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Cohort profile: prognostic factors of disability progression in multiple sclerosis in real life: the OFSEP-high definition (OFSEP-HD) prospective cohort in France

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Title: **Cohort profile: prognostic factors of disability progression in multiple sclerosis in real life: the OFSEP-high definition (OFSEP-HD) prospective cohort in France**

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Abstract: 299 words (max 300)

Purpose. To determine prognostic factors of disability in multiple sclerosis (MS), i.e. 1) identify determinants of the dynamics of disability progression; 2) study the effectiveness of disease-modifying treatments (DMTs); 3) merge determinants and DMTs for creating patient-centered prognostic tools; and 4) conduct an economic analysis.

Participants. Individuals registered in the French Observatoire Français de la Sclérose en Plaques (OFSEP) database were included in this OFSEP-HD cohort if they had a diagnosis of MS, were ≥15 years old, and had an Expanded Disability Status Scale (EDSS) score <7. The outcomes will be assessed annually: 1) time to reach irreversible EDSS scores of 4, 6 and 7; 2) relapses and disease progression; 3) MRI-based progression, patient-reported outcomes, social consequences; and 4) combined outcomes on activity and progression. Clinical and quality-of-life data, MRI results and biological (blood, serum) samples will be collected at each follow-up.

Findings to date. A cohort of 2,842 individuals, 73.4% females, mean (SD) age 42.7 (11.6) years, median disease duration 8.8 years, has been recruited from July 2018 to September 2020. The course of MS was remittent relapsing in 67.7%, secondary progressive in 11.9%. The mean annual relapse rate was 0.98. The disease modifying treatment received were highly effective therapy in 50.3% and moderately effective therapy in 30.7%.

Future plans. The participants will be followed until December 2026. Disease course up to four landmarks will be examined as predictors of disease progression: 1) diagnosis of MS; 2) relapse activity worsening and independent progression; 3) any recent disease activity; and 4) any visit with absence of disease activity in the past 5 years. The marginal effectiveness and tolerability of treatments will be assessed. Stratified algorithms will be proposed for medical decision-making. Economic evaluation of disease cost and cost-effectiveness of new DMTs will be conducted from a public payer perspective.

Keywords: multiple sclerosis, prognosis, disability, patient-reported outcome, dynamic modelling

Strengths and limitations of this study

- This cohort will be unique and large enough for comprehensive analysis integrating multiple potential determinants of MS prognosis, including socio-demographic, clinical, imaging data and treatments.

- Multimodal disability including clinical, imaging and patient-reported outcomes will be the target for prediction from specific landmarks, corresponding to strategic times in MS evolution.
- The collection of health-related quality of life will constitute a major advantage to evaluate the usefulness of prognostic tools in stratified medicine.
- Statistical analysis including specific landmarks integrated into dynamic modelling will allow for developing accurate prognostic analysis over time.
- A maximum follow-up no longer than 8 years will be a limitation to the prediction.

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Introduction

Multiple sclerosis (MS) is a chronic disease affecting the central nervous system. It is the most common cause of non-traumatic neurological disability in young adults. With a mean age of diagnosis of 32 years and a 2:1 ratio of females to males, about 2.9 million persons worldwide are affected (1) and nearly 2 in 1000 individuals in France in 2021 (2). MS leads to permanent disability for decades, with marginal effect on life expectancy (3). The burden of MS is huge for societies, estimated at about 14.6 billion euros per year in Europe in 2010. It is rapidly increasing with the approval and wide use of expensive new disease-modifying therapies (DMTs) (4), reaching an annual cost burden of 2.7 billion euros in France in 2020 (5). However, disease progression remains difficult to treat even with the most recently approved drugs.

One major unmet need for MS patients is a sufficient knowledge of the factors associated with disease progression. Also, reliable predictive tools that could be applied at the individual level and at different key moments in the disease course (landmarks) are lacking. Despite many cohort-based studies helping to identify prognostic factors and sometimes propose prognostic scores (6–8), developing a tool accurate enough to predict the many dimensions of outcomes in MS faces several challenges that have not been addressed together. Mostly issued from disease onset (i.e., inception cohorts) and from data collected during routine visits to the neurologist, tools to predict long-term prognosis are hampered by intermediate evolution events (e.g., relapses over time) that may modify the prognosis. A recent Cochrane review (9), searching for prognostic models to be used any time after diagnosis for predicting future disease course, identified 75 models that were insufficiently validated to be recommended for clinical routine use. Of note, the reports did not describe prognostication at key clinical landmarks when the neurologist needs to decide on a change in management during the disease course.

However, the gain of knowledge about many factors, particularly the progress in cerebral and spinal-cord MS lesion imaging, the standardization and/or new definitions of clinical assessments (10), the genetic background (11,12), and, above all, the recent availability of an increasing number of DMTs (8), may considerably change the prognosis of the disease and the ability to predict its evolution. The evolution also depends on demographic, socio-economic

context (education, profession), environmental (13) and behavioral (alcohol consumption (13), smoking (14) and eating (15)) factors.

The aim of the present study is to develop a tool accounting for this multiplicity of factors, the use of DMTs, and the disease events that may occur over time for predicting clinical, MRI and patient-reported outcomes (PROs) important for both clinicians and patients with MS. Such a multidimensional approach should be applicable at significant moments (landmarks) and requires the collection of many variables at inclusion and during the follow-up of a large cohort.

Few registries or cohorts used PROs, in particular health-related quality of life (QoL), as outcomes or even prognostic factors of MS progression (16–18). Measuring the perception of the disease evolution from the patient point of view using PROs is of importance in the context of personalized medicine. It can be used to identify points that could be improved in the patient's point of view not considered by standard clinical evaluation. In addition, QoL can be used as a prognostic tool in other diseases (19,20). In the scope of health-economic analysis, the national and international health authorities recommend conducting cost-utility analysis whenever QoL is a major consequence of health interventions (21,22).

To our knowledge, no cohort study of MS patients has yet proposed the prospective, multicentric, and standardized collection of such multi-source and multi-modal data to 1) describe the disease progression and identify its determinants (i.e., socio-economic and clinical characteristics, QoL, behavioral and environmental factors, MRI, DMT use and biologic samples); 2) develop patient-centered prognostic tools for the main landmarks of MS progression and to help in decision-making; 3) evaluate the effectiveness of DMTs by clinical trial emulations; and 4) assess the cost of MS disease and the cost-effectiveness of DMTs. According to the existing Observatoire Français de la Sclérose en Plaques (OFSEP) initiative (23), the main innovative feature of the OFSEP-high definition (OFSEP-HD) cohort is to propose for the first time a database for the national and international community of researchers in MS, from fundamental studies of biomarkers to projects in public health. In parallel with these objectives, relevant methodological challenges must be addressed to improve the quality of results.

