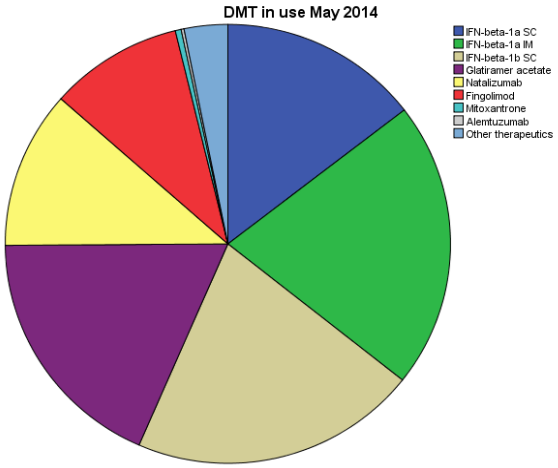


Figure 35. Distribution of types of DMT in our total population that is on DMT.

From the total population classified as RRMS at diagnosis (n=508), then excluding those cases that were diagnosed as "RRMS already on SP" at diagnosis, we observe that 88,4% were under treatment in May 2014, independently of having reached SPMS in the meanwhile (which actually happened in 9,4% of these patients). 90,4% (n=415) of RRMS patients that were considered not to have reached SP phase (n=459), that's to say of patients "currently in RRMS", were under DMT in May 2014. The distribution of their treatments is shown in Figure 36and Figure 37. Interferons and GA together (first line therapies) totalize 76,6% of cases, Natalizumab and Fingolimod togeteher (2nd line therapies) totalize 21,5% of cases. "Other therapies" in Figure 37 include mycophenolate mofetil, azathioprine and human immunoglobulin.

Nome da terapêutica modificadora da doença em Maio 2014					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Int B-1a SC 22ug 3xW	26	5,7	5,7	5,7
	Int B-1a SC 44ug 3xW	34	7,4	7,4	13,1
	Int B-1a IM 1xW	92	20,0	20,0	33,1
	Int B-1b SC dias alternados	88	19,2	19,2	52,3
	Acetato de Glatirâmero	78	17,0	17,0	69,3
	Natalizumab	51	11,1	11,1	80,4
	Fingolimod	38	8,3	8,3	88,7
	Mitoxantrona	2	,4	,4	89,1
	Azatioprina	1	,2	,2	89,3
	Outro ou outro esquema	5	1,1	1,1	90,4
	NAO FAZ TX MOD DOENÇA	44	9,6	9,6	100,0
	Total	459	100,0	100,0	

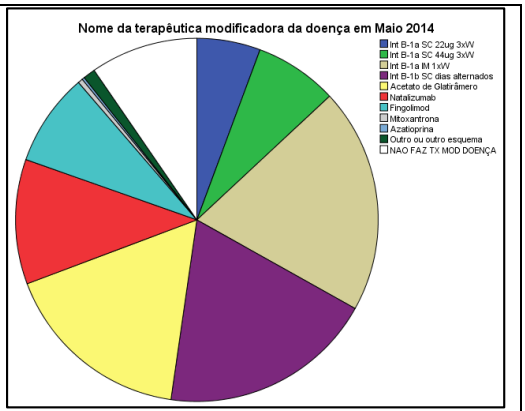


Figure 36. Distribution of treatments all the population that remains in RRMS phase (not excluding those not on DMT).

Distribution of RRMS population by type of DMT		
	N	%
IFN-beta 1a SC	60	14.5
IFN-beta 1a IM	92	22.2
IFN-beta 1b SC	88	21.2
Glatiramer acetate	78	18.8
Natalizumab	51	12.3
Fingolimod	38	9.2
Mitoxantrone	2	0.5
Other therapeutics	6	1.4
Total	415	100

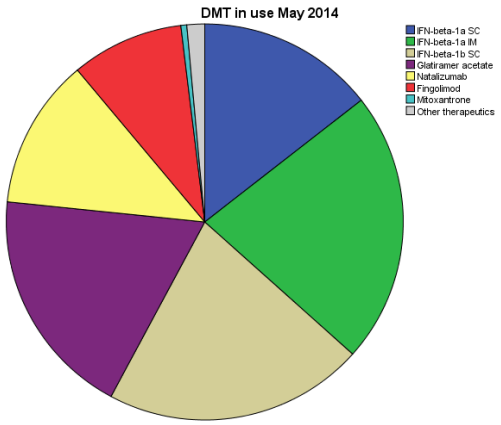


Figure 37. Distribution of types of DMT in our population of currently in RRMS that is on DMT.

In total there were 53 patients with SPMS by inclusion: 38 were in RRMS at diagnosis, 5 were already in SPMS by diagnosis (Figure 38). Considering all patients in SPMS under DMT (**Erro! A origem da referência não foi encontrada.**), interferons and GA together complete 63.2% of cases, Natalizumab and Fingolimod together complete 26.3%, "other therapies" include ocrelizumab, mycophenolate mofetil and azathioprine.

Nome da terapêutica modificadora da doença em Maio 2014					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Int B-1a SC 22ug 3xW	1	2,1	2,1	2,1
	Int B-1a SC 44ug 3xW	5	10,4	10,4	12,5
	Int B-1a IM 1xW	4	8,3	8,3	20,8
	Int B-1b SC dias alternados	5	10,4	10,4	31,3
	Acetato de Glatirâmero	6	12,5	12,5	43,8
	Natalizumab	3	6,3	6,3	50,0
	Fingolimod	6	12,5	12,5	62,5
	Alemtuzumab	1	2,1	2,1	64,6
	Outro ou outro esquema	3	6,3	6,3	70,8
	NAO FAZ TX MOD DOENÇA	14	29,2	29,2	100,0
	Total	48	100,0	100,0	

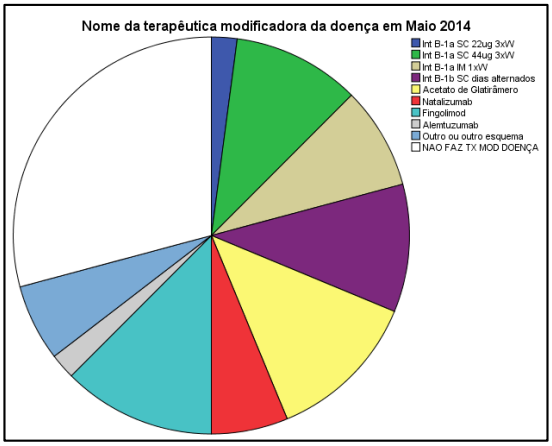


Figure 38. Distribution of treatments in SPMS population who were on RR phase by time of diagnosis (n=48).

Distribution of SPMS population by type of DMT		
	N	%
IFN-beta 1a SC	6	15.8
IFN-beta 1a IM	6	15.8
IFN-beta 1b SC	6	15.8
Glatiramer acetate	6	15.8
Natalizumab	3	7.9
Fingolimod	7	18.4
Alemtuzumab	1	2.6
Other therapeutics	3	7.9
Total	38	100.0

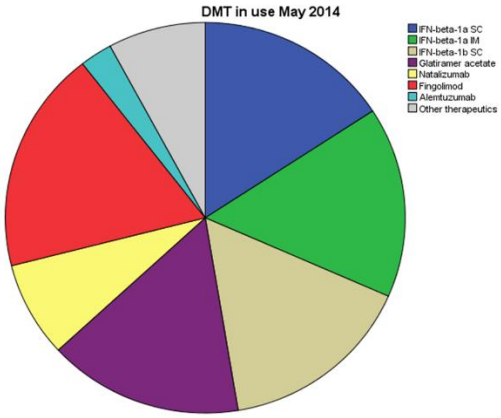


Figure 39. Distribution of treatments of all patients in SPMS at inclusion on our study and on DMT in May 2014 (patients not on DMT excluded).

Figure 40 and Figure 41 show the distribution of DMT in the PPMS population. The 6 patients under "other drugs" represent: ocrelizumab (3 patients), azathioprine (2 patients)) and MMF (1 patient)

Nome da terapêutica modificadora da doença em Maio 2014					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Int B-1a SC 44ug 3xW	2	5,3	5,3	5,3
	Int B-1b SC dias alternados	3	7,9	7,9	13,2
	Acetato de Glatirâmero	3	7,9	7,9	21,1
	Fingolimod	1	2,6	2,6	23,7
	Ocrelizumab	2	5,3	5,3	28,9
	Azatioprina	1	2,6	2,6	31,6
	Outro ou outro esquema	2	5,3	5,3	36,8
	NAO FAZ TX MOD DOENÇA	24	63,2	63,2	100,0
	Total	38	100,0	100,0	

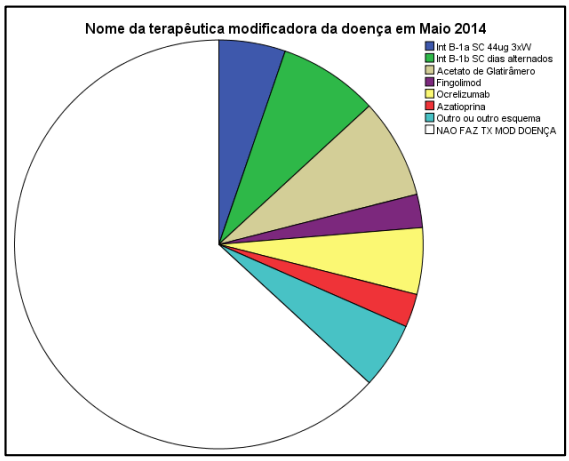


Figure 40. Distribution of DMT in the total population of PPMS patients (with or without relapses).

Distribution of PPMS population by type of DMT		
	N	%
IFN-beta 1a SC	2	10.0
IFN-beta 1a IM	2	10.0
IFN-beta 1b SC	5	25.0
Glatiramer acetate	3	15.0
Natalizumab	1	5.0
Fingolimod	1	5.0
Other therapeutics	6	30.0
Total	20	100.0

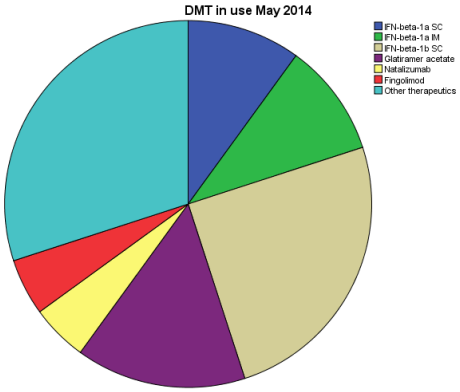


Figure 41. Distribution of DMT in the total population of PPMS patients (with or without relapses) that are under DMT.

Level of education

The mean number of years at school of the total population is 12±4,5 years (P25: 9; P75: 16 years; min: 0; max: 27 years). If we only analyze patients older than 20 or 30 year-old, in an effort to exclude those cases that could still have their education incomplete by time of analysis, the result is about the same (in part this is due to the fact that we have only eight patients 20 years-old or younger and 102 patients 30 years-old or younger, but this could also mean that by time of diagnosis the overwhelming majority of patients have their education complete or interrupt it).

There is no difference between male and female patients (Figure 42).

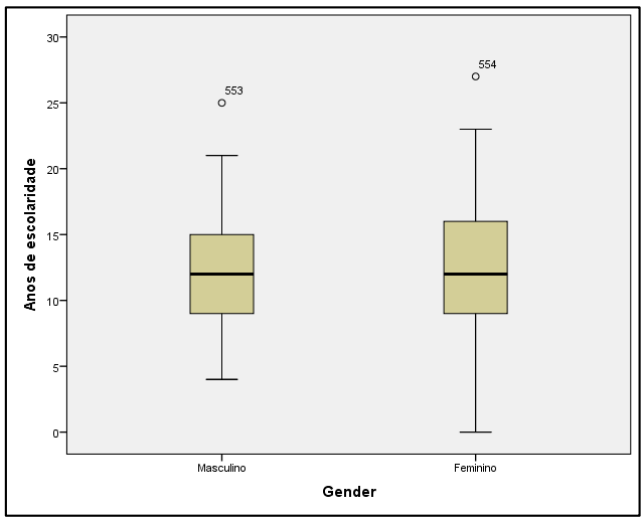


Figure 42. Number of years of school per gender, total population of our database.

There is a weak, although significant, correlation between year of birth (or age) and years of education (r=0,34, p<0,001, Pearson correlation), with older patients showing lower levels of education. If we only analyze patients older than 20 or 30 year-old in an effort to exclude those cases that could still have their education incomplete by time of analysis, the result is about the same (reasons pointed out above).

Similarly, patients diagnosed more recently have generally higher levels of education (weak correlation) (**Erro! A origem da referência não foi encontrada.**).

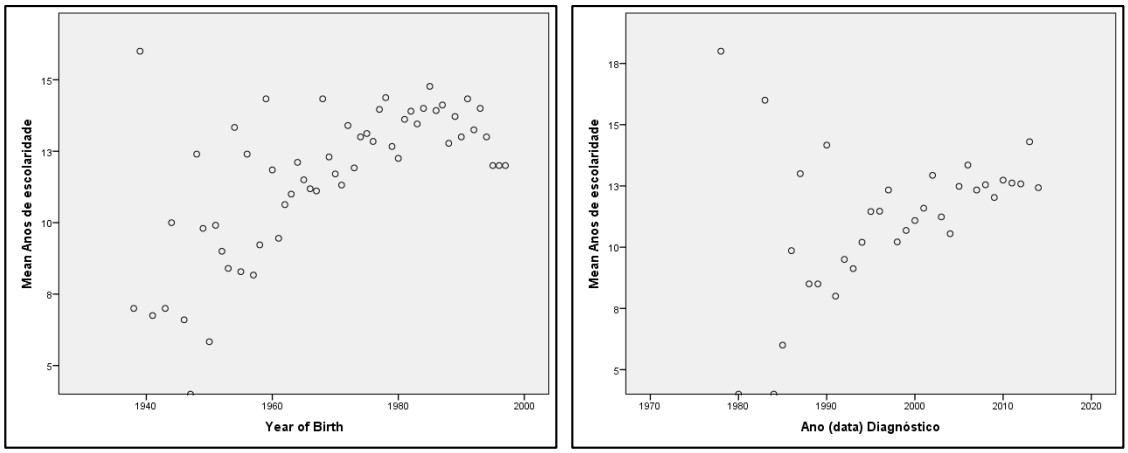


Figure 43. Mean years at school per year of birth of patients (left) and per year in time at which diagnosis occurred (right).