Cohort description

Study design

The OFSEP-HD cohort. The OFSEP-HD cohort is nested in the OFSEP cohort. Patient enrolment started on July 10, 2018 and ended on September 11, 2020 in 28 French MS centers. Individuals were eligible if they had 1) a diagnosis of MS according to the most recent criteria at entry into the HD cohort (24), 2) were ≥ 15 years old at inclusion, 3) had an MS diagnosis after the study start or, if MS onset occurred before the study start, had at least one visit every 2 years after follow-up in an MS center with prospective OFSEP data collection; 4) had an irreversible Expanded Disability Status Scale (EDSS) score ≤ 7.0 (permanent use of a wheelchair) at inclusion in the study; and 5) signed a written consent form. The criterion 3 for MS onset date allowed for mixing incident and prevalent cases, accelerating recruitment while benefiting from quality data collected during the OFSEP cohort follow-up, extending the possibility to fund the follow-up of included patients over time and increasing the probability to observe landmarks. Non inclusion criteria were an inability to answer questionnaires and pregnancy at the time of inclusion (Figure 1).

With a sample size of 2,842 patients, a factor with a hazard ratio of 1.2 could be detected if the exposure rate was 30%, and one with a hazard ratio of 1.6 could be detected if the exposure rate was 5% (power=0.8; α risk=0.05; SD=0.5).

This protocol is registered at ClinicalTrials.gov: NCT03603457.

The OFSEP cohort. The French OFSEP cohort is a nationwide systematic longitudinal study of individuals with MS followed in MS centers with more than 70,000 patient records collected in June 2018. The first objective was to provide a unique source of information on MS epidemiology, with a particular focus on pharmaco-epidemiology of recently introduced DMTs. Since 2011, the centers have collected data with a standardized form as well as a minimal set of mandatory clinical data (23). They collect, organize, and maintain the clinical database by using the MS-specific EDMUS software (25). In 2015, the OFSEP MRI working group published recommendations on the sequences to be used for regular brain and spinal-cord MRI acquisitions of MS patients (26,27), and standardized acquisition protocols have been disseminated. Pseudonymized MRI data are transferred to a centralized imaging resource center, the Shanoir platform (http://shanoir.org). Moreover, biological samples are collected for a subsample of OFSEP patients and stored in a biobank (28).

Multi-source data collection

During the inclusion visit in OFSEP-HD, historical clinical data were collected from medical records if they were incomplete from the OFSEP database. The OFSEP-HD follow-up visits are annual, with a time window of ± 2 months around the anniversary inclusion date. In case of detection of recent disease activity (see landmarks paragraph below), a new baseline assessment at this key step of the disease (re-baseline) will be done, which will lead to restarting the annual follow-up (Figure 2). The re-baseline process is allowed only once for a patient.

Four main landmarks are considered, corresponding to four strategic times in the MS evolution: 1) the first visit when the diagnosis of MS is set; 2) the first visit when the diagnosis of progression (primary or secondary) is set; 3) any visit with recent disease activity, defined by the occurrence of a relapse and/or MRI activity detected with gadolinium enhancement in the past 3 months (or gadolinium-enhanced lesion in the 3 months after an annual visit); and 4) any visit with absence of disease activity in the past 5 years.

At the inclusion and annual OFSEP-HD follow-up visits, the following multi-source data are collected. First, the investigators oversee the collection of socio-demographic data, geographic residence, neurological episodes, EDSS, DMTs (date of onset and stopping, reasons for stopping), serious adverse events (OFSEP minimal report form), standardized brain and whenever possible spinal-cord MRI results following OFSEP recommendations for MRI acquisitions (26,27), and additional clinical evaluation with T25FW, 9-HPT (29) and CSCT (30). They also collect brain MRI results obtained in one of the labeled centers using the OFSEP acquisition protocols in a 3-month period before or after the inclusion visit and in a 2-month period before or after the follow-up visit. This time window is necessary to not undermine the routine follow-up of the patient, but special attention will be paid to organize the MRI examinations as close as possible to the visits. Biological samples (blood, serum) were collected at inclusion for constitution of a biobank (28) and to dose 1) biomarkers (NF-light, Tau, GFAP, UCHL-1) with Simoa Human Neurology 4-Plex assay and every 2 years with 2-Plex (NFL, GFAP) of Quanterix, which detects sub-picogram levels of biomarkers, a very sensitive (limit of 0.32 pg/ml) and reproducible (coefficient of variation in the 10% range) method, and 2) vitamin D with mass spectrometry, which is very sensitive and reproducible. When necessary, we will use a part of the historical OFSEP biological collection. Establishing such a biological collection will help validate new serum biomarkers of MS in the future (e.g., other neuronal or

glial markers, cholesterol, oxidative stress, cytokine profile, auto-antibodies) as well as persistent organic pollutants possibly involved in the progression of MS.

Second, patient self-reporting questionnaires will be used to assess PROs (see below).

Third, the OFSEP-HD cohort will be linked to the French Système national des données de santé (SNDS) claims database registering all data for reimbursed health prescriptions and hospital stays covered by the national health insurance system (2,31). Sick leave and disability status/pension will be obtained from the SNDS, as will use of health care (specific to and apart from MS), and geographic location with related socio-economic variables and access to care.

Outcomes

Clinical outcomes. These refer to physical disability commonly assessed with the EDSS (32) and other parameters, such as activity and progression, as defined in the 2013 Lublin clinical classification (33). Clinical evaluations will be completed with more specific measures of physical and cognitive disability:

- Relapses defined as the occurrence, recurrence, or worsening of symptoms of neurological dysfunction lasting > 24 hr and usually ending with remission, partial or complete. Symptoms occurring within 1 month are considered part of the same relapse.
- Progression defined as the steady worsening of symptoms and signs for at least 6 months, whether superimposed with relapses or not (34), including relapse activity worsening.

Disability is defined as irreversible when the assignment to a given score has been reached and persists for at least 6 months, excluding any transient worsening of disability related to relapses (35).

MRI outcomes. These data represent surrogate markers of disease activity and progression. MRI annual acquisitions will conform to OFSEP recommendations for MRI standardized acquisitions in France (26,27). Because raw acquisitions will be available (3D FLAIR, 3D T1, diffusion images), many MRI measures will be assessable, in particular:

- T2/FLAIR image lesion load and identification of new lesions compared to previous MRI acquisitions, with measurement of their volume and number.

- Brain volume and atrophy using T1 images.

Patient-reported outcomes. These include the following questionnaires:

- Health-related QoL measured with the Medical Outcomes Study 12-items Short Form (SF-12), a self-reporting questionnaire based on the generic QoL SF-36 questionnaire (36). The SF-12 was scored with item response theory weights (RAND-12 HSI) that provide physical, mental and global scores (37).
- The MusiQoL questionnaire related to specific MS characteristics (38).
- Self-perceived health states with the EQ-5D 5L. These health states are associated with utility weights that can be used in an econometric approach (39,40).
- Social consequences assessed by employment situation, sick leave occurrence and duration, unemployment, or dependency. Employment situation will be declared by MS patients at annual visits.

Combined outcomes. By considering both clinical and MRI data, combined outcomes allow for stratifying patients into active and progressive groups as defined by the last Lublin classification (33), in activity defined on clinical and/or MRI features and progression on clinical features only:

- No evidence of disease activity (NEDA) is a composite of measures related to disease activity and progression. It is derived from the post-hoc analyses of contemporary phase 3 clinical trials of, for example, natalizumab and cladribine (41–43),
- The Rio score (44) and the modified Rio score (45) combine new T2 image lesions and relapses,
- Progression independent of relapse activity (PIRA) will be also considered (10).

Potential prognostic factors

Factors with a potential prognostic value will be studied in two different sets. First, specific attention will be paid to socio-demographic and clinical determinants and biomarkers of the progression of disability. Such characteristics include age, sex, level of education, occupation, residency, initial relapse, clinical MS form (primary progressive, relapsing-remitting, and secondary progressive), past and current disease activity, DMTs and comorbidities including health behaviors (smoking, alcohol, BMI etc.). Comorbidities are assessed using the Functional Comorbidity Index (46) and the Charlson Comorbidity Index adapted for claims databases (47).

To enrich prognostic models with potential predictors of disease evolution, questionnaires will be annually proposed.

Second, high efficacy classes of DMT and switches as well as off-label prescriptions are available since disease onset. Nine DMTs are currently available for relapsing-remitting MS and secondary progressive MS with activity. These drugs include interferons, glatiramer acetate, teriflunomide, sphingosine 1-phosphate receptor modulators, fumarates, cladribine, and five types of monoclonal antibodies (8,48).

Findings to date.

A cohort of 2,842 individuals has been recruited from July 2018 to September 2020. Their characteristics are described in Table 1. They are 73.4% females, with mean (SD) age at inclusion 42.7 (11.6) years. Their mean age at onset was 31.7 (10.2) years and median disease duration was 8.8 [4.3-15.7] years. At inclusion, the mean EDSS was 2.4 (1.9) and the course of MS was a unique episode in 14.4%, remittent relapsing in 67.7%, secondary progressive in 11.9% and primary progressive in 6.0%. The mean annual relapse rate was 0.98 [0.80-1.19]. The disease modifying treatment received were highly effective therapy in 50.3%, moderately effective therapy in 30.7%, while 6.4% were naïve of DMT, and 12.5% had no current treatment. Landmarks at inclusion was documented by a MS diagnosis for less than 6 months in 4.4%, MS progression in the past 12 months in 1.2%, relapse or MRI activity in the past 3 months in 25,5% (with 369 missing values) and remission (NEDA 3) in the past 5 years in 10.7% (with 34 missing values).

Future plans

The study participants will be followed until December 8, 2026.

Statistical analysis strategy. Several prognostic models will be developed and validated. The model development will be based on a training cohort consisting of a random selection of two thirds of the centers. The above list of prognostic factors (i.e., first, socio-demographic, clinical, imaging, biological variables and comorbidities and second, treatments and the four landmarks) will be considered as three blocks. The prognostic factors will be considered to achieve dynamic predictions (49) of the following times to events: reaching irreversible EDSS scores of 4, 6 and 7; first relapse; disease progression; MRI outcomes; PROs (QoL), social consequences, and combined outcomes of clinical and MRI data reflecting activity and disease progression.

To consider the longitudinal predictors up to the landmark time, we will adapt the methodology proposed by Devaux et al. (50).

According to data from the remaining one third of centers in the validation cohort, we will use several metrics to appraise the predictive capacities of the models.

In a stratified medicine perspective, we aim to develop stratified algorithms for medical decision-making for maximizing the number of years without disease progression and with the best QoL, this last dimension depending on both the disease activity and the treatment adverse events. The knowledge gained will allow for a clear picture of the history of MS in the 2010-2020s and the various determinants of outcomes. This landmark approach will identify some prognostic factors that play a permanent role and others to be considered at some stages of the disease course for more appropriate decision-making for care, regardless of treatment. We will study the potential of the new classification of disease activity and progression to modify the prognostic classification of cases initially developed using the classical progressive-relapse-secondary progressive classification.

Economic analysis plan. Two types of economic analysis will be conducted: 1) a cost-of-illness analysis for identifying the current cost burden to society, together with the identification of the main cost drivers, and 2) a cost-effectiveness analysis for exploring the efficiency of recent DMT treatments, namely biotherapies, compared to standard treatments. The effectiveness of new treatments for previously defined outcomes will be assessed after controlling for the prognostic information determined above.

Collaboration. Scientific collaboration based on data sharing with other teams in the scientific community will be open and encouraged, in line with the funding body policy. Any scientific project will be examined by the OFSEP scientific committee, also in consideration of technical feasibility and full respect of general data protection rules.

Patient and public involvement. Patient associations are already involved in different ways in the OFSEP project. To include patient representatives more formally in the governance of OFSEP, one patient representative from UNISEP, the national federation of MS patient associations, has joined the Steering Committee, with a voting right. Patients were not involved in the OFSEP-HD study research question or design.

Ethics and dissemination

In accordance with French laws, ethical approval was obtained by a national institutional review board (ethical approval received on June 15, 2018 (no. CPP18-036a/2018-A00882-53). Dissemination of the OFSEP purpose and objectives and dissemination of results will involve different directions and publics.

- The international scientific community through papers in peer-reviewed journals and abstracts in conferences.
- The French neurological community and participants of the OFSEP cohort.
- Patients and the public: this will be a good opportunity to give concrete examples of the impact of research, with direct impact on the management of patients. The involvement of a patient representative will allow for a better understanding of patient expectations and needs.

Data availability statement. Data will be available upon reasonable request to the scientific committee. Its availability will follow the rules previously established for the OFSEP project in general, meeting the ANR (funding body) requirements of wide access to the international research community.

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Competing interests:

- AH has nothing to disclose.
- CR has nothing to disclose.
- EJ has nothing to disclose.
- FY has nothing to disclose.
- GF has nothing to disclose.
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Figure legends:

Figure 1. OFSEP-HD cohort recruitment flow diagram

Figure 2: Design of the OFSEP-HD cohort

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Table 1. Characteristics of the MS subjects at inclusion in the OFSEP-HD cohort (n=2842)*

			Number	%
	Socio-demographic			
Age at inclusion (years)				
	mean (SD)		42.7 (11.6)	
median (Q1-Q3)			42.0 [34.0-51.0]	
Sex	male		757	*26.6*
	Female		2085	*73.4*
Level of education		university > 3yrs	529	*19.6*
		university ≤ 3yrs	843	*31.3*
		college	1324	*49.1*
		missing	*146*	
Occupation	employed		1731	63.6
	sick leave		443	16.4
	retired		175	6.4
	student		109	4.0
	unemployed		261	9.6
	missing		*123*	
	Lifestyle			
Tobacco	never smoker		1025	38.4
	former smoker		857	32.2
	current smoker		781	29.4
	missing		*179*	
Alcohol	≥ once a week		972	35.3
	2-3 times a month		548	19.9
	≤ once a month		577	20.9
	non consumer		249	11.3
	never over lifetime		339	12.3
	missing		*157*	
	Clinical			
Age at disease onset (years)				
mean (SD)			31.7 (10.2)	
median (Q1-Q3)			30.4 [24.3-38.3]	
Age at diagnosis (years)				