Globally, if we look to the relation between age at diagnosis and number of years at school, there is no apparent relationship. It would be interesting to look only at diagnoses occurring before age 20 (then excluding cases that less probably would still have their of education on course by the time they were diagnosed with MS) for patients that have now 20 years-old or older (to assure those patients have had enough time to accomplish their complete education), but we have very few patients in that situation (Figure 44).

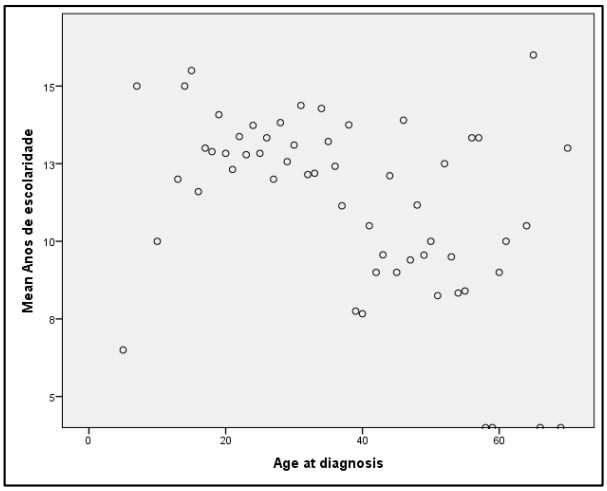


Figure 44. Mean number of years at school that patients that were diagnosed at each specific age accomplished.

The number of total years at school is different in our populations of RRMS and PPMS (Figure 45). As we showed before, these populations have different ages at present time: PPMS were born a longer time ago. External social factors not related to MS could then interfere with this result. An analysis controlled for age at present time or for year of birth will have to be performed.

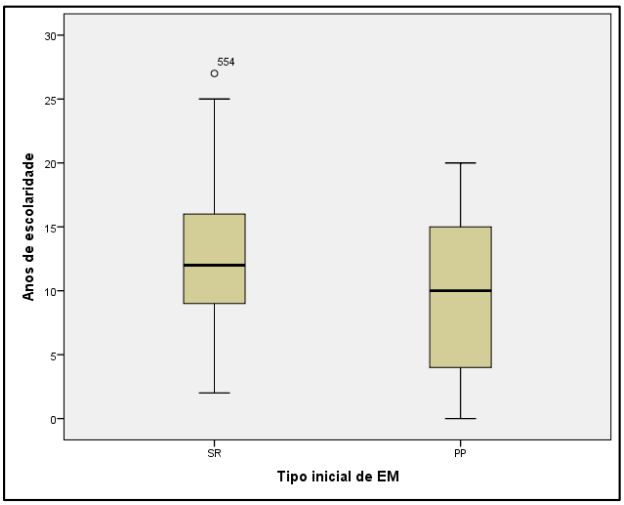


Figure 45. Number of total years at school is different in RRMS and PPMS but these populations have different ages at present time.

Economic activity and status of employment

Considering the week immediately before inclusion, and according to ICSE-93, 61,5% (n= 345) of our total sample is classified as “economically active population” (Figure 46). 86,51% of these have un employment (or various), 13,49% are unemployed (Figure 47).

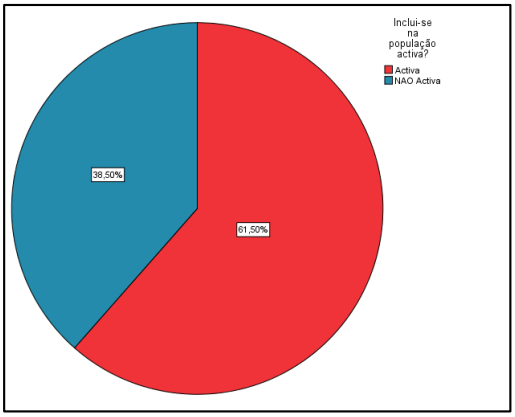


Figure 46. Distribution of our total population in terms of economic activity.

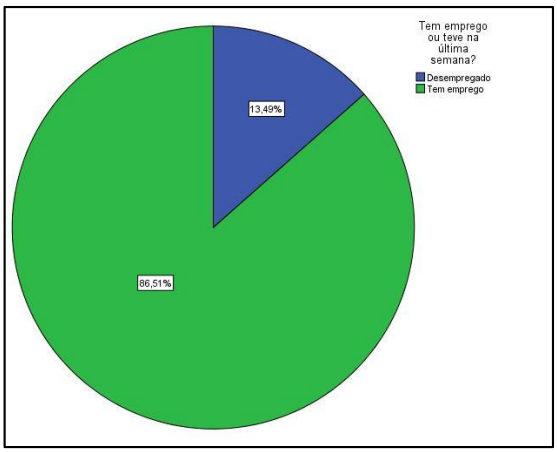


Figure 47. Distribution of our total economically active population in terms of employment / unemployment.

In Table 30we show the proportion of economically active and the unemployment rate for all our sample and for the group “RRMS at inclusion”. Data is shown for a selection of categories of gender, EDSS and age in each group. The difference in constitution between these 2 groups is essentially the presence of SPMS and PPMS in the whole sample.

Older patients, patients with higher EDSS and women show a smaller proportion of economic activity.

Patients currently in RRMS have also a higher proportion of economically active than the whole sample (which, as stated, includes progressive forms). We had seen before that progressive forms are older at inclusion and have higher EDSS than patients in group RRMS at "inclusion".

This difference in the proportion of economically active patients between the 2 groups is, though, apparent even inside the same age category. This could be related with higher EDSS of patients in progressive forms even inside the same age category.

Rates of unemployment seem higher in women, higher EDSS and higher ages, all classes that already have less economic activity.

	All sample			RRMS at inclusion		
Group	N	Economically active	Unemployed	N	Economically active	Unemployed
All	561	61,5%	13,5%	459	71%	12,7%
All males	164	68,9%	8,9%	131(*)	80,2%	9,3%
All females	397	58,4%	15,7%	328(*)	67,4%	15,7%
All EDSS <= 4.0	404	74,3%	12,5%	388	75,5%	12,4%
All EDSS 4.5-6.0	95	34,7%	12,1%	57	45,6%	11,5%
All EDSS >=6.5	62	19,4%	45,5%	14	50%	33,3%
Current Age 20-29	85	82,4%	20,3%	83	83,1%	19,1%
Current Age 30-39	164	85,4%	14,4%	150	88,7%	13,6%
Current Age 40-49	131	68,7%	9,0%	113	74,3%	8,4%
Current Age 50-59	111	31,5%	5,7%	73	41,1%	3,3%
Current Age 60-69	55	16,4%	22,2%	30	30%	22,2%
(*) RRMS at inclusion females: age 41,2±12,1 years-old, median EDSS 2.0; RRMS at inclusion males: age 39,2±10,1 years-old, median EDSS 2.0.						

Table 30. Proportion of economically active and the unemployment rate (in the week before inclusion) for selected categories of our sample and for RRMS at inclusion.

InTable 31we show the same data for patients SPMS at inclusion and PPMS (with or without relapses).

	All SPMS at inclusion			All PPMS at inclusion		
Group	N	Economically active	Unemployed	N	Economically active	Unemployed
All	53	17%	44,4%	45	17,8%	12,1%
All males	13	23,1%	0%	19	26,3%	0%
All females	40	15%	66,7%	26	11,5%	33,3%
All EDSS <= 4.0	1	-	-	12	41,7%	20%
All EDSS 4.5-6.0	22	18,2%	25%	15	20%	0%
All EDSS >=6.5	30	16,7%	60%	18	0%	-
Current Age 20-29	1	-	-	1	-	-
Current Age 30-39	5	60%	33,3%	7	28,6%	50%
Current Age 40-49	11	27,3%	33,3%	7	42,9%	0%
Current Age 50-59	20	10%	50%	17	17,6%	0%
Current Age 60-69	14	0%	-	11	0%	-
In view of the low number of patients in many categories, this table should only be interpreted as a general perspective on the subject.						

Table 31. Rates of economic activity and uenmployment in SPMS and PPMS patients.

In Table 32 we compare the main characteristics of Active and Non-Active populations. As already suggested in the previous tables, non-actives are older (but mean age is only 50 years-old), more frequently females, have more progressive forms (less RRMS at diagnosis) and higher EDSS. They are also less educated. The comparison of EDSS (in May 2014) between economically active and non-active patients is shown in Figure 48.

	All economically active population	All economically non-active pop.	p
N	345	216	-
Age at inclusion	38,27±9,2	50,4±13,3	p<0,001 (Independent-samples Mann-Whitney U test)
% of females	67,2%	76,4%	p=0,021 (Pearson Chi-Square test, Cochran criteria verified)
% of RRMS	95%	62,3%	p<0,001 (Pearson Chi-Square test, Cochran criteria verified).
Years of education	13,57±3,6	9,59±4,7	p<0,001 (Independent-samples Mann-Whitney U test)
Median EDSS (May 2014)	1,5 (P25: 1,0; P75: 3,0)	5,0 (P25: 3,0; P75: 6,0)	p<0,001 (after grouping EDSS into categories, Pearson Chi-Square test, Cochran criteria verified)

Table 32. Comparison of the main characteristics of Active and Non-Active populations.

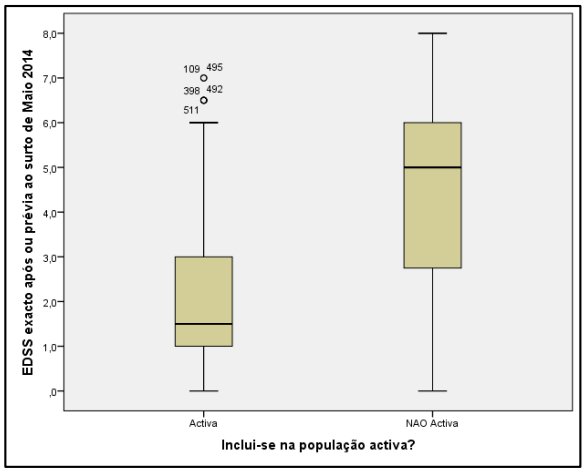


Figure 48. Comparison of EDSS (in May 2014) between economically active and non-active patients.

In Table 33 we compare the main characteristics of Active and Non-Active RRMS at inclusion patients. Non active RRMS patients are older, they are more frequently female, they are less educated and they have higher EDSS than their economically active counterparts. More than half of them are under 50 years-old though, a good part of them have a mild to moderate EDSS.

	RRMS economically active	RRMS economically non active	p
N	326	134	-
Age at inclusion	38±9,2	47,2±14	p<0,001 (Independent-samples Mann-Whitney U test)
% of females	67,8%	80,5%	p=0,006 (Pearson Chi-Square test, Cochran criteria verified)
Years of education (mean)	13,6±3,6 vs	10,1±4,5	p<0,001 (Independent-samples Mann-Whitney U test)
Median EDSS (May 2014)	1,5	3,5	p<0,001 (after grouping EDSS into categories, Pearson Chi-Square test, Cochran criteria verified)

Table 33. Comparison of the main characteristics of Active and Non-Active currently RRMS populations.

In **Erro! A origem da referência não foi encontrada.** it is apparent that unemployed patients are slightly older and are more frequently females but this doesn't attain statistical significance. Education and type of MS don't differ. Unemployed have a slightly higher EDSS. Our data shows, then, explanations for the fact patients are in the economically active or non-active groups, but, once inside the economically active group, the explanation for the distribution between employed and unemployed seems to be other factors that are not comprised in our dataset.

	All active employed	All active unemployed	p
N	295	46	-
Age at inclusion	38,7±9,2 years-old	35,5±9,3	n.s. (Independent-samples Mann-Whitney U test)
% of females	65,4%	78,3%	n.s. (Pearson Chi-Square test, Cochran criteria verified)
Years of education	13,53±3,7	13,63±2,7	n.s. (Independent-samples Mann-Whitney U test)
% of RRMS	95,9%	89,1%	
Median EDSS (May 2014) (**Erro! A origem da referência não foi encontrada.**)	1,5 (P25: 1,0; P75: 3,0)	2,75 (P25: 1,0; P75: 4,0)	p=0,008 (after grouping EDSS into categories, Pearson Chi-Square test, Cochran criteria verified)

Table 34. Comparison of employed vs unemployed populations (both part of the active population).

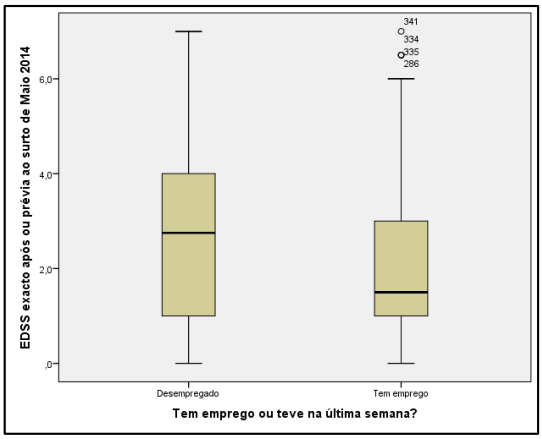


Figure 49. EDSS (May 2014) of all employed and all unemployed patients.

In Table 35 we present the comparison between employed RRMS patients and unemployed RRMS ones. It is not very different from the comparison between employed and unemployed in the global sample because there is only a small part of progressive patients that belong to the economically active group. Here younger age seems associated with more unemployment (unemployment of younger people is a phenomenon known in Portuguese society in actuality.)

	RRMS employed	RRMS unemployed	p
N	281	41	-
Current age	38,5±9,1	35,1±9,3	p=0,012 (Independent-samples Mann-Whitney U test)
Proportion of females	66,5%	75,6%	n.s. (Pearson Chi-Square test, Cochran criteria verified)
Years of education (mean)	13,6±3,8	13,6±2,7	n.s. (Independent-samples Mann-Whitney U test)
Median EDSS	1.5	2.0	n.s.

Table 35. Comparison between employed RRMS patients and unemployed RRMS ones.

98,2% of all the employed patients in our sample said they had only one job, 1,8% had various jobs.

For the main job, the status of employment is represented in fig xxx. 81,6% are “employees”, only 3,4% are employers.

The type of contract (the bond) with the main job is shown in fig xx. 80% have a regular contract with no term.

Employed patients reported 40,13±10,9 hours of work per week.

We also asked patients if their disease interfered with their ability to work: 69% said no, 31% said yes.

The type of unemployment: voluntary in 29,8%, involuntary in 70,2%.

95% of unemployed had an employment before.

52% of unemployed think MS is not the main cause of their unemployment; 26,1% say it’s the major cause, the others say it’s one amongst other causes.

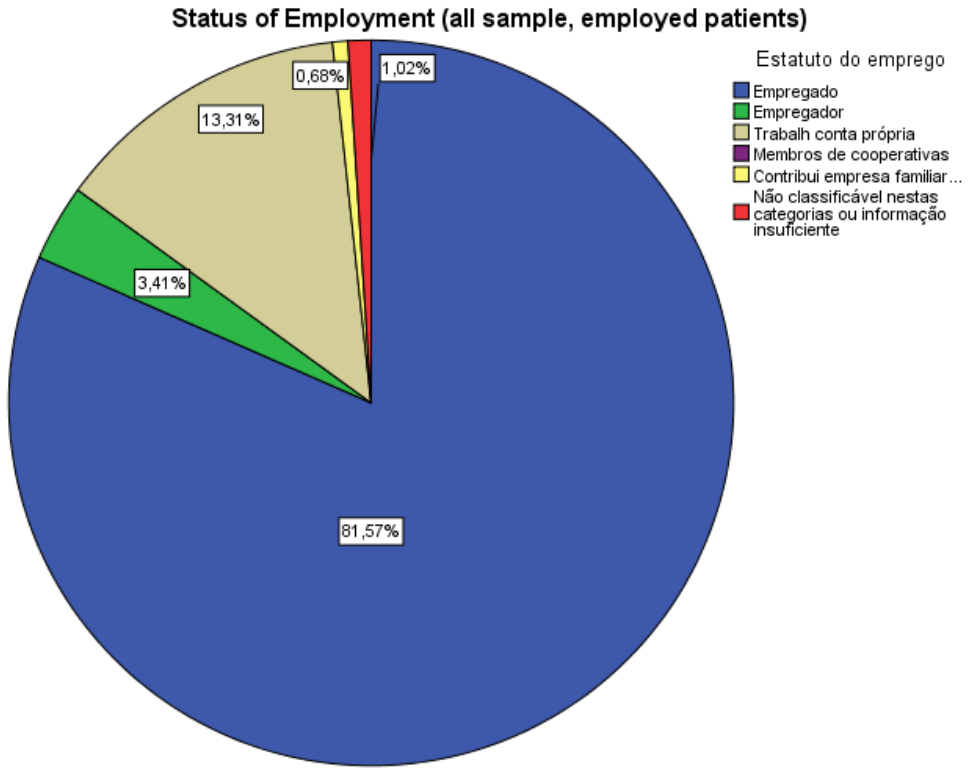


Figure 50. Distribution of the employed population in terms of the employment status (for their main job, as part of patients had several jobs).

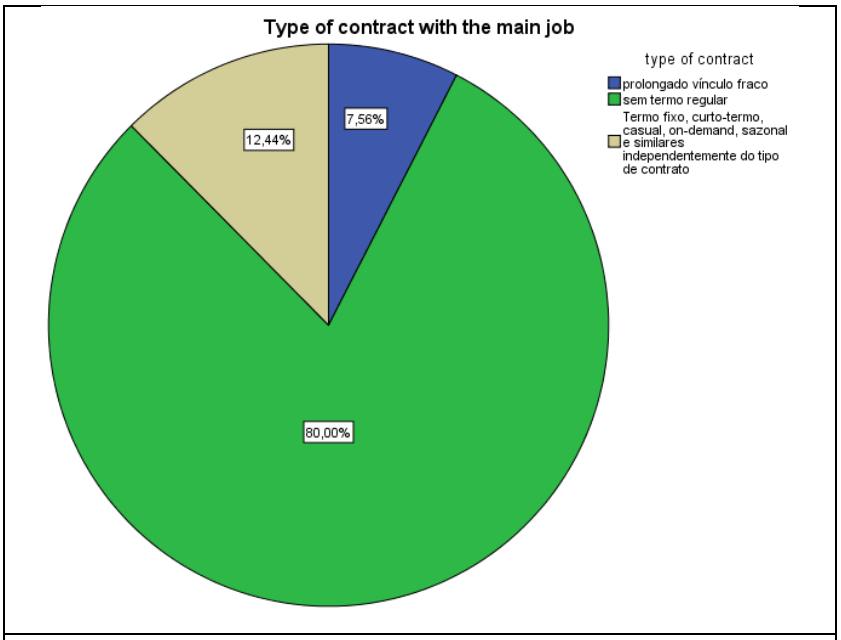


Figure 51. Types of contract in the mane job.

Non-active population constitutes 38,5% (n= 216) of our total cases. Stratifying these patients by their economic situation shows that the great majority (74,1%) have a retirement due to disease, receiving compensation for that (Figure 52).

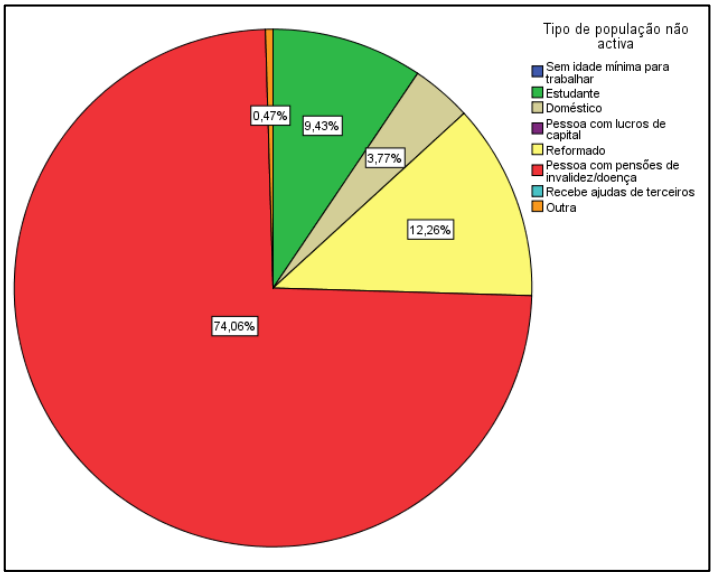


Figure 52. Distribution of all Non-Active population by subtypes of economic situation.

RRMS at inclusion economically non-active: 69,5% retired due to disease, 13,7% student, 11,5% retired due to age, 5,3% other.

Pregnancy

Of 397 women in our database, we have data on gestations and live births, before and after the diagnosis of MS, for 394 (99%). Mean age at diagnosis of women in our database was 34±11,5 years-old. 15,0% had live births after the diagnosis of MS.

When we compare only the population of women whose diagnosis occurred during the years 1991 to 2000 versus those whose diagnosis occurred during the decade 2001-2010 (we have low numbers before 1990 and diagnosis after 2009 are also still few and they have a short follow up), the percentage of women that had live births is, correspondingly, 15% and 19% (n.s., Pearson Chi-Square test). So, even considering the fact that this late group has a shorter follow-up (some of these patients could still become pregnant) and that births in Portugal have been decreasing (according the Portuguese National Statistical Institute - INE), the proportion of women becoming pregnant after the diagnosis of MS, increased (Table 36).

Década de diagnostico * Num_NadosVivosApósEM Crosstabulation

			Num_NadosVivosApósEM		
			Women with NO births after MS	Women with BIRTHS after MS	Total
Década de diagnostico	1971-80	Count	1	1	2
		% within Década de diagnostico	50,0%	50,0%	100,0%
	1981-90	Count	16	7	23
		% within Década de diagnostico	69,6%	30,4%	100,0%
	1991-00	Count	69	12	81
		% within Década de diagnostico	85,2%	14,8%	100,0%
	2001-10	Count	151	35	186
		% within Década de diagnostico	81,2%	18,8%	100,0%
	2011-20	Count	101	4	105
		% within Década de diagnostico	96,2%	3,8%	100,0%
Total		Count	338	59	397
		% within Década de diagnostico	85,1%	14,9%	100,0%

Table 36. Percentage of women with and without live births after diagnosis per decade in time at diagnosis.

When we only consider the women whose diagnosis occurred before 35 years-old (then excluding a part of the population less prone to become pregnant), this difference is even larger:

23,8% of females whose diagnosis occurred in the decade of 1991 to 2000 and that were under 35 years-old at the time of diagnosis (n= 42) had live births till the date of CRF filling whereas this same number for the corresponding diagnosis occurring in the years 2001-2010 (n=108) is 31,5% (n.s., Pearson Chi-Square test).

	Women diagnosed MS 1990-99	Women diagnosed MS 2000-09	p
N	70	173	
Age at 1st symptoms	30,76±11,0	31,1±10,8	
Age at diagnosis	34,74±11,1	34,1±11,1	
Disease duration (diagnosis to inclusion)	18,0±2,8	9,1±3,0	
Age at inclusion	52,81±11,0	43,2±11,3	
RR at diagnosis	91,4%	94,8%	
RR at diagnosis that progressed to SP at inclusion	23,4%	9,8%	
EDSS (May 2014)	4,0 (n=58 data available	2,0 (n=139)	
Level of education (years)	10,9±4,9	12,2±4,6	
Had gestations before diagnosis	65,2% (data for n=46)	61,9% (data for n=118)	
Mean number of gestations (for those pregnant) before diagnosis	1,97 (data for n=46)	1,6 (data for n=118)	
Had live births before diagnosis	63% (data for n=46)	57,6% (data for n=118)	
Mean number of live births (for those	1,7 (data for n=46)	1,5 (data for n=118)	

pregnant) before diagnosis			
Had gestations after diagnosis	17,1% (data for all 70)	23,1% (data for n=169)	
…of which had been pregnant before			
Mean number of gestations (for those pregnant) after diagnosis	1,3 (data for all 70)	1,3 (data for n=169)	
Had live births after diagnosis	17,1% (data for all 70)	18,3% (data for n=169)	
Mean number of live births (for those pregnant) after diagnosis	1,3 (data for all 70)	1,1 (data for n=169)	

Familial MS

7,8% (43 patients out of 553 with data available) of our population reported to have some blood-related family with a confirmed diagnosis of MS (**Erro! A origem da referência não foi encontrada.**). Even if we, arbitrarily, select a subgroup of older MS patients by the time of CRF filling, these percentage remains relatively stable (mean age at diagnosis of cases with positive and cases of negative family history is, approximately the same, as we could confirm).

		Frequency	Percent	Valid Percent
Valid	irmão/irmã	6	1,1	1,1

	filho/filha	4	,7	,7
	pai/mãe	8	1,4	1,4
	tio/tia em primeiro grau materno ou paterno	4	,7	,7
	primo(a) direito(a) materno ou paterno	12	2,1	2,2
	outro	6	1,1	1,1
	varios	3	,5	,5
	NENHUM	510	90,9	92,2
	Total	553	98,6	100,0
Missing		8	1,4	
Total		561	100,0	

Table 37. Distribution of patients with positive family history by relative degree.

The proportion of positive family history in male and female patients is similar (8,7% vs. 7,4%, respectively).

The proportion of PPMS patients (with or without relapses) with positive family history is not different from the corresponding value within RRMS patients (6,7% of 45 patients vs. 7,9% of 513, respectively).

Although we found a bigger proportion of patients with positive family history for those with a diagnosis in the decade of 1991-2000 (11% of 118 patients) than for those with a diagnosis during the decade of 2001-2010 (6,7% of 268 patients), we are unsure about the significance of this and we will confirm this data when we will have a bigger number of patients (for other decades we have a smaller number of patients).

Other data

We currently have very little variability in race/ethic origin in our database, for which an analysis is deferred.

Issues related with migrations will be analyzed posteriorly, as will data on the place of residency at birth, place of residency at first symptoms and place of residency at diagnosis. Some of these analyses will need confrontation with general epidemiological national data.

For what concerns data on participation in clinical trials we detected an error on the interpretation on the question after perceiving, in our data, an unexpected high number of

patients reported to have participated in clinical trials (compared to what is the common notion of neurologists working in the field in Portugal). Some investigators had accepted fase IV trials and other observational studies without intervention as iterventional clinical trials. We are considering to review the data of all patients on this matter.

Other data on pregnancy and miscarriages, other data on level of education and status of employment, data on BMI, attribution of the legal status of physical/mental incapacity and need for a caregiver (and other data), are waiting for analysis.

Discussion

Our study is the first multicentric national wide study to provide epidemiological and clinical data on MS patients in Portugal. Considering the estimated prevalence of MS in Portugal, patients included in this pilot PORT-MS study represent approximately 10% of all MS patients in our country.

Our study has, of course, various limitations. The main ones are:

- Cross-sectional and retrospective collection of data, with many possible recall bias. To diminish this limitation we used every source of information we could (the patients' file and direct interviews with the patient himself and the treating neurologist);
- Use of a hospital-based instead of community-based source. A selection bias can be present. In these 7 big dimension hospitals there could be a tendency to over represent more severe cases or cases being treated with more 2nd line drugs. On the other hand, although we performed sequential recruitment in all areas of the hospital where we could find these patients, we know that the most disabled or institutionalized patients, some of them having stopped the use of DMT, don't come to the hospital so frequently. Some of these bias could be overcome by the recruitment of all the population of MS patients in each hospital, which is one of our objectives.
- We still have a globally small number of patients and a superior number of MS centers has to be integrated. In certain clinical groups (such as PPMS), or in some ethnic groups, we have relatively few patients, which limits the analysis of clinical characteristics of these patients.
- We detected an erroneous interpretation of the questions regarding the participation of patients in clinical trials, as stated in the results section, and we will have to correct that.

Our study has, has on the other hand, comparing to other European registries on MS patients, superior range of details in some aspects, namely regarding the educational level, the status of employment or the obstetric data in MS female patients (Fig 46 shows a summary of the PORT-MS pilot study results). Our objective was not to be exhaustive, though. We aimed at a general, well performed, portrait of the Portuguese MS population, and, above all, we avoided a too complex CRF that investigators wouldn't easily accept.