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mean (SD)		35.0 (10.7)	
median (Q1-Q3)		34.1 |27.0-42.1]	
MS phenotype	unique episode	409	14.4
	remittent relapsing	1925	67.7
	secundary progressive	337	11.9
	primary progressive	171	6.0
EDSS (0-10)			
mean (SD)		2.4 (1.9)	
median (Q1-Q3)		2.0 [1.0-4.0]	
Annual relapse rate in the past 2 years [CI 95]		0.98 [0.80-1.19]	
Comorbidity	number**		
mean (SD)		0.46 (1.07)	
median (Q1-Q3)		0.0 (0-1)	
	Groll index	1.82 (1.23)	
	Charlson index	0.46 (0.85)	
BMI (kg/m²)			
mean (SD)		24.6 (5.1)	
median (Q1-Q3)		23.5 [21.0-27.1]	
Disease activity			
Episode in the past 3 months		191	6.7
Episode in the past 12 months		558	19.6
MRI activity in the past 3 months		561	19.7
	missing	*369*	
MRI activity in the past 12 months		951	33.5
	missing	*203*	
Remission (NEDA 3) in the past 12 months		850	29.9
	missing	*399*	
Landmarks at inclusion			
MS diagnosis for less than 6 months		124	4.4
MS progression in the past 12 months		38	1.3
Relapse or MRI activity in the past 3 months		631	25.4
	missing	*360*	
Remission (NEDA 3) in the past 5 years		305	10.7
	missing	*34*	

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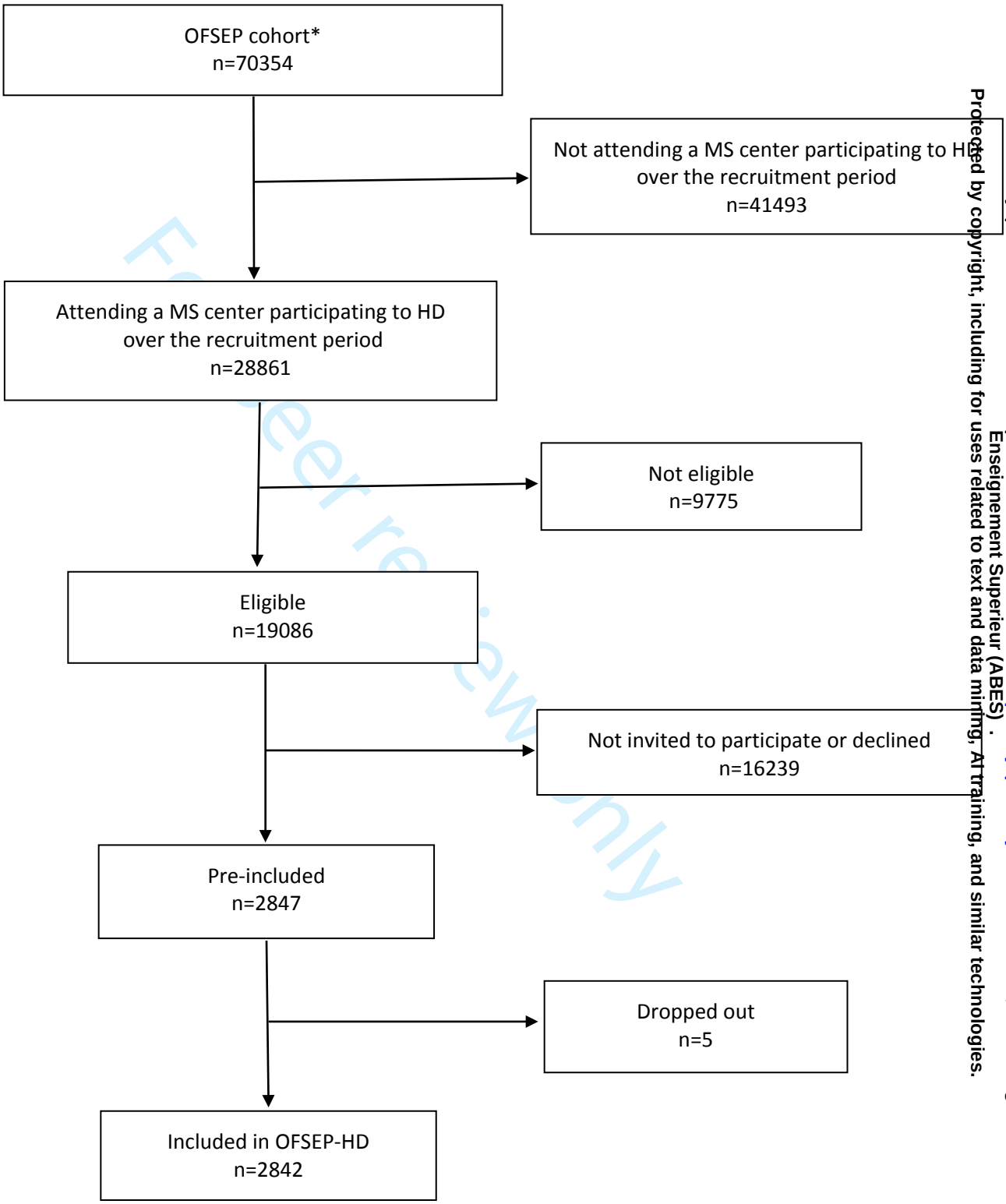
	MS past monitoring		
Brain MRI density (nbr per year) [CI 95]		0.54 [0.41-0.70]	
Medullar MRI density (nbr per year) [CI 95]		0.23 [0.15-0.34]	
	Disease modifying treatment		
Naive		182	6.4
No treatment		355	12.5
Highly effective therapy		1429	50.3
Moderately effective therapy		872	30.7
Off label therapy or clinical trial		4	0.1
Quality of life			
SF12***	physical component (0-100)	59.7 (27.0)	
	missing		*242*
	mental component (0-100)	54.9 (31.4)	
	missing		*242*
	Global score (0-100)	53.6 (22.5)	
	missing		*242*
MusiQol index (0-100)		70.5 (16.1)	
	missing		*354*
EQ-5D-5L (0-1)		0.867 (0.169)	
	missing		*191*

* missing values are indicated where applicable; **reported by the neurologist;