General demographics and disease milestones

Our data are generally similar to those obtained from other countries' MS registries. Regarding the average age of the patients, the disease duration, the age at onset and the transition from the onset of the illness to the diagnosis, we found closer similarity to the German MS registry (44.2±11.5 years; 12.7 ± 9.2 years; 31.4 ± 10.2 years; 3.4 ± 5 years, respectively – data from the two-year pilot study) (Flachenecker 2008). This makes us believe, despite the limitations stated above, that our sample may be representative of the population of interest.

When we analysed the age of onset (firs symptoms) and age at diagnosis in each decade in time, we found a slight increase in more recent times. This contrasts with the significant decreasing observed in the National Swedish MS Register (Boström 2012). We have currently no definitive explanation to this fact, it will have to be confirmed with a larger number of patients. One theoretical explanation could be the more accurate diagnosis of progressive patients in more recent times. We registered, on the contrary, a the tendency to decrease in the time from first symptoms to diagnosis more recently, which is also reported in other registries, and in agreement with the effect expected from better diagnostic methods available nowadays.

The significant higher age of onset when we compare the PP with the RR forms in our study is according to the literature (McDowell 2010).

The female to male ratio of our sample fits the interval found by Pugliatti in his review article about the women-to-men ratio for MS in Europe (1.1-3.4) (Pugliatti 2006). Several studies (in Canada, New Zealand, Denmark, Sweden, among others) have demonstrated an increased women-to-men ratio in MS throughout decades, presumably due to an increased incidence in women rather than a decline in men (Orton 2006, Trojano 2012, Koch-Henriksen 2011, Boström 2012). However, the proportion of male to female seems globally stable in our study, when analyzing by date of birth or by decade in time at which the diagnosis was made. Similar to the Norwegian MS Registry (Kampman 2013), in our study the overall sex ratio of MS is strongly determined by cases with RR onset, as in our PP patients, women and men are almost equally affected (1.1:1).

Clinical course

The distribution of prevalent cases by disease course is a hard task. Some disease subgroups are not considered in some reports (like PPMS with relapses, which is equivalent to PRMS). Other times, classically distinguished groups like PPMS and SPMS are treated as one group. Additionally, in some articles, these two last categories are sometimes omitted.

RRMS ranged from 24% (The Netherlands) to 88% (Greece) of prevalent cases. In PORT-MS it is 82%.

In our study, only 10,8% (60/558) have combined RPMS+SPMS. As we can see in the Figure 53, whereas combined proportion of RPMS and SPMS ranged from 4% (Sweden) to 50% (Bulgaria), in PORT-MS that value is relatively low. There is a substantial discrepancy between PORT-MS and the results of the extension phase 2005/2006 of a German study, with a much higher number of combined SPMS+RPMS cases in the Germany study: 10,8% vs. 32%, respectively. The survey was not population-based, relying instead on specific data provided by study centers, which may have led to selection bias (Flachenecker 2008).

Frequency of PPMS (without relapses) was 6,9% in PORT-MS, which is in the lower end of the range from 4% (Austria) to 35% (The Netherlands) (Pugliatti 2006). Subjectively the authors believe that PPMS patients (which no longer do DMT, are older and very disabled patients) come less frequently to the outpatient clinic, if at all, which may bias our sample even if the recruitment is strictly sequential. This may, at least partially, justify our low proportion of progressive forms of MS.

Regarding the initial MS type, our results are comparable to a recent study in the Spanish population (based on EDMUS), in which the clinical course was RRMS in 93.3% of the patients (PORT-MS 91,4%) and PP in the other 6.7% (in PORT-MS 8,6% of patients started with PPMS, with or without superimposed relapses) (Romero-Pinel 2010).

The difference in proportion of RRMS and SPMS between PORT-MS and studies prior to the date of 1993 (approval of the first DMT) may eventually reflect some effect of therapies (although that effect has been difficult to prove in the long-term course of this disease) (Derwenskus 2011). In studies after 1993, differences between the countries could also be related with different availability of DMT (the advent of DMT probably changed the population that more frequently come to clinics).

In PORT-MS study, the percentage of patients that progressed to SPMS at 10 years of evolution was 3,3% and at 15 years 5%. These values are lower than those of a Germany study of 2006 for example, where after approximately 10 to 15 years, 30% to 40% of patients with initial RRMS enter the SPMS. It shows that the patients included in our study have less SPMS diagnosis and this could be probably due to selection or recall bias, with misinterpretation of retrospective data from patients (Flachenecker 2006).

As stated above, from those patients initially diagnosed with RRMS, the mean age for patients not progressing to SPMS is 41 years-old at present time, whereas those that evolved to SPMS is 55 years-old. The shorter the disease duration, the fewer the cases with SPMS within the population of cases having an initial RR course.

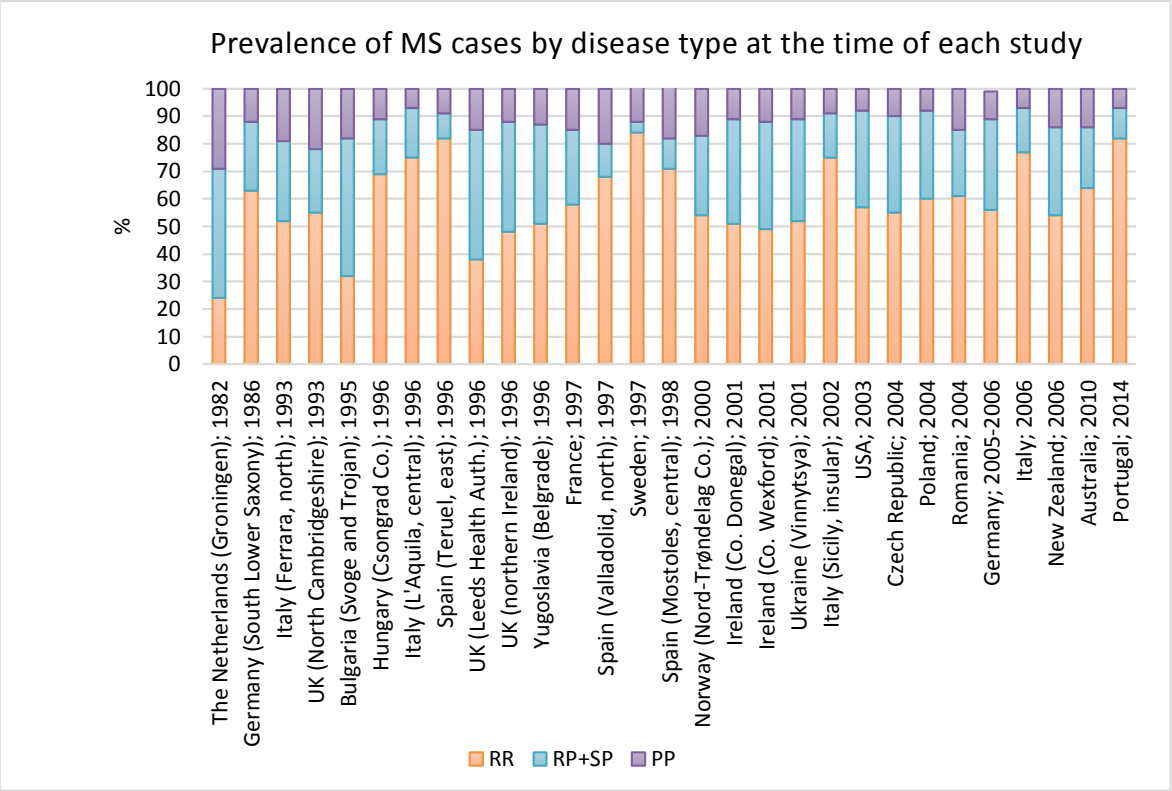


Figure 53. Percentage of MS patients by disease type at each study time, in the World. Adapted from: Pugliatti 2006.

EDSS

In the extension phase 2005/2006 of the Germany nationwide MS registry, the median EDSS score was 3.5 (PORT-MS - Median EDSS for the 465 patients with exact EDSS available is 2,5) (Flachenecker 2008). In a Portuguese study about the prevalence of MS in the District of Santarém (n=29) the mean EDSS was 3,2 (De Sá 2006).

In total, 51% of patients were fully ambulatory (EDSS < 4) (PORT-MS – EDSS ≤ 4 – 72,7%), 28% of patients required assistance (cane, crutch, brace) to walk 100 m (EDSS ≥6 and < 8) (PORT-MS – 18,0%), and 6% were confined permanently to a wheelchair (EDSS≥8) (PORT-MS – 1,1%) (Flachenecker 2008).

Analysing patients in PORT-MS database for whom we have exact EDSS, we ascertain, for the RRMS group (n= 420), a median EDSS of 2,0 and for PPMS patients a median EDSS of 6,0. A British study showed similar results: median EDSS of 2,75 and 6,0 respectively (Anderson 2010).

Treatment

84.5% of all patients and 44.4% of PPMS patients were under DMT in May 2014. In a German study 71% of patients received immunomodulatory treatment, 20% of the PPMS population did receive immunoprophylactic treatment (Flachenecker 2008).

If we include only the patients on Interferon, Glatiramer Acetate, Natalizumab and Fingolimod, the proportion of use by type of treatment is shown on Figure 54. 22% of our patients were under second-line immunomodulatory treatment (Natalizumab/Fingolimod). Higher values were ported in Australia 2013 (33%) and USA 2010-2011 (32%) (Hollingworth 2014, Bergvall 2014, Windt 2013).

37% of PPMS and 70.8% of SPMS patients were under DMT in May 2014 - for the year 2009, outpatient setting, German Bavaria population, the values for PPMS and SPMS were significantly lower (20% and 59%, respectively) (Hoer 2014). Also for another German study concerning the employement analysis among patients with MS the values were 7% and 40% respectively (Boe Lunde 2014).

	Interferon β1B	**Interferon β1A**	**Glatiramer Acetate**	**Natalizumab**	**Fingolimod**
PORT-MS, 2014 (n=456)	**22%**	**37%**	**19%**	**12%**	**10%**
Australia, 2013	11%	44%	12%	12%	21%
USA, 2010-2011 (n=3.750)	36%		33%	8%	24%

Figure 54. Proportion of the different DMT used in MS in various studies.

Education and status of employment

Concerning this subject, the current national MS registries available worldwide do not include the educational level nor the employment status on their published data (Cristiano 2009, Otero 2010, Hurwitz 2010, Ahlgren 2011, Koch-Henriksen, Brønnum-Hansen 2011).

Our study shows that, on average, the Portuguese MS patients possess a higher educational level compared to the general Portuguese population and the correlation demonstrated between the year of diagnosis and the educational level may be interpreted from the point of view of social and economic changes that the country has suffered in the last decades.

Other studies have previously shown the relevance of sustaining employment after the diagnosis of MS, in particular, concerning health-related quality of life (Patti 2007, Van der Hiele 2014).

The rate of unemployment in PORT-MS patients is 13,5% (comparable with the 13,9% Portugal unemployment rate in the second quarter of 2014 reported by the Statistics Portugal). However,

the overall rate of unemployment in the MS population has a marked range and its value can reach 80%. This variation may be due to factors related to the country, differences in patients, disease and work-related characteristics as well as the definition of employment used (Shahrbanian 2013).

Our data concerning the employment status in the previous week show a higher percentage of economically active population compared to several countries namely Netherlands, Norway and United Kingdom (Van der Hiele 2014, Lunde 2014, Jones 2013).

Employed patients had a median EDSS of 1,5 and unemployed a median of 2,75. Data of a sample of patients attending an MS outpatient clinic in UK showed values of EDSS of 5,7 and 6,8 respectively (O'Connor 2005). So, as previously shown in several other studies, we demonstrate that lower levels of neurological disability are associated with employment status (Van der Hiele 2014, Lunde 2014).

PORT-MS showed that the great majority of non-active MS patients (74,1%) have a disability pension, which is consistent with data from previous studies (Lunde 2014, Cores 2014). Another study based on data from 9,721 MS patients in Sweden during 2005 also showed high prevalence of disability pension among MS patients (61,7%) compared to 14.2% among the controls (Tinghög 2013).

We may recognize as a limitation of our study the fact that we did not search for other factors contributing to unemployment or early retirement, namely the co-occurrence of other diseases such as depression and certain MS symptoms such as fatigue and cognitive impairment.

Pregnancy

During the first half of the 20th century, female MS patients were often discouraged from becoming pregnant (Borisow 2014). It is now known that fertility is not affected in MS, that the risk of relapse declines during pregnancy and that the course of pregnancy and obstetrical outcomes are similar to those of women without MS (Hellwig 2014). Our results suggest that, although in Europe and Portugal the number of live births is currently declining, the proportion of MS female patients giving birth to live children is increasing. We can speculate that the wider knowledge of the disease and the largest range of treatments available at present explain this reduced uncertainty on the part of women with MS to get pregnant. Concerning this subject, data are scarce in the existent national registries (Cristiano 2009, Otero 2010, Hurwitz 2010, Ahlgren 2011, Koch-Henriksen 2011, Brønnum-Hansen 2011) and there are only a few small studies approaching pregnancy prevalence in MS patients (Andersen 2013).

Familial MS

Our prevalence of familial MS of 7.8% is slightly lower than the generally accepted in the literature (Farez 2014, Hader 2014), although there are few studies, namely Spanish ones, with similar prevalence (Iglesias 2014, Viswanathan 2013).

Concerning family history, we did not enquire about the dimension of families, ease of access to health care or history of unknown healthcare status of relatives, all factors that could influence these data.

Conclusions

General epidemiological or demographic are not different from what has been described in other European or North American studies, notably in what concerns the age at first symptoms and diagnosis and the proportion of females to males. The time from first symptoms to diagnosis has decreased recently. This gives us the idea that patients are correctly identified and followed-up. PPMS takes more time to be diagnosed than RRMS.

Globally there is a big proportion of patients under DMT in Portugal, including in high EDSS and progressive forms. Second line therapies are underrepresented. This gives us the idea that Portuguese doctors are willing to treat this patients but somehow they use less frequently more recent or more efficacious (and more risky?) therapies.

Mildly incapacitated patients have rates of activity and employment similar to general population; these are much reduced in relatively young patients with moderate and high incapacity, essentially due to retirement due to disease. This

In Table 38 the main results of PORT-MS study are shown.