Figure 1. OFSEP-HD cohort recruitment flow diagram



*at the end of the recruitment period

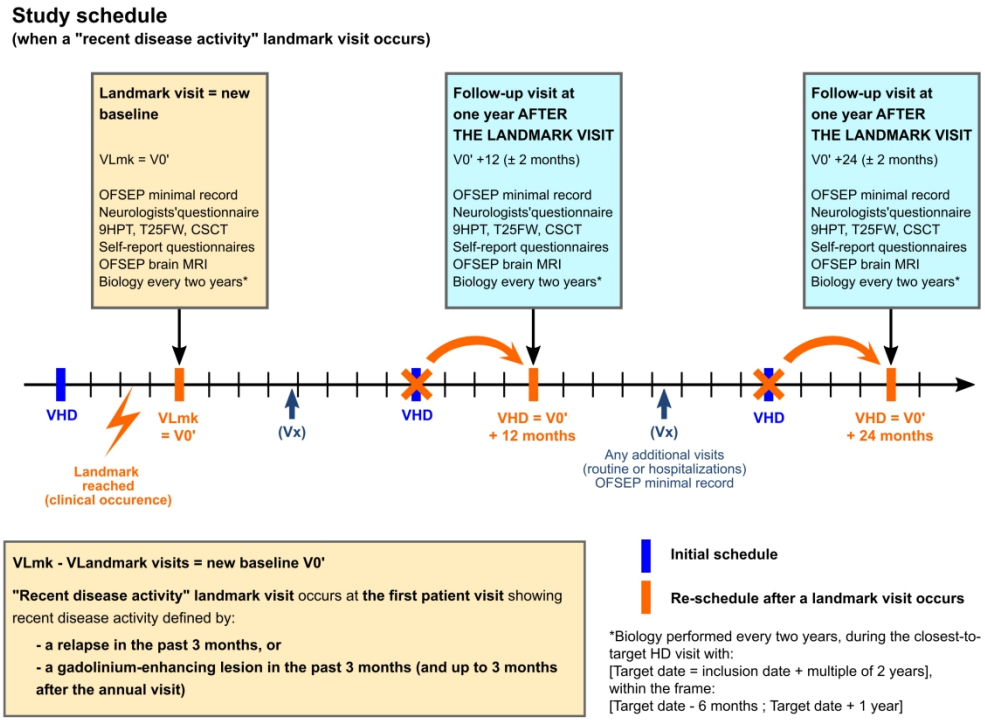


Figure 2: Design of the OFSEP-HD cohort

681x499mm (118 x 118 DPI)

BMJ Open

Cohort profile: prognostic factors of disability progression in multiple sclerosis in real life: the OFSEP-high definition (OFSEP-HD) prospective cohort in France

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Version R1.4 – february 2025

Title: **Cohort profile: prognostic factors of disability progression in multiple sclerosis in real life: the OFSEP-high definition (OFSEP-HD) prospective cohort in France**

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Abstract: 299 words (max 300)

Purpose. To determine prognostic factors of disability in multiple sclerosis (MS), i.e. 1) identify determinants of the dynamics of disability progression; 2) study the effectiveness of disease-modifying treatments (DMTs); 3) merge determinants and DMTs for creating patient-centered prognostic tools; and 4) conduct an economic analysis.

Participants. Individuals registered in the French Observatoire Français de la Sclérose en Plaques (OFSEP) database were included in this OFSEP-HD cohort if they had a diagnosis of MS, were ≥15 years old, and had an Expanded Disability Status Scale (EDSS) score <7. The outcomes will be assessed annually: 1) time to reach irreversible EDSS scores of 4, 6 and 7; 2) relapses and disease progression; 3) MRI-based progression, patient-reported outcomes, social consequences; and 4) combined outcomes on activity and progression. Clinical and quality-of-life data, MRI results and biological (blood, serum) samples will be collected at each follow-up.

Findings to date. A cohort of 2,842 individuals, 73.4% females, mean (SD) age 42.7 (11.6) years, median disease duration 8.8 years, has been recruited from July 2018 to September 2020. The course of MS was relapsing remitting in 67.7%, secondary progressive in 11.9%. The mean annual relapse rate was 0.98. The disease modifying treatment received were highly effective therapy in 50.3% and moderately effective therapy in 30.7%.

Future plans. The participants will be followed until December 2026. Disease course up to four landmarks will be examined as predictors of disease progression: 1) diagnosis of MS; 2) relapse activity worsening and independent progression; 3) any recent disease activity; and 4) any visit with absence of disease activity in the past 5 years. The marginal effectiveness and tolerability of treatments will be assessed. Stratified algorithms will be proposed for medical decision-making. Economic evaluation of disease cost and cost-effectiveness of new DMTs will be conducted from a public payer perspective.

Keywords: multiple sclerosis, prognosis, disability, patient-reported outcome, dynamic modelling

Strengths and limitations of this study

- This cohort will be unique and large enough for comprehensive analysis integrating multiple potential determinants of MS prognosis, including socio-demographic, clinical, imaging data and treatments.

- Multimodal disability including clinical, imaging and patient-reported outcomes will be the target for prediction from specific landmarks, corresponding to strategic times in MS evolution.
- The collection of health-related quality of life will constitute a major advantage to evaluate the usefulness of prognostic tools in stratified medicine.
- Statistical analysis including specific landmarks integrated into dynamic modelling will allow for developing accurate prognostic analysis over time.
- A maximum follow-up no longer than 8 years will be a limitation to the prediction.

Version R1.4 – february 2025

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Introduction

Multiple sclerosis (MS) is a chronic disease affecting the central nervous system. It is the most common cause of non-traumatic neurological disability in young adults. With a mean age of diagnosis of 32 years and a 2:1 ratio of females to males, about 2.9 million persons worldwide are affected [1] and nearly 2 in 1000 individuals in France in 2021 [2]. MS leads to permanent disability for decades, with marginal effect on life expectancy [3]. The burden of MS is huge for societies, estimated at about 14.6 billion euros per year in Europe in 2010. It is rapidly increasing with the approval and wide use of expensive new disease-modifying therapies (DMTs) [4], reaching an annual cost burden of 2.7 billion euros in France in 2020 [5]. However, disease progression remains difficult to treat even with the most recently approved drugs.

One major unmet need for MS patients is a sufficient knowledge of the factors associated with disease progression. Also, reliable predictive tools that could be applied at the individual level and at different key moments in the disease course (landmarks) are lacking. Despite many cohort-based studies helping to identify prognostic factors and sometimes propose prognostic scores [6–8], developing a tool accurate enough to predict the many dimensions of outcomes in MS faces several challenges that have not been addressed together. Mostly issued from disease onset (i.e., inception cohorts) and from data collected during routine visits to the neurologist, tools to predict long-term prognosis are hampered by intermediate evolution events (e.g., relapses over time) that may modify the prognosis. A recent Cochrane review [9], searching for prognostic models to be used any time after diagnosis for predicting future disease course, identified 75 models that were insufficiently validated to be recommended for clinical routine use. Of note, the reports did not describe prognostication at key clinical landmarks when the neurologist needs to decide on a change in management during the disease course.

However, the gain of knowledge about many factors, particularly the progress in cerebral and spinal-cord MS lesion imaging, the standardization and/or new definitions of clinical assessments [10], the genetic background [11,12], and, above all, the recent availability of an increasing number of DMTs [8], may considerably change the prognosis of the disease and the ability to predict its evolution. The evolution also depends on demographic, socio-economic

context (education, profession), environmental [13] and behavioral (alcohol consumption [13], smoking [14] and eating [15]) factors.