Result	Value	Additional data
Total number of patients in PORT-MS	561	Estimated to correspond to 10% of the Portuguese patients with MS
Race / ethnicity	98,9% white	
Place of birth	92,9% in Portugal	
Nationality	94,3% Portuguese	
Gender proportion	2,5♀: 1 ♂	2,5♀: 1 ♂in RRMS, 1,1♀: 1 ♂ in PPMS, p<0,05. Gender proportion has been stable throughout the last decades and at different ages at diagnosis.
Age at first symptoms	30,2±10,5 years-old	29,2±10 for RRMS, 39,4±11,7 for PPMS, p<0,001. It has slightly increased in the last decades (p=0,009).
Time from first symptoms to diagnosis	*3,2±5,3 years*	*3,0±5,1 in RRMS, 4,9±2,5 in PPMS, p=0,002. Stable in the last few decades, apparent decrease in the last few years.*

Age at diagnosis	33,4±11,1 years-old	32,3±10,4 in RRMS, 44,2±11,6 in PPMS, p<0,001 It has slightly increased over the last few decades (p=0,035).
RR versus PP at onset and at diagnosis	91,9% started with RR type of disease (although some were already in SP at diagnosis), 8,1% with PPMS, with or without relapses.	This proportion has been stable throughout the last few decades. Patients diagnosed later in life show a higher proportion of PPMS (p<0,001).
Years of evolution after diagnosis	9,4±7,2 years	no difference between RR at diagnosis and PPMS at diagnosis
Age at present time	42,9±12,4 years-old	42,0±12,1 for RRMS at diagnosis, 52,5±11,3 for PPMS at diagnosis, p<0,001
% of patient initially diagnosed in RRMS phase that evolved to SPMS	9,5%	Patients that reached SPMS have more time of evolution of disease and are older. This value is: 2,3% at 5 years after diagnosis, 3% at 7 years, 3,3% at 10 years, 5% at 15 years, 6,6% at 20 years.
Median EDSS at present time	2,5	2,0 for currently RRMS, 6,0 for PPMS.
Proportion of total patients on DMT	84,5%	90,4% of currently in RRMS; 88,4% of RRMS at diagnosis; 71,6% of all currently SPMS; 59,2& of all progressive forms together; 44,4% specifically in PPMS.
Mean number of years at school of the total population	12±4,5 years	Equal for male and female. Younger patients have higher levels of education.
Economically active versus non active population	61,5% active, 38,5% non-active.	
Unemployment rate	13,5%	
Retirement due to disease	74,1% of non-active population	
Women that became pregnant after diagnosis of MS	15%	
Proportion of cases with positive family history	7,8%	

Table 38. Summary table of the main PORT-MS study results.

Summary of contributions

The main contributions of this work for the resolution of the problems stated in the introduction of this dissertation are:

- The successful development of collaborative multicentric work between different hospitals and different regions of our country, notably in the field of MS, which, historically, has not been frequent;
- The production of the first national data on the characteristics of M, of MS patients and of MS care, even if for now including only 10% of the national population of MS;
- To foster a national registry of this disease, similar to what happens in the majority of the developed countries.

See Table 38, where the main data we produced is presented.

Future research

After November 2014, a “phase 2” of this study started, during which the PORT-MS study aims, during the next 1-2 years, to include the totality of patients of each center and involve additional centers in Portugal.

The development of the PORT-MS registry is also in my plans, as in the plans of the other co-authors, co-investigators and of Portuguese MS neurologist in general. My idea would be to start with an update of a selected group of data every May. I’m personally designing PORT-MS 2015 / PORT-MS registry.

Ideally we intend to create a PORT-MS web-system available for every neurologist in the country who treats patients with MS and wishes to include his patients in the database.

Such a registry could be used as a tool to other studies, providing samples of patients for clinical research, case-control studies and prospective studies.

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Appendices

Complete study protocol

In the following pages I present the complete study protocol as it was submitted to study centers, ethics committees and CNPD (the National Committee for data protection). I was the author of this protocol and the national coordinator of the study, although many colleagues reviewed it with me. The global document is originally in English language, although a Portuguese version was created to submission to the CNPD exclusively. The CRF and the informed consent, which are part of the protocol, are in Portuguese language.

CLINICAL STUDY PROTOCOL

INVESTIGATOR-INITIATED STUDY (IIS)

Title: PORT-MS (PORTuguese database of Multiple Sclerosis) – A national survey to describe current demographic and clinical characteristics of patients with Multiple Sclerosis in Portugal

Study code: PORT-MS

Type of study: Observational

Date of protocol: 27/Mar/2014

Version no.: 3

Name of Coordinating Investigator (on behalf of PORT-MS study Group)	Paulo Alegria
Date and Signature	
Contact	(Serviço de Neurologia, Hospital Beatriz Ângelo, Av. Carlos Teixeira 3, 2674-514 Loures, Potugal, telephone (351) 917801000, serranoalegria@outlook.com).

PRINCIPAL INVESTIGATOR SIGNATURE PAGE *(to be signed by the PI from each participating center)*

Study Title: PORT-MS (PORTuguese database of Multiple Sclerosis) – A national survey to describe current demographic and clinical characteristics of patients with Multiple Sclerosis in Portugal

Study Code: PORT-MS

Protocol Version/Date: version 3 / 27th March 2014

Center Number: *A number should be assigned to each participating center*

Principal Investigator: Dr. Paulo Alegria, MD, Neurologist, Serviço de Neurologia, Hospital Beatriz Ângelo, Av. Carlos Teixeira 3, 2674-514 Loures, Potugal, telephone (351) 917801000, serranoalegria@outlook.com).

I, the undersigned, am responsible for the conduct of the study at this site and affirm that:

I understand and will conduct the study according to the protocol, any approved protocol amendments, and all applicable Health Authority requirements and national laws.

I will not deviate from the protocol without prior written permission from the PORT-MS Study Group, except where necessary to prevent immediate danger to the subject.

Signature	Date of Signature

INDEX

1. PROTOCOL SYNOPSIS

Title:	PORT-MS (PORTuguese database of Multiple Sclerosis) – A national survey to describe current demographic and clinical characteristics of patients with Multiple Sclerosis in Portugal
Study Code:	PORT-MS
Authors:	Paulo Alegria1, João Ferreira2, João Sequeira3, José Tomás4, Miguel Grilo5, Raquel Samões6, Sara Varanda7, José Vale1, Maria José Sá5 1 – Serviço de Neurologia, Hospital Beatriz Ângelo, Loures, Portugal ; 2 – Serviço de Neurologia, Hospital de Santa Maria, Centro Hospitalar de Lisboa Norte, Lisboa, Portugal; 3 – Serviço de Neurologia, Hospital de Santo António dos Capuchos, Centro Hospitalat de Lisboa Central, Lisboa, Portugal; 4 – Serviço de Neurologia, Centro Hospitalar Universitário de Coimbra, Coimbra, Portugal; 5 – Serviço de Neurologia, Centro Hospitalar de São João, Porto, Portugal; 6 – Serviço de Neurologia, Hospital de Santo António, Centro Hospitalar do Porto, Porto, Portugal; 7 - Hospital de Braga, Braga, Portugal
Study Phase (optional):	Not applicable
Disease/Condition	Multiple Sclerosis
Rational	In Portugal, demographic and epidemiological clinical data about Multiple Sclerosis at a regional or national level are scant. There is no national registry for this condition and never a simultaneous and systematic collection of data from the whole country has been performed for this disease. Neurologists who follow patients with MS in Portugal will be invited to collaborate in this study as investigators and recruit patients (after approval by competent institutions and informed consent) and collect data (hospital-based study) about basal demographic and clinical characteristic of their patients, referent to the month of May 2014. A first step of the study will run in the centers the authors of the study are connected to and recruit until August 2014. A second step will extend the study to the whole country and aim at the maximum number of patient possible.
Primary Objective:	To describe basal demographic and clinical characteristics (taking May 2014 as the reference date) of the largest possible number of patients with the diagnosis of Multiple Sclerosis that are on medical follow-up by neurologists in Portugal.
Secondary Objective(s):	• To compare Portuguese data with previous national and international published data. • To analyze data of MS patients comparing them with data from the general population, as for instance in geographic patterns of place of birth and place of residency, education and labour. • To analyze the attractiveness of the country for the implementation of

	future clinical trials considering the data collected and especially the number of patients naïve to trials.
Exploratory Objective(s), if any:	There are no other specific exploratory objectives besides what is stated above.
Primary hypotheses (if applicable):	There are no specific primary hypotheses.
Study Design:	This is an observational, cross-sectional, descriptive, multicentric, national study.
Inclusion Criteria:	Patients alive and with the diagnosis of MS in any day of May 2014 (Positive McDonald 2010 criteria for Multiple Sclerosis, including "no better explanation"). Informed consent.
Exclusion Criteria:	No positive McDonald 2010 criteria. This includes the exclusion of patients with an alternative clinical diagnosis more plausible than Multiple Sclerosis even if other aspects of McDonald 2010 are satisfied. No informed consent.
Withdrawal criteria (if any)	Patients that withdraw consent Patients for whom an alternative diagnosis was discovered after inclusion in this study
Expected number of subjects:	Based in previous estimates, the number of MS patients in Portugal is around 5000. The aim of this study is to recruit the maximum number of patients that is possible. For "step 1" of this study (see below) the expected number of subjects is around 500.
Expected number of sites:	All public and private hospitals and clinics that are known to have MS patients on follow-up and treatment by neurologists will be invited to integrate the study. The expected number of sites is around 50.
Subject selection	Neurologists will recruit patients directly from outpatient clinics (or, more rarely, during hospital admission for any reason).
Intervention/exposure/ diagnostic test:	Not applicable.
Study Procedures:	This is an observational cross-sectional study. After informed consent by the patient, data will be collected at a single time point from the patient's file and from patient's interview (to complete missing information). The participant's contribution will then be finished and he won't be subjected to any other intervention.
Main data collected:	Main variables include: date of birth, place of birth, sex, ethnic origin, race, date of first symptoms, place of residency at first symptoms, date of diagnosis, place of residency at diagnosis, initial type of MS, date of start of secondary progressive MS, current treatment and date of start of that treatment, EDSS, employment status, previous participation in clinical trials. Please see CRF for details.
Endpoints	Not applicable.
Statistical methods	Variables will be described through descriptive statistics, namely absolute (n) and relative frequencies (%) for qualitative variables and mean, median, standard deviation (SD), minimum and maximum for quantitative variables. All patients with data at least in date of birth, sex and date of diagnosis will be considered, even if missing variables exist. Missing values will not

	be substituted.
Overall Study Duration:	Three years, starting from first center approved around June 2014.
Study timelines:	Estimated EC Approval - first center approved by June 2014. Recruitment is expected to occur between June 2014 and August 2014 for the first step of this study, until June 2015 for the second step. The Implementing/Scientific Committees may prolong recruitment for one year. Data analysis will be continual, for around 3 years starting from recruitment.

2 INTRODUCTION

2.1 CLINICAL BACKGROUND

Clinical registries, surveys of regional and national level and epidemiological studies, whether cross-sectional or longitudinal, physician- or patient-driven, are useful to increase knowledge about a certain disease or condition in many ways, including in aspects related with the etiology, clinical characterization, diagnosis, treatment, demography and epidemiology of that condition. Even relatively simple registries or surveys can be of extreme importance for a correct (cost-effective and adapted) planning of healthcare resources allocation in a certain region or country.

Beginning in the 5th and 6th decades of the previous century with several epidemiological studies, mainly focused on incidence and prevalence, now it's widely recognized that multiple sclerosis (MS) is one of the neurological diseases with the best-documented epidemiological studies (1). Registries of patients with MS constitute important repositories of information on the long-term course of the disease and provide complementary and valuable data in parallel with clinical trials, namely related to a better understanding of risk factors, disease process and progression. One of its major strengths is the inclusion of a very large number of patients that would be difficult to recruit in other studies, overcoming some limitations of the power of many clinical trials. Registries in MS are best suited to provide information about the prevalence, current treatment patterns, and patients' outcomes, and are particularly informative if multiple registries confirm the same findings. Some of the major criticisms, that have been pointed out to this type of observational study, are ascertainment bias due to incomplete registries and the huge commitment and effort that is required, so keeping a consistently collection of a minimum amount of information and obtaining the maximum possible ascertainment in a region or population are important factors to get high-quality information (2,3).

Several registries have been established worldwide, especially in Canada, United States and Europe (3). The Danish Multiple Sclerosis Registry (DMSR) registry is one of the oldest in existence. This MS database is unique because it has existed for 60 years and covers a whole country with a high rate of ascertainment. DMSR is one fine example of how these observational studies have contributed to a better understanding of MS. For example, during the last 25 years, over 40 studies have been published based on this registry (4).

In Portugal, demographic and epidemiological clinical data about Multiple Sclerosis at a regional or national level are scarce. A retrospective study was conducted in 1983 in order to estimate MS prevalence around Lisbon, based on the data of its main MS treatment centers. A prevalence of 12.9/100000 was calculated (5,6). A population-based prospective study conducted over a period of 5 years and published in 2006 revealed a prevalence of 46.3/100 000 in the district of Santarém (6,7). In 2010 a national transversal study using a survey determined a self-reported MS prevalence in

continental-Portugal, among adults of 54/100 000 and an estimated number of patients of 4287 (varying between 2700 and 5875) (8). There is no national registry for this condition and never a simultaneous and systematic of data from the whole country has been performed for this disease.

2.2 RATIONALE

The fundamental aim of this study is to gather efforts from an assembly of neurologists that follow MS patients in Portugal to constitute a study group that will produce a more complete (cross-sectional) national portrait of the population of patients with that disease in Portugal in 2014. This portrait will essentially focus on the verification of some demographic and clinical characteristics that are typical in MS (like age at diagnosis, preponderance of female gender, preponderance of certain ethnic, "race" and geographical origins (9), proportion of subtypes of MS and others) in an attempt to detect (or exclude) any deviation in the Portuguese patients compared to the other European populations. A brief characterization of the current treatment will also permit a comparison of medical standards with other countries. A collection of data about education and labor, crossed with disease stage, will permit a comparison with the general population and eventually render some types of cost of this disease more clear in this country. Hopefully this study would also stimulate other studies that would focus on some points of interest detected in this first attempt of general characterization. The month of reference for the study will be May 2014.

The actual planning of this study was born from a group of doctors that met in the context of a Pharma Industry (Biogen Idec Portugal) and GEEM (Grupo de Estudos de Esclerose Múltipla, the Portuguese national medical society for MS) – sponsored course of Multiple Sclerosis ("EMIN" 2nd edition) occurring during 2014.

In a first step of this study, the mentioned group (the "Coordinating Committee" of this study) will use knowledge and resources of that course and work with the objective of implementing the study essentially in their centers and collect preliminary data until August 2014.

Once accomplished that objective, collection of data continues in a second step aiming to recruit the maximum number of patients possible in Portugal, both by continuing recruitment in those original centers and by extending recruitment to other centers around the country.

The Coordinating Committee will invite all neurologists who follow patients with MS in Portugal to integrate the study as investigators and recruit patients and introduce their data, if approved by theirs institutions' superiors and ethics committees and consented by each patient (hospital-based study). As mentioned, only a nuclear group of centers is aimed at the first step of the study, neurologists from other centers will be invited subsequently. All neurologists that will contribute to the collection of data are investigators and authors and constitute the PORT-MS study group (please see study procedures section and authorship policy later in this protocol).

To help the Coordinating Committee analyzing data and publishing it (please see authorship policy later in this protocol), a Scientific Committee will be constituted amongst the main contributors to the PORT-MS data during 2015. This Scientific Committee will be composed by a representative of each of the 7 top recruiting centers.

Of course, sponsors of the EMIN course, as other possible subsequent sponsors of financing, will have no access to data. Once the first step of this project and the EMIN course is completed, the project will run autonomously and without any commitment linked to EMIN.

The Coordinating Committee functions are:

- Conception of the study, diffusion, helping the practical implementation of the study in all centers, permanent contact with centers
- Data assembly, data maintenance, data analysis, expectedly by working with other experts from PORT-MS study Group, and eventually with external experts (epidemiologists, statisticians and others)
- Regular reports to the scientific committee about general progress of the study seeking advice in data analysis and publishing the results. The final list of authors for publications will be set up in accordance with the scientific committee (see authorship policy)
- Seek financing and administration of finances (with reports to the scientific committee)
- Report at least annually to all study investigators and preferentially more regularly by a mailed newsletter
- Make available to every investigator a declaration stating that he/she is an investigator in the registry (eventually with the number of patients included) for him/her to use as he/she wishes.

The Scientific Committee functions are:

- Listen to the reports of the Implementing Committee and help analyze data and select the data to publish.
- agree with the coordinanting committee a final list of authors for publications

OBJECTIVES

2.1 PRIMARY OBJECTIVE

To describe basal demographic and clinical characteristics (taking May 2014 as the reference date) of the largest possible number of patients with the diagnosis of Multiple Sclerosis that are on medical follow-up by neurologists in Portugal.

2.2 SECONDARY OBJECTIVES

• To compare Portuguese data with previous national and international data.
• To analyze data of MS patients comparing them with data from the general population, as for instance in geographic patterns of place of birth and place of residency, education and labour.
• To analyze the attractiveness of the country for the implementation of future clinical trials considering the data collected.

3 STUDY DESIGN

This is an observational, cross-sectional, descriptive, multicentric, national study.

4 STUDY TIMELINES

Estimated EC Approval - first center approved by June 2014.

Recruitment is expected to occur between June 2014 and June 2015.
The Implementing/Scientific Committees may prolong recruitment for one extra year.
Data analysis will be continual, for around 3 years starting from recruitment.

5 STUDY POPULATION

All the patients with the diagnosis of Multiple Sclerosis in May 2014 that are on follow-up by a Neurologist in Portugal during the recruitment period. In each center, consecutive recruitment in the outpatient clinic will be stimulated to avoid selection bias.

5.1 INCLUSION CRITERIA

Study subjects must fulfill the following criteria:

1. Patients alive and with the diagnosis of MS in any day of May 2014 (Positive McDonald 2010 criteria for Multiple Sclerosis, including "no better explanation").
2. Informed consent.

5.2 EXCLUSION CRITERIA

Subjects will be excluded if at least one of the following criteria is met:

1. No positive McDonald 2010 criteria. This includes the exclusion of patients with an alternative clinical diagnosis more plausible than Multiple Sclerosis even if other aspects of McDonald 2010 are satisfied.
2. No informed consent.

6 STUDY PROCEDURES/INFORMATION TO BE COLLECTED

All neurologists in Portugal who follow patients with MS will be contacted (or can contact the PORT-MS study Coordinating Committee directly) to integrate the study as investigators and introduce data from their patients (hospital-based study). If a certain neurologist is willing to participate, he/she will contact his institution's (Neurology department) director and other superiors, or the Coordinating Committee will accomplish that role, to ask permission to carry the study there. The study will then be submitted to the ethics committee of each institution (as well as to the hospital administration) and wait for approval. As a principal investigator (PI) must be identified for each institution, in those places where various neurologists will be investigators, the PI will try to stimulate recruitment by reminding their colleagues or by helping collecting/gathering data from the patient, if the neurologist that recruited and follows the patient consents.

After identifying their patients and ask for informed consent, data will be collected from the patient's file and he/she could answer to some questions to complete informations that are missing, both at a single time point. The participant's contribution will then be finished and he won't be subjected to any other evaluation.

Data will be introduced in a paper CRF. The CRF will be mailed to an address to the Coordinating Committee.

Informed consent should be kept in the patients' hospital file and an entry in that file should state that the patient has been included in the PORT-MS study and eventually describe his/her number in that database (CRF code). This will permit future doctors of that patient to be sure his data has been introduced in the database.

Data can actually be collected/gathered by any other investigator of that same institution if that's the wish of the recruiting investigator and if it's easier in terms of institutional organization. For each patient there are 3 investigators involved (corresponding to different roles in the process) and listed (the same person can assume the 3 roles, though): the investigator that gathered the data and introduces it the CRF; the investigator that is actually the doctor that follows and treats that patient and recruited it; and a general responsible for the consultation of MS in that institution or the service director.

Please refer to the CRF later in this protocol to analyze data that will be collected.

Recruitment is expected to occur between June 2014 and August 2014 for the first step, until June 2015 for the second step. It may be prolonged for one year.

7 ENDPOINTS

7.1 PRIMARY ENDPOINT

Main variables include: date of birth, place of birth, sex, ethnic origin, race, date of first symptoms, place of residency at first symptoms, date of diagnosis, place of residency at diagnosis, initial type of MS, date of start of secondary progressive MS, current treatment and date of start of that treatment, EDSS, employment status, previous participation in clinical trials. Please see CRF for details.

7.2 SECONDARY ENDPOINTS

Not applicable.

7.3 DEFINITIONS OF INTEREST

Not applicable.

8 STATISTICAL ANALYSIS

Variables will be described through descriptive statistics, namely absolute (n) and relative frequencies (%) for qualitative variables and mean, median, standard deviation (SD), minimum and maximum for quantitative variables.
All patients with data at least in name initials, date of birth, sex and date of diagnosis will be considered, even if missing variables exist. Missing values will not be substituted.
SPSS (Statistical Package for the Social Sciences) software will be used.

9 PHARMACOVIGILANCE

New safety findings that can potentially affect the risk/benefit profile of a medicinal product identified during the conduct of epidemiological studies will be reported promptly to the Health Authorities, according to local pharmacovigilance regulations.

10 ETHICAL AND LEGAL ASPECTS

10.1 ETHICS

The study will be conducted according to the ethics principles originated from the Declaration of Helsinki and the applicable privacy laws.
A copy of the protocol, proposed informed consent form and other written subject information will be submitted to the local Ethics Committee for written approval. A copy of the written approval of the protocol and informed consent form must be received by the Investigator before recruitment of subjects and data collection.
The investigator will submit and, where necessary, obtain approval from the local Ethics Committee for all subsequent protocol amendments and changes to the informed consent document.

10.2 RISK/BENEFIT ASSESSMENT

This is an observational study. The sole specific procedure the patient will be subjected to is to answer the questions of the CRF questionnaire.

10.3 INFORMED CONSENT

Before any protocol specific procedures are performed, the investigator is responsible for obtaining written informed consent from the subject (or authorized representative) and after an adequate and clear explanation of the aims, methods, anticipated benefits, and potential hazards of the study.
The informed consent process should be documented in the subject's medical charts, and the informed consent form should be signed and personally dated by the subject (or authorized representative, if applicable) and by the person who conducted the informed consent discussion (not necessarily an investigator). The original signed informed consent form should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject or authorized representative.

11 DATA HANDLING

11.1 CONFIDENTIALITY

The investigator is responsible for ensuring that the subject's confidentiality is maintained.
Questionnaires, database and other documents generated in this study will be identified by a unique subject identification number only. This number will be assigned sequentially, based on subject's recruitment schedule. Each study site will also be assigned a number.
The study will be notified to the Comissão Nacional para Protecção de Dados, under the scope of "Lei de Protecção de Dados de Carácter Pessoal Dec. 67/98 de 26 de Outubro" and Deliberação da CNPD nº 227/2007.

11.2 DATA COLLECTION

All study data will be obtained from review of medical charts and subject's interview. All the information will be collected into a structured questionnaire (case report form), specifically designed for this research.

The investigator will be responsible for ensuring that all findings and data are accurately and reliably recorded in the case report form.
All corrections in the data originally recorded in the case report form or in any other study document should be performed in a way that the original record is still legible, and should be dated and signed by the investigator.

11.3 STUDY ARCHIVE

The investigator will keep and adequate archive of all study documentation with access restricted to study team. The study archive will be kept at each site for at least 15 years from the study's close out.

11.4 PUBLICATION POLICY

All documents and results generated from this clinical study are exclusive property of the PORT-MS Study Group, represented by the Coordinating and Scientific Committees. Any related publications must be previously approved in written by the Coordinating Investigator.

All investigators who contribute to the collection of data by implementing the study in their center, by recruiting their patients or by actually collecting data, will be mentioned in the CRF, are authors of publications and constitute part of the "PORT-MS study group".

To accomplish the objectives of the EMIN course of MS and the first step of this study mentioned in the Rationale section of this protocol, one or two publications with initial procedures and preliminary results can be submitted by the Implementing Committee as sole authors (expectedly by the end of 2014).

Afterwards, publications will be coordinated by the coordinating investigator and the coordinating committee with the help and review of the scientific committee. Other experts, coming from the PORT-MS study group or external, may be integrated as necessary. Work groups can be set for a particular matter or paper.

As articles and other types of works or presentations have a limited number of authors visible, a ranking of authors apply as follows: the group of investigators that directly contributes to that particular work or paper (by analyzing data, writing the article, etc.) – presumably elements from the Implementing Committee and the Scientific Committee plus experts integrated - followed by the list of investigators in the registry ordered by the number of patients included (or "used") in that particular study, until the maximum number of authors permitted. The designation "PORT-MS study group" must always be referred in any work that includes any part of data coming from this registry and, whenever possible (for instance in online appendixes of articles), a complete list of contributors should be added.

It's not an objective of this study no analyze the number of patients per hospital or per doctor and that data will not be published or known outside the Coordinating Committee of the PORT-MS study group.

12 REFERENCES

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13 APPENDICES

Appendix A

Paper CRF. Data collected by the CRF will be in Portuguese, as follows:

Este caderno de recolha de dados deve ser preenchido pelo médico retirando dados do processo do doente e questionando o doente directamente (após o devido consentimento informado).

Gere um código para este CRF do seguinte modo iniciais do doente como põe em baixo na primeira questão seguido dos algarismos da data de nascimento. Exemplo: JMF02051968. Deste modo pode colocar no processo do doente que o mesmo foi integrado no MS-PORT.

Código gerado para este CRF:_____

Iniciais dos primeiros 3 nomes do doente ☐☐☐

Instrução: Conta o nome como está no BI/cartão do cidadão do doente e não como está no processo hospitalar. Exemplo: Tânia Nunes Gonçalves será TNG. Os nomes hifenizados separam-se. Anulam-se apenas as partículas “de”/ “da”/”do”/”e”. Maria de Fátima Antunes será apenas MFA; Ribeiro-da-Cunha fica RC. Outras partículas estrangeiras ficam e quando juntas ao nome fica apenas a primeira letra: O'Neil será apenas O; D'Orey fica D; McGregor será M. Caso o doente só tivesse 2 nomes introduza “A” como inicial do 3º nome.

Comentário: O único propósito desta colheita é detectar, junto com a data de nascimento, doentes repetidos, quer porque foram introduzidos em duplicado no mesmo centro, quer porque são seguidos em 2 centros diferentes

Data de Nascimento __/__/_____ Instrução:dd/mm/aaaa	Sexo (à nascença) ☐Masculino / ☐Feminino

Este doente nasceu em Portugal (território actual, continental e insular)?

☐Sim/☐Não

Se nasceu em Portugal, Freguesia e Concelho em que nasceu.

Freguesia_____

Concelho_____

Comentário: Pretende-se detectar eventuais regiões com número de doentes assimetricamente elevado por comparação com a população de base. Vai-se depois tentar saber o código postal (aproximado) dessa freguesia para fazer um mapa de distribuição da doença. O propósito do

concelho é diferenciar entre freguesias com nomes iguais.

Nascimento fora de Portugal e períodos em que viveu fora de Portugal.

País_____ ; permaneceu desde idade (*)_____ até idade (*)_____ ; permaneceu desde data (ano)_____ até data (ano)_____

País_____ ; permaneceu desde idade (*)_____ até idade (*)_____ ; permaneceu desde data (ano)_____ até data (ano)_____

País_____ ; permaneceu desde idade (*)_____ até idade (*)_____ ; permaneceu desde data (ano)_____ até data (ano)_____

Instrução: Consideraremos o nascimento fora de Portugal sempre assinalável mesmo que tenha regressado para o país ou tenha transitado para outra região com menos de 1 ano de vida. Assim, se nasceu fora de Portugal, coloque o país onde nasceu, na idade de início escreva "nascimento" e depois até quantos dias/meses/anos de idade lá esteve. Clarifique com "dias" ou "meses" ou "anos". Para situações que não envolvam o nascimento considere apenas períodos de residência fora do país superiores a um ano. Escolha esclarecer entre uma data e outra ou entre uma idade e outra (ou ponha ambas, se puder). Assume-se que fora os que estão referidos neste quadro o doente residiu em Portugal.