The aim of the present study is to develop a tool accounting for this multiplicity of factors, the use of DMTs, and the disease events that may occur over time for predicting clinical, MRI and patient-reported outcomes (PROs) important for both clinicians and patients with MS. Such a multidimensional approach should be applicable at significant moments (landmarks) and requires the collection of many variables at inclusion and during the follow-up of a large cohort.

Few registries or cohorts used PROs, in particular health-related quality of life (QoL), as outcomes or even prognostic factors of MS progression [16–18]. Measuring the perception of the disease evolution from the patient point of view using PROs is of importance in the context of personalized medicine. It can be used to identify points that could be improved in the patient's point of view not considered by standard clinical evaluation. In addition, QoL can be used as a prognostic tool in other diseases [19,20]. In the scope of health-economic analysis, the national and international health authorities recommend conducting cost-utility analysis whenever QoL is a major consequence of health interventions [21,22].

To our knowledge, with the exception of the MS PATHS initiative [17], a cohort similar to Observatoire Français de la Sclérose en Plaques (OFSEP), though not organized with as accurate and structured measurement times as in OFSEP-high definition (OFSEP-HD), no other cohort study of MS patients has yet proposed the prospective, multicentric, and standardized collection of such multi-source and multi-modal data to 1) describe the disease progression and identify its determinants (i.e., socio-economic and clinical characteristics, QoL, behavioral and environmental factors, MRI, DMT use and biologic samples); 2) develop patient-centered prognostic tools for the main landmarks of MS progression and to help in decision-making; 3) evaluate the effectiveness of DMTs by clinical trial emulations; and 4) assess the cost of MS disease and the cost-effectiveness of DMTs. According to the existing OFSEP initiative [23], the main innovative feature of the OFSEP-HD cohort is to propose for the first time a database for the national and international community of researchers in MS, from fundamental studies of biomarkers to projects in public health. In parallel with these objectives, relevant methodological challenges must be addressed to improve the quality of results.

Cohort description

Study design

The OFSEP-HD cohort. The OFSEP-HD cohort is nested in the OFSEP cohort. Patient enrolment started on July 10, 2018 and ended on September 11, 2020 in 25 French MS centers. Individuals were eligible if they had 1) a diagnosis of MS according to the most recent criteria at entry into the HD cohort [24], 2) were ≥ 15 years old at inclusion, 3) had an MS diagnosis after the study start or, if MS onset occurred before the study start, had at least one visit every 2 years after follow-up in an MS center with prospective OFSEP data collection; 4) had an irreversible Expanded Disability Status Scale (EDSS) score ≤ 7.0 (permanent use of a wheelchair) at inclusion in the study; and 5) signed a written consent form. The criterion 3 for MS onset date allowed for mixing incident and prevalent cases, accelerating recruitment while benefiting from quality data collected during the OFSEP cohort follow-up, extending the possibility to fund the follow-up of included patients over time and increasing the probability to observe landmarks. Non inclusion criteria were an inability to answer questionnaires and pregnancy at the time of inclusion (Figure 1).

With a sample size of 2,842 patients, a factor with a hazard ratio of 1.2 could be detected if the event rate was 30%, and one with a hazard ratio of 1.6 could be detected if the event rate was 5% (power=0.8; α risk=0.05; SD=0.5)[25]. We acknowledge that our power calculation does not account for multiple testing, as do other cohorts with many exploratory objectives.

This protocol is registered at ClinicalTrials.gov: NCT03603457.

The OFSEP cohort. The French OFSEP cohort is a nationwide systematic longitudinal study of individuals with MS followed in MS centers with more than 70,000 patient records collected in June 2018. The first objective was to provide a unique source of information on MS epidemiology, with a particular focus on pharmaco-epidemiology of recently introduced DMTs. Since 2011, the centers have collected data with a standardized form as well as a minimal set of mandatory clinical data [23]. They collect, organize, and maintain the clinical database by using the MS-specific EDMUS software [26]. In 2015, the OFSEP MRI working group published recommendations on the sequences to be used for regular brain and spinal-cord MRI acquisitions of MS patients [27,28], and standardized acquisition protocols have been disseminated. Pseudonymized MRI data are transferred to a centralized imaging resource

center, the Shanoir platform (http://shanoir.org). Moreover, biological samples are collected for a subsample of OFSEP patients and stored in a biobank [29].

Multi-source data collection

During the inclusion visit in OFSEP-HD, historical clinical data were collected from medical records if they were incomplete from the OFSEP database, including oligoclonal bands and IgG index from cerebrospinal fluid at diagnosis. The OFSEP-HD follow-up visits are annual, with a time window of ± 2 months around the anniversary inclusion date. In case of detection of recent disease activity (see landmarks paragraph below), a new baseline assessment at this key step of the disease (re-baseline) will be done, which will lead to restarting the annual follow-up (Figure 2). The re-baseline process is allowed only once for a patient.

Four main landmarks are considered, corresponding to four strategic times in the MS evolution: 1) the first visit when the diagnosis of MS is set; 2) the first visit when the diagnosis of progression (primary or secondary) is set; 3) any visit with recent disease activity, defined by the occurrence of a relapse and/or MRI activity detected with gadolinium enhancement in the past 3 months (or gadolinium-enhanced lesion in the 3 months after an annual visit); and 4) any visit with absence of disease activity in the past 5 years.

At the inclusion and annual OFSEP-HD follow-up visits, the following multi-source data are collected. First, the investigators oversee the collection of socio-demographic data, geographic residence, geographic area of origin, neurological episodes, EDSS, DMTs (date of onset and stopping, reasons for stopping), serious adverse events (OFSEP minimal report form), standardized brain and whenever possible spinal-cord MRI results following OFSEP recommendations for MRI acquisitions [27,28], and additional clinical evaluation with Time 25-Foot Walk, 9-Hole Peg Test [30] and Computerized Speed Cognitive Test [31]. They also collect brain MRI results obtained in one of the labeled centers using the OFSEP acquisition protocols in a 3-month period before or after the inclusion visit and in a 2-month period before or after the follow-up visit. This time window is necessary to not undermine the routine follow-up of the patient, but special attention will be paid to organize the MRI examinations as close as possible to the visits. Biological samples (blood, serum) were collected at inclusion for constitution of a biobank [29] and to dose 1) biomarkers (neurofilament light chain (NFL), Tau, Glial fibrillary acidic protein (GFAP), ubiquitin C terminal hydrolase L1) with Simoa Human Neurology 4-Plex assay and every 2 years with 2-Plex (NFL, GFAP) of Quanterix, which

detects sub-picogram levels of biomarkers, a very sensitive (limit of 0.32 pg/ml) and reproducible (coefficient of variation in the 10% range) method, 2) vitamin D with mass spectrometry, which is very sensitive and reproducible, and 3) genetic ancestry. When necessary, we will use a part of the historical OFSEP biological collection. Establishing such a biological collection will allow to assess other markers (e.g. EBV status) and help validate new serum biomarkers of MS in the future (e.g., other neuronal or glial markers, cholesterol, oxidative stress, cytokine profile, auto-antibodies) as well as persistent organic pollutants possibly involved in the progression of MS.