Nacionalidade(s) (actuais)	Peso_____Kg
_____	Altura_____cm

Origem étnica / "raça", escolha:

☐Branca / ☐Negra / ☐Cigana / ☐Árabe (norte de África e Médio Oriente) / ☐ Sul asiática (Índia, Paquistão e países da região) / ☐ Sudeste asiática (Tailândia, Indonésia e países da região) / ☐Extremo Oriente (China, Japão países da região) / ☐Mista / ☐Outra, especifique _____

Data dos primeiros sintomas de EM

__/____

Instrução: Mm/aaaa. Detalhe o máximo que souber mas pode pôr mês-ano ou só ano. Esta informação reveste-se de alguma valorização subjectiva quando se trata de colheita anamnéstica restrospectiva. Com base no seu julgamento clínico terá que valorizar o que pensa terem sido os primeiros sintomas.

Estes primeiros sintomas, escolha uma:

☐ São apenas valorizados e referidos retrospectivamente pelo doente não tendo sido especificamente observado por um médico por causa deles (porque, por exemplo, o doente não valorizou na altura ou não teve oportunidade de recorrer a médico)

☐ Terão sido observados por um médico (e portanto terá havido registos contemporâneos em algum

lugar tenha ou não acesso a eles) mas não terão sido correctamente interpretados ou investigados e acabaram por não desencadear o diagnóstico

☐ Terão sido observados por um médico (e portanto terá havido registos contemporâneos em algum lugar tenha ou não acesso a eles) e foram em termos gerais adequadamente interpretados tendo contribuido para o diagnóstico final (nessa altura ou mais tarde)

Freguesia e Concelho de residência na altura dos primeiros sintomas

Freguesia_____

Concelho_____

Comentário: Pretende-se detectar eventuais regiões com número de doentes assimetricamente elevado por comparação com a população de base. Vai-se depois tentar saber o código postal (aproximado) dessa freguesia para fazer um mapa de distribuição da doença. O propósito do concelho é diferenciar entre freguesias com nomes iguais.

Data do diagnóstico

__/____

Instrução: Mm/aaaa. Os critérios de diagnóstico têm variado ao longo das últimas décadas, sendo hoje possível diagnosticar a doença mais cedo no seu percurso do que anteriormente. Considere os critérios de diagnóstico referentes à época em que o diagnóstico foi efectuado não sendo necessário mudar essa data baseado nos conhecimentos actuais. Se o doente tiver sido diagnosticado fora do seu hospital ou por outro clínico, poderá ter que considerar a data em que pela primeira vez um neurologista achou que o diagnóstico era EM e que estavam cumpridos os critérios da altura. Detalhe o máximo que souber mas pode pôr mês-ano ou só ano.

Freguesia e Concelho de residência na altura do diagnóstico

Freguesia_____

Concelho_____

Comentário: Pretende-se detectar eventuais regiões com número de doentes assimetricamente elevado por comparação com a população de base. Vai-se depois tentar saber o código postal (aproximado) dessa freguesia para fazer um mapa de distribuição da doença. O propósito do concelho é diferenciar entre freguesias com nomes iguais.

Tipo inicial de EM

☐SR (surto-remissão) / ☐SR (surto-remissão) mas na altura do diagnóstico já estava em SP (secundária progressiva) / ☐PP (primária progressiva) / ☐PP com surtos / ☐fase muito inicial ainda tenho duvidas no perfil de evolução do doente.

Instrução: escolha aquilo que retrospectivamente acha que é o tipo de EM inicial do doente.

Para os doentes que terão iniciado sob forma de surto-remissão: este doente já atingiu no seu entender a fase secundária progressiva?

☐Não / ☐Sim, desde __/____

Instrução: Detalhe o máximo que souber mas pode pôr mês-ano ou só ano.

Em Maio de 2014 este doente estava sob terapêutica modificadora da doença?

☐Sim:

QUAL: ☐Interferão B-1a sub-cutâneo 22ug 3 x por semana / ☐Interferão B-1a sub-cutâneo 44ug 3 x por semana / ☐Interferão B-1a intramuscular 1 x por semana / ☐Interferão B-1b sub-cutâneo em dias alternados / ☐Acetato de Glatirâmero / ☐Natalizumab / ☐Fingolimod / ☐Mitoxantrona / ☐Dimetilfumarato / ☐Teriflunomida / ☐Alemtuzumab / ☐Rituximab / ☐Ocrelizumab / ☐Azatioprina / ☐Outro ou outro esquema, especifique_____

DESDE QUANDO?

__/____

Instrução: Mm/aaaa. Detalhe o máximo que souber mas pode pôr mês-ano ou só ano. Refira-se apenas à terapêutica que estava a fazer em Janeiro de 2014 (a última que fez nesse mês, se por acaso começou a primeira ou mudou de terapêutica nesse mês)

HAVIA EFECTUADO OUTRAS TERAPÊUTICAS MODIFICADORAS DA DOENÇA PREVIAMENTE?

☐Sim / ☐Não

☐Não

Não estava sob terapêutica sobretudo por decisão do doente (independentemente da razão)?

☐Sim / ☐Não

HAVIA EFECTUADO TERAPÊUTICAS MODIFICADORAS DA DOENÇA PREVIAMENTE?

☐Sim / ☐Não

EDSS em Maio de 2014

.

Instrução: caso o doente estivesse se encontrasse num decurso de um surto em Maio 2014 ponha a EDSS após a recuperação total desse surto caso tenha acesso a ela, ou a EDSS prévia a esse surto caso não esteja disponível a EDSS após o surto.

Valor de EDSS exacto, se disponível: _____

Se não dispuser de EDSS exacto, tente colher informação para escolher uma das seguintes categorias:

☐ 0-4.0 (totalmente ambulatório, capaz de caminhar 500 m sem ajuda ou descanso)

☐ 4.5 (capaz de caminhar sem ajuda ou descanso 300m)

☐ 5.0 (capaz de caminhar sem ajuda ou descanso 200m)

☐ 5.5 (capaz de caminhar sem ajuda ou descanso 100m)

☐ 6.0 (necessita de ajuda intermitente ou constante (nesta caso apenas unilateral) (bengala, canadiana, tala) para caminhar 100m com ou sem descanso)

☐ 6.5 (necessita de ajuda constante bilateral (bengalas, canadianas, talas) para caminhar 100m com ou sem descanso)

☐ 7.0-7.5 (essencialmente confinado a cadeira de rodas)

☐ 8.0-9.5 (desde “maior parte do dia na cama” até totalmente acamado)

EDSS sub-ítem Funções Mentais em Maio de 2014

☐ 0 Normal

☐ 1 Alteração do humor

☐ 2 Dimiuição mental ligeira

☐ 3 Diminuição mental moderada

☐ 4 Diminuição mental marcada (síndroma cerebral orgânica crónica moderada)

☐ 5 Demência ou síndroma cerebral orgânica crónica grave

☐ V Desconhecido

Em Maio 2014 o doente encontrava-se no decurso de um surto?

☐Não / ☐Sim

Considera que existem interferências significativas na captura da EDSS deste doente por outras doenças ou condições que tornem este resultado pouco fidedigno para estadiar a incapacidade relacionada com a EM?

☐Sim / ☐Não

A incapacidade global permanente (física e mental, incluindo neurológica não apenas relacionada com EDSS e não neurológica – exemplos: insuficiência cardíaca severa, problemas ortopédicos marcados) deste doente:

☐ Relaciona-se essencialmente com a Esclerose Múltipla

☐ Existem outras patologias com peso semelhante ao da Esclerose Múltipla ou pelo menos bastante considerável

☐ É essencialmente relacionada com outras patologias

Este doente tentou alguma vez obter um grau de incapacidade junto da segurança social?

☐Sim / ☐Não

Se tentou, conseguiu?

☐Não / ☐Sim.

Indique o grau ou, pelo menos, se é >60%

Grau _____%, ☐>60%

Anos de escolaridade _____

Instrução: soma dos anos de estudo (tempo primordialmente dedicado aos estudos) em instituição que fornece graus académicos reconhecidos, reflectindo o nível de escolaridade referido abaixo (anos repetidos não contam)

Nível de escolaridade

☐Analfabeto / ☐Sem escolaridade mas sabe ler e escrever / ☐Frequentou a escola primária / ☐Completou 4a classe / ☐Frequentou ensino preparatório ou secundário (ou antigas escola comercial ou industrial) / ☐Completou 9º ano (antigo 5º ano dos liceu ou escola comercial ou industrial) / ☐Completou curso profissionalizante após o 9º ano / ☐Completou 12º ano (antigo 7º ano dos liceus) / ☐Completou bacharelato ou frequentou ensino superior / ☐Completou licenciatura / ☐Completou mestrado / ☐Completou doutoramento

Situação Laboral

Instrução:

Tome por referencia a última semana antes deste questionário.

Emprego é trabalho pago ou originando ganho, na semana em que estamos a considerar, podendo ser muito tansitório ou com contrato precário (implicito, explícito, oral, escito), independentemente do número de horas. Aquilo que comumente se designa por “doméstico” não constitui um emprego, assim como não o é a produção agrícola em baixa quantidade para consumo próprio - se essa pessoa não procura um emprego ou não deja um, classifica-se como população não activa, se o desejar e procurar classifica-se com activa desempregada. Trabalhos exclusivamente transitórios por determinação do indíviduo, como é exemplo trabalho em férias escolares, numa pessoa que fora isso não procura um emprego, não consideraremos emprego. Não nos interessa aqui a natureza específica do trabalho ou aspectos legais, se auferir ganhos com o seu trabalho está empregado. A única excepção é se receber subsídio de desemprego, nesse caso consideraremos desempregado.

POPULAÇÃO ACTIVA: tem um emprego ou, não tendo emprego, deseja um (está "disponível" para um emprego) e procura-o activamente. Classifica-se assim independentemente de, simultaneamente, ser reformado, estudante etc.

POPULAÇÃO NÃO ACTIVA: não tem emprego e ou não deseja um ou não o procura (ou ambos).

☐ Este doente inclui-se na população ACTIVA – está a executar algum tipo de trabalho remunerado ou que lhe origina ganhos ou, não tendo emprego, deseja um (está "disponível") e procura-o activamente.

☐Tem emprego / teve na última semana. (Pessoas apenas temporariamente fora do emprego por qualquer razão mas mantendo algum vínculo com ele são incluidas aqui.)

☐Tem (ou teve na última semana) apenas um emprego / ☐ Vários

Detalhe o estatuto do emprego (caso tenha vários, detalhe o mais relevante deles):

☐ a) Empregado (o habitual "por conta de outrém", pago a unidade de tempo, de produto produzido, podendo incluir comissões, etc.)

☐Emprego prolongado mas com vínculo fraco (exemplo: empregada doméstica com contrato oral)

☐Emprego sem termo com contrato regular (com contribuições para segurança social etc)

☐Termo fixo, curto-termo, casual, on-demand, sazonal e similares independentemente do tipo de contrato

☐ b) Empregador (Trabalhador por conta própria e tem sob contrato pelo menos uma pessoa como empregado, independentemente do tipo de contrato.)

☐ c) Trabalhador por conta própria. (A remuneração depende do lucro que se obterá com o produto e pode variar no tempo. Comissões e similares não cabem nesta definição, geralmente trata-se de trabalho por conta de outrém.)

☐ d) Membros de cooperativas

☐ e) Contribui para uma empresa familiar não sendo propriamente um "sócio" dessa empresa e geralmente não pago directamente

☐ f) Não classificável nestas categorias ou informação insuficiente

_____

Quantas horas trabalha em média por semana (ou na última semana, se trabalhos inconstantes) – inclui horas extraordinárias mesmo em casa e pagas apenas parcialmente se directamente relacionado com o emprego em questão _____h

Considera o doente que a Esclerose Múltipla actualmente interfere na capacidade de desempenho ou o número de horas de trabalho de forma "SIGNIFICATIVA"? (não só na última semana, aqui referimo-nos em termos gerais)

☐Não / ☐Sim

Se sim, é capaz de dar uma idéia do número de horas que teve que eventualemente reduzir no seu volume de trabalho semanal, em média, por comparação com um período em que não tinha a doença ou que a doença não interferia com a sua capacidade laboral? _____h

Segundo o doente, a interferência da doença deve-se sobretudo a (pode escolher várias):

☐ Alterações físicas e/ou mentais da doença ou dela decorrentes (como por exemplo depressão)

☐ Aspectos práticos como ida a consultas, levantamento da medicação, exames etc.

☐ Outros_____

☐Está desempregado (não tem um trabalho assalariado ou por conta própria + está disponível para trabalhar (deseja-o, seja por que motivo for) + procura activamente emprego).

Se possível, escolha a melhor opção:

☐ a) Desemprego Voluntário (Não econtra o emprego com as características que quer (função ou salário) e portanto não se emprega. Pode estar a receber benefícios do estado ou não. Seria possivel arranjar outro emprego noutra área mas não está interessado.)

☐ b) Desemprego Involuntário (restantes situações)

_____

Já trabalhou no passado (no sentido de “ter um emprego” segundo a definição atrás mencionada)?

☐Sim / ☐ Não

Considera o doente que a Esclerose Múltipla interefe significativamente com a sua oportunidade de encontrar emprego?

☐Sim, é a principal interferência

☐Sim, mas é apenas uma interferência entre várias outras causas

☐Não

☐Este doente inclui-se na população NÃO ACTIVA – não tem actualmente emprego e não deseja um ou não o procura. (Não pode escolher simultaneamente activa e não activa, escolha apenas uma destas opções.)

Dentro desta opção, escolha a situação mais relevante neste caso. Se existem várias situações comente as secundárias em baixo, assim como outras dúvidas:

☐Sem idade mínima para trabalhar (em Portugal pode-se trabalhar excepcionalmente e com condicionantes abaixo dos 16 anos se já tiver concluido a escolaridade obrigatória ou estiver a fazer formação para a concluir, pode-se trabalhar a partir dos 16 anos se tiver concluido a escolaridade obrigatória ou estiver a fazer formação para a concluir, é-se livre de trabalhar a partir dos 18)

☐Estudante (frequência regular de instituição educacional pública ou privada para instrução sistemática em qualuer nível educacional)

☐"Doméstico" (actividades no seu próprio domicilio para "consumo" do mesmo)

☐Pessoa com lucros de capital (investimentos, rendas,etc)

☐Reformado (tem pensão de actividade económica prévia ou tem reforma da segurança social "por idade")

☐Pessoa com pensões de invalidez/doença

☐Recebe ajudas de terceiros (ajudas de privados, de instituições públicas ou privadas, etc)

☐Outra situação / várias situações / comentários _____

_____

Gostaria de ter um emprego mas sente-se desencorajado e desistiu de procurar (hidden unenmployment)?

☐Sim / ☐Não

Se sim, pensa do doente que a Esclerose múltipla é a principal razão desta situação?

☐Sim / ☐Não

Cuidador

Por causa da Esclerose Múltipla, o doente considera que precisa de um cuidador de forma "SIGNIFICATIVA" e do qual não precisaria sem a doença?

☐Não / ☐Sim

Este doente alguma vez participou num ensaio clinico (estudo intervencional - fase III ou anterior) com um medicamento modificador da doença?

☐Sim / ☐Não

Este doente tem algum familiar directo com EM?

Instrução: Considerar apenas casos mais consistentes em que esses familares são ou terão seguidos por neurologista

☐Sim: ☐irmão/irmã ; ☐filho/filha ; ☐pai/mãe ; ☐avô/avó paterno ou materno ; ☐tio/tia em primeiro grau materno ou paterno ; ☐primo(a) direito(a) materno ou paterno; ☐outro

☐Não

Para doentes do sexo feminino

Número de gestações após o diagnóstico de EM _____

Número de partos (nados vivos) após o diagnóstico de EM _____

Médico que introduz os dados

Nome clínico_____ / OM_____

Médico que segue o doente

Nome clínico_____ / OM_____

Responsável pela consulta de EM / Director de serviço

Nome clínico_____ / OM_____

Nota: a colheita do nome dos médicos envolvidos no recrutamento deste doente é feita apenas por questões de autoria de publicações relacionadas com este estudo.

DATA DE PREENCHIMENTO DO CRF ___ / ___/_____

Appendix B –
Informed consent in Portuguese

INFORMAÇÃO AO DOENTE
E DECLARAÇÃO DE CONSENTIMENTO LIVRE E ESCLARECIDO para o Estudo PORT-MS

O seu neurologista está a convidá-lo para participar neste estudo porque tem o diagnóstico de Esclerose Múltipla.
Trata-se de um estudo observacional, durante o qual o seu médico o seguirá e tratará de acordo com a prática clínica habitual, procedendo apenas à recolha de dados sobre si. Este estudo pretende fazer um retrato demográfico e clínico básico dos doentes com Esclerose Múltipla em Portugal ao longo de 2014 e até 2016. Pretende-se integrar o maior número possível de doentes com Esclerose Múltipla em Portugal. Está prevista apenas uma colheita sumária de dados de cada doente numa única altura e depois todos os dados serão analizados em conjunto. Esses dados incluem a idade de início dos sintomas, a idade com que foi diagnosticado, a sua freguesia de nascimento, a freguesia em que reside, o tipo de doença que tem e o tratamento que está a fazer, assim como dados básicos acerca da sua escolaridade, emprego, cuidador e família. Alguns dados poderão já constar do seu processo pelo que com a sua permissão o neurologista poderá retirá-los de forma anónima. Poderá ter que responder a algumas questões para completar os dados. Os seus dados serão colhidos de forma anónima, apenas com as suas iniciais e a sua data de nascimento. Os dados serão misturados com os dados de centenas ou milhares de outros doentes.

A realização do estudo foi aprovada pela Comissão de Ética para Saúde (CES) do seu hospital. As comissões de ética são também responsáveis pela proteção dos direitos das pessoas que participam em investigação clínica.

É obrigatório participar no estudo?
A sua participação neste estudo é completamente voluntária. Cabe-lhe a si decidir se quer ou não participar. Se decidir participar, é livre de desistir em qualquer altura. Caso desista, não incorrerá em qualquer penalização e tal não afetará o seu tratamento nem os cuidados médicos a que tem direito.

Quais são os possíveis riscos e benefícios?
A sua participação neste estudo não envolve riscos, uma vez que não será alterada a prática médica habitual e apenas se procederá à recolha de dados. Não vemos nenhuma desvantagem específica para sí ao integrar este estudo fora o facto de poder ter que responder a algumas questões para completar dados que não constam do seu processo clínico. Também não há vantagens directas específicas fora o facto de contribuir para que a doença seja mais conhecida, estudada e falada em Portugal. Ao integrar os dados de todos os doentes estaremos mais perto da realidade. Se muitos doentes ficarem de fora não conheceremos a realidade tal como ela é a a doença terá uma imagem falsa na comunidade.

Não terá qualquer encargo financeiro adicional por participar neste estudo.

Não está previsto nenhum pagamento ao seu médico para integrar os seus dados nesta base de dados embora este estudo procure financiamento de várias entidades para pagar múltiplos tipos de custos e alguns médicos ou outros profissionais que vão trabalhar os dados centralmente possam ser pagos.

A participação é confidencial?
Sim, foi pedida autorização à Comissão Nacional de Proteção de Dados (CNPD) para a recolha e uso dos seus dados de saúde, garantindo a sua confidencialidade, de acordo com a Legislação Portuguesa sobre Proteção de Dados, nomeadamente a Lei nº 67/98 de 26 de Outubro e a

Deliberação 227/2007, de 28 de Maio. Assim, todos os dados recolhidos serão utilizados de forma completamente anónima, apenas identificados por um código numérico, sem fazer referência aos seus dados pessoais, permanecendo a sua identidade confidencial. Se der o seu consentimento para participar neste estudo, os seus registos médicos poderão ser analisados pelas autoridades regulamentares, Comissões de Ética para a Saúde e pelos monitores do responsável pelo tratamento dos dados, para garantir que os dados e procedimentos do estudo estão a ser efetuados de acordo com o protocolo e requisitos legais. Esta validação será realizada, sempre que possível, na presença dos investigadores do estudo, que são responsáveis pela garantia da confidencialidade dos seus dados. Os dados anonimizados não serão transmitidos para países fora da União Europeia (UE).
Ao assinar este consentimento, está a dar a sua permissão para que tal possa ocorrer. Esta informação permanecerá estritamente confidencial e nenhuma informação que o identifique será tornada pública.
Os resultados deste estudo podem vir a ser publicados em revistas médicas e apresentados em reuniões científicas. No entanto, não será identificado pelo nome em nenhuma destas publicações.

Se tiver alguma pergunta sobre o estudo, por favor contacte o seu médico:

Dr(a):_____
Telefone: _____

☐Aceito participar neste projeto e autorizo a recolha dos meus dados para um caderno de recolha de dados específico do estudo, de acordo com os pressupostos descritos atrás.

_____
Nome do Doente (em letra de imprensa)

_____ _____
Assinatura do Doente Data

Se o doente estiver mentalmente incapacitado para dar o seu consentimento:
☐Aceito participar neste projeto e autorizo a recolha dos dados para um caderno de recolha de dados específico do estudo, de acordo com os pressupostos descritos atrás.

Nome do Representante Legal (em letra de imprensa)

_____ _____
Assinatura do Representante Legal Data

Se o doente não estiver em condições para dar o seu consentimento por escrito, apenas oral (doente iletrado ou fisicamente incapacitado):
☐ Aceito participar neste projeto e autorizo a recolha dos dados para um caderno de recolha de dados específico do estudo, de acordo com os pressupostos descritos atrás.

_____
Nome da 1ª testemunha (em letra de imprensa)

_____ _____
Assinatura da 1ª testemunha Data

_____
Nome da 2ª testemunha (em letra de imprensa)

_____ _____
Assinatura da 2ª testemunha Data

Se o doente for menor de idade:
Sou eu que decido participar, ou não, neste estudo. Seja qual for a minha decisão, ninguém ficará zangado comigo. Se eu quiser sair do estudo, basta dizer aos meus pais ou ao meu médico.
☐ Concordo em participar no estudo.

_____ _____
Assinatura do doente Data

A natureza deste estudo de investigação clínica e o papel do doente foram descritos a _____(nome do doente) de forma adequada ao seu nível de desenvolvimento. Ele/ela compreende e aceita participar no estudo.

_____ _____
Assinatura dos pais/ tutor legal Data

O doente foi por mim informado sobre a natureza e objetivo deste estudo.

_____
Nome do Médico (em letra de imprensa)

_____ _____
Assinatura do Médico Data

Constitution of the PORT-MS Study Group

All the investigators that participated in this study until the present phase are listed in Table 39. Professor Armando Sena, who contributed to the review of this Master's Dissertation, is the only contributor not represented in the Table. Like the case of Professor Armando Sena, other investigators will be added as needed in the following phases of the study.

The roles of the investigators are explained in the Protocol section.

Center	Investigators
Hospita de Braga	Sara Varanda Filipa Sousa João Cerqueira
Centro Hospitalar de São João **(Hospital de São João) (Porto)**	Miguel Grilo Carlos Andrade Pedro Abreu Joana Guimarães José Reis Maria José Sá
Centro Hospitalar do Porto **(Hospital de Sto António)**	Raquel Samões Ernestina Santos Ana Martins da Silva
Centro Hospitalar Universitário de Coimbra	José Tomás Carla Cecília Nunes Sónia Baptista Carmo Macário Lívia Sousa
Hospital Beatriz Ângelo (Loures)	Paulo Alegria Rita Simões José Vale
Centro Hospitalar de Lisboa Norte **(Hospital de Sta Maria)**	João Ferreira Ruth Geraldes João Sá

Centro Hospitalar de Lisboa Central **(Hospital de Santo António dos Capuchos)**	João Sequeira Joana Morgado Carlos Capela Paula Esperança Rui Pedrosa

Table 39. Constitution of the PORT-MS study group.

Public presentations of results of the PORT-MS study

1. Alegria P, Samões R, Ferreira J, Sequeira J, Grilo M, Tomás J, Varanda S, Cerqueira J, Sousa L, Pedrosa R, da Silva AM, Sá J, Vale J, Sá MJ; PORT-MS Study-Group. A cross-sectional national study on the demography, disease characteristics and socioeconomic status of the Portuguese patients with Multiple Sclerosis - the PORT-MS study. Oral presentation. Reunião de Outono do GEEM (Grupo de Estudos de Esclerose Múltipla da Sociedade Portuguesa de Neurologia), session dedicated to the presentation of the final works developed during the EMIN 2nd edition course (a one year duration course on MS for residents in Neurology sponsored by the GEEM and Biogen Idec); 2014 December 13th; Lisbon, Portugal. Portuguese/English. Winner on the EMIN 2nd edition course.

2. Miguel Grilo, João Sequeira, José Tomás, Sara Varanda, João Ferreira, Raquel Samões, Carlos Capela, Ernestina Santos, Sónia Batista, Pedro Abreu, João Cerqueira, Lívia Sousa, Rui Pedrosa, Ana Martins da Silva, João Sá, José Vale, Maria José Sá, Paulo Alegria; PORT-MS Study-Group. Demography, clinical characteristics and socioeconomic status of the Portuguese patients with Multiple Sclerosis in 2014 – results of the national cross-sectional PORT-MS study. Poster presentation. Third International Porto Congress of Multiple Sclerosis; 2015 Feb; Porto, Portugal.

3. Sara Varanda, Raquel Samões, João Ferreira, José Tomás, Miguel Grilo, João Sequeira, Joana Morgado, Carlos Andrade, Jorge Reis, Joana Guimarães, Lívia Sousa, João Cerqueira, José Vale, Maria José Sá, João Sá, Ana Martins da Silva, Rui Pedrosa, Paulo Alegria; PORT-MS Study-Group. Trends in the treatment of Multiple Sclerosis in Portugal in 2014 – results of the national cross-sectional PORT-MS study. Third International Porto Congress of Multiple Sclerosis; 2015 Feb; Porto, Portugal. Winner of the best oral communication.

4. J. Tomás, J. Dias Ferreira, J. Sequeira, M. Grilo, R. Samoes, S. Varanda, J. Morgado, J. Guimaraes, C. Nunes, J. J. F. C. A. Cerqueira, J. M. Vale Santos, M. J. Sá, A. A. D. M. Silva, L. M. A. F. D. Sousa, R. M. G. Pedrosa, J. de Sa, P. Alegria; PORT-MS Study-Group. Demography, clinical characteristics and socioeconomic status of the Portuguese patients with Multiple Sclerosis in 2014 – results of the national cross-sectional PORT-MS study. European Academy of Neurology 2015. Accepted.

5. R. Samoes, S. Varanda, M. Grilo, J. Sequeira, J. Tomás, J. Ferreira, M. D. C. R. R. M. Macário, C. M. C. Capela, E. Santos, L. M. A. F. D. Sousa, R. M. G. Pedrosa, J. de Sa, M. J.

Sá, J. M. Vale Santos, J. J. F. C. A. Cerqueira, A. A. D. M. Silva, P. Alegria; PORT-MS Study-Group. Economic activity and employment of the Portuguese patients with Multiple Sclerosis in 2014 - results of the national cross-sectional PORT-MS study. European Academy of Neurology 2015. Accepted.

6. João Sequeira, José Tomás, Raquel Samões, João Ferreira, Sara Varanda, Miguel Grilo, Sónia Batista, Rita Simões, Paula Esperança, José Vale, Maria José Sá, João de Sá, Ana Martins da Silva, Rui Pedrosa, Lívia Sousa, João Cerqueira, Paulo Alegria; PORT-MS Study-Group. Tratamento da Esclerose Múltipla em Portugal em 2014 – resultados do estudo transversal multicêntrico PORT-MS. Forum 2015 da Sociedade Portuguesa de Neurologia. Submitted.

Prizes

Presentations of parts of these work won the following prizes:

- Best work (first prize) of the EMIN 2nd edition, a one year duration course on MS for residents in Neurology sponsored by the GEEM (Grupo de Estudos de Esclerose Múltipla of the Sociedade Portuguesa de Neurologia) and Biogen Idec. Attributed during the meeting Reunião de Outono do GEEM 2014; 2014 December 13th; Lisbon, Portugal.
- Best oral communication of the Third International Porto Congress of Multiple Sclerosis; 2015 Feb; Porto, Portugal.