Second, patient self-reporting questionnaires will be used to assess PROs (see below).

Third, the OFSEP-HD cohort will be linked to the French Système national des données de santé (SNDS) claims database registering all data for reimbursed health prescriptions and hospital stays covered by the national health insurance system [2,32]. Sick leave and disability status/pension will be obtained from the SNDS, as will use of health care (specific to and apart from MS), and geographic location with related socio-economic variables and access to care.

Outcomes

Clinical outcomes. These refer to physical disability commonly assessed with the EDSS [33] and other parameters, such as activity and progression, as defined in the 2013 Lublin clinical classification [34]. Clinical evaluations will be completed with more specific measures of physical and cognitive disability:

- Relapses defined as the occurrence, recurrence, or worsening of symptoms of neurological dysfunction lasting > 24 hr and usually ending with remission, partial or complete. Symptoms occurring within 1 month are considered part of the same relapse.
- Progression defined as the steady worsening of neurological symptoms and signs for at least 6 months, whether superimposed with relapses or not [35], including relapse activity worsening.

Disability is defined as irreversible when the assignment to a given score has been reached and persists for at least 6 months, excluding any transient worsening of disability related to relapses [36].

MRI outcomes. These data represent surrogate markers of disease activity and progression. MRI annual acquisitions will conform to OFSEP recommendations for MRI standardized acquisitions in France [27,28]. Because raw acquisitions will be available (3D FLAIR, 3D T1, diffusion images), many MRI measures will be assessable, in particular:

- T2/FLAIR image lesion load and identification of new lesions compared to previous MRI acquisitions, with measurement of their volume and number.
- Brain volume and atrophy using T1 images.

Patient-reported outcomes. These include the following questionnaires:

- Health-related QoL measured with the Medical Outcomes Study 12-items Short Form (SF-12), a self-reporting questionnaire based on the generic QoL SF-36 questionnaire [37]. The SF-12 was scored with item response theory weights (RAND-12 HSI) that provide physical, mental and global scores [38].
- The MusiQoL questionnaire related to specific MS characteristics [39].
- Self-perceived health states with the EQ-5D 5L. These health states are associated with utility weights that can be used in an econometric approach [40,41].
- Social consequences assessed by employment situation, sick leave occurrence and duration, unemployment, or dependency. Employment situation will be declared by MS patients at annual visits.

Combined outcomes. By considering both clinical and MRI data, combined outcomes allow for stratifying patients into active and progressive groups as defined by the last Lublin classification [34], in activity defined on clinical and/or MRI features and progression on clinical features only:

- No evidence of disease activity (NEDA) is a composite of measures related to disease activity and progression. It is derived from the post-hoc analyses of contemporary phase 3 clinical trials of, for example, natalizumab and cladribine [42–44],
- The Rio score [45] and the modified Rio score [46] combine new T2 image lesions and relapses,
- Progression independent of relapse activity (PIRA) will be also considered [10].

Potential prognostic factors

Factors with a potential prognostic value will be studied in two different sets. First, specific attention will be paid to socio-demographic and clinical determinants and biomarkers of the progression of disability. Such characteristics include age, sex, level of education, occupation, residency, initial relapse, clinical MS form (primary progressive, relapsing-remitting, and secondary progressive), past and current disease activity, DMTs and comorbidities including health behaviors (smoking, alcohol, body mass index (BMI), etc.). Comorbidities are assessed using the Functional Comorbidity Index [47] and the Charlson Comorbidity Index adapted for claims databases [48]. To enrich prognostic models with potential predictors of disease evolution, questionnaires will be annually proposed.

Second, high efficacy classes of DMT and switches as well as off-label prescriptions are available since disease onset. Nine DMTs are currently available for relapsing-remitting MS and secondary progressive MS with activity. These drugs include interferons, glatiramer acetate, teriflunomide, sphingosine 1-phosphate receptor modulators, fumarates, cladribine, and five types of monoclonal antibodies [8,49].

Findings to date.

A cohort of 2,842 individuals has been recruited from July 2018 to September 2020. Their characteristics are described in Table S1. They are 73.4% females, with mean (SD) age at inclusion 42.7 (11.6) years. Their mean age at onset was 31.7 (10.2) years and median disease duration was 8.8 [4.3-15.7] years. At inclusion, the mean EDSS was 2.4 (1.9) and the course of MS was a unique episode in 14.4%, relapsing remitting in 67.7%, secondary progressive in 11.9% and primary progressive in 6.0%. The mean annual relapse rate was 0.98 [0.80-1.19]. The disease modifying treatment received were highly effective therapy in 50.3%, moderately effective therapy in 30.7%, while 6.4% were naive of DMT, and 12.5% had no current treatment. Landmarks at inclusion was documented by a MS diagnosis for less than 6 months in 4.4%, MS progression in the past 12 months in 1.2%, relapse or MRI activity in the past 3 months in 25,5% (with 369 missing values) and remission (NEDA 3) in the past 5 years in 10.7% (with 34 missing values).

We compared the characteristics of 2847 included and 16239 non included individuals among 19806 eligible MS individuals, according to inclusion criteria, attending the 25 centers over the period. The data are presented in supplementary Table S2, and show that among eligible MS individuals, those included have less MRI activity in the past 3 months, a MS diagnosis for

more than 6 months, a moderate EDSS, and receive more highly effective therapy, with a significant heterogeneity of recruitment across MS centers.

A comparison of their characteristics at inclusion showed that individuals with missing data on clinical outcomes (22.4%), PROs (13.5%), and landmarks (19.2%), were older, with MS onset or MS diagnosed at older age, had slightly lower education, more progressive phenotype, higher EDSS score, and received less active treatment than those without missing data (Tables S3-S5).

Future plans

The study participants will be followed until December 8, 2026.

Statistical analysis strategy. Several prognostic models will be developed and validated. The model development will be based on a training cohort consisting of a random selection of two thirds of the centers. The above list of prognostic factors (i.e., first, socio-demographic, clinical, imaging, biological variables and comorbidities and second, treatments and the four landmarks) will be considered as three blocks. The prognostic factors will be considered to achieve dynamic predictions [50] of the following times to events: reaching irreversible EDSS scores of 4, 6 and 7; first relapse; disease progression; MRI outcomes; PROs (QoL), social consequences, and combined outcomes of clinical and MRI data reflecting activity and disease progression.

To consider the longitudinal predictors up to the landmark time, we will adapt the methodology proposed by Devaux et al. [51].

According to data from the remaining one third of centers in the external validation cohort, we will use several metrics to appraise the predictive capacities of the models. We will randomize centers and not individuals for learning and validation, because the latter strategy would have been considered as internal validation, questioning the generalization of the results [52].

In a stratified medicine perspective, we aim to develop stratified algorithms for medical decision-making for maximizing the number of years without disease progression and with the best QoL, this last dimension depending on both the disease activity and the treatment adverse events. The knowledge gained will allow for a clear picture of the history of MS in the 2010-2020s and the various determinants of outcomes. This landmark approach will identify some prognostic factors that play a permanent role and others to be considered at some stages of the disease course for more appropriate decision-making for care, regardless of treatment. We will study the potential of the new classification of disease activity and progression to modify the prognostic classification of cases initially developed using the classical progressive-relapse-secondary progressive classification.

Economic analysis plan. Two types of economic analysis will be conducted: 1) a cost-of-illness analysis for identifying the current cost burden to society, together with the identification of the main cost drivers, and 2) a cost-effectiveness analysis for exploring the efficiency of recent DMT treatments, namely biotherapies, compared to standard treatments. The effectiveness of new treatments for previously defined outcomes will be assessed after controlling for the prognostic information determined above.

We expect the findings of this research from the OFSEP-HD cohort to have an impact on MS diagnosed adult, with limited disability progression and preserved ambulatory ability, whatever the disease duration, potentially eligible to DMT, and followed in a French expert center, so representing a large proportion of French MS ambulatory people.

Collaboration. Scientific collaboration based on data sharing with other teams in the scientific community will be open and encouraged, in line with the funding body policy. Any scientific project will be examined by the OFSEP scientific committee, also in consideration of technical feasibility and full respect of general data protection rules.

Patient and public involvement. Patient associations are already involved in different ways in the OFSEP project. To include patient representatives more formally in the governance of OFSEP, one patient representative from UNISEP, the national federation of MS patient associations, has joined the Steering Committee, with a voting right. Patients were not involved in the OFSEP-HD study research question or design.

Ethics and dissemination

In accordance with French laws, ethical approval was obtained by a national institutional review board (ethical approval received on June 15, 2018 from the Comité de Protection des Personnes Sud-Ouest et Outre-Mer IV (no. CPP18-036a/2018-A00882-53)). Dissemination of the OFSEP purpose and objectives and dissemination of results will involve different directions and publics.

- The international scientific community through papers in peer-reviewed journals and abstracts in conferences.
- The French neurological community and participants of the OFSEP cohort.
- Patients and the public: this will be a good opportunity to give concrete examples of the impact of research, with direct impact on the management of patients. The involvement

of a patient representative will allow for a better understanding of patient expectations and needs.

Data availability statement. Data will be available upon reasonable request to the scientific committee. Its availability will follow the rules previously established for the OFSEP project in general, meeting the ANR (funding body) requirements of wide access to the international research community.

Version R1.4 – february 2025

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Francis Guillemin (GF) is the guarantor.

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Competing interests:

- AH has nothing to disclose.
- CR has nothing to disclose.
- EJ has nothing to disclose.
- FY has nothing to disclose.
- GF has nothing to disclose.
- LD has received consulting and lecturing fees, travel grants and unconditional research support from Alexion, Biogen, Egle, Janssen, Merck, MSD, Novartis, Roche, and Sanofi.
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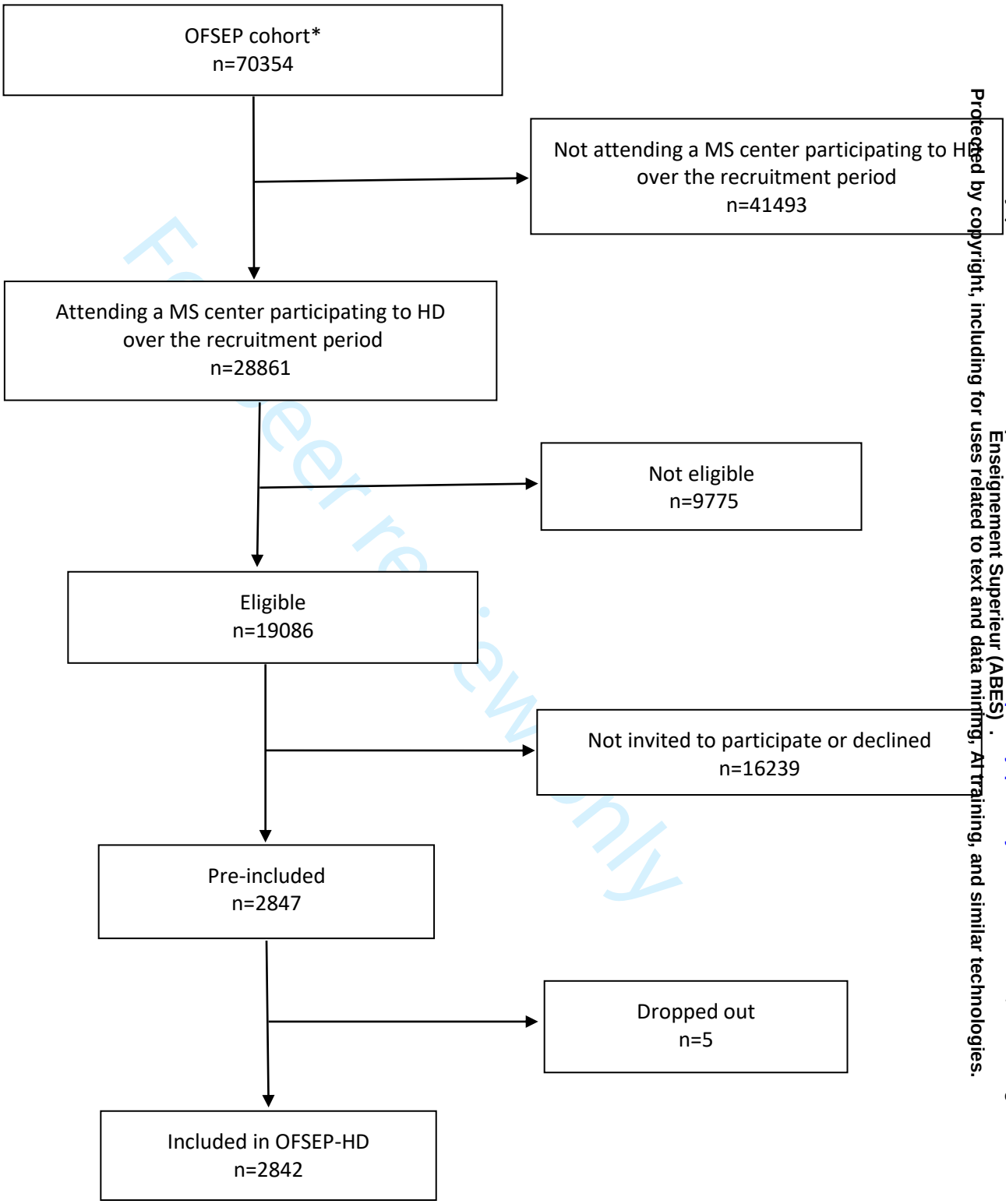
Figure legends:

Figure 1. OFSEP-HD cohort recruitment flow diagram

Figure 2: Design of the OFSEP-HD cohort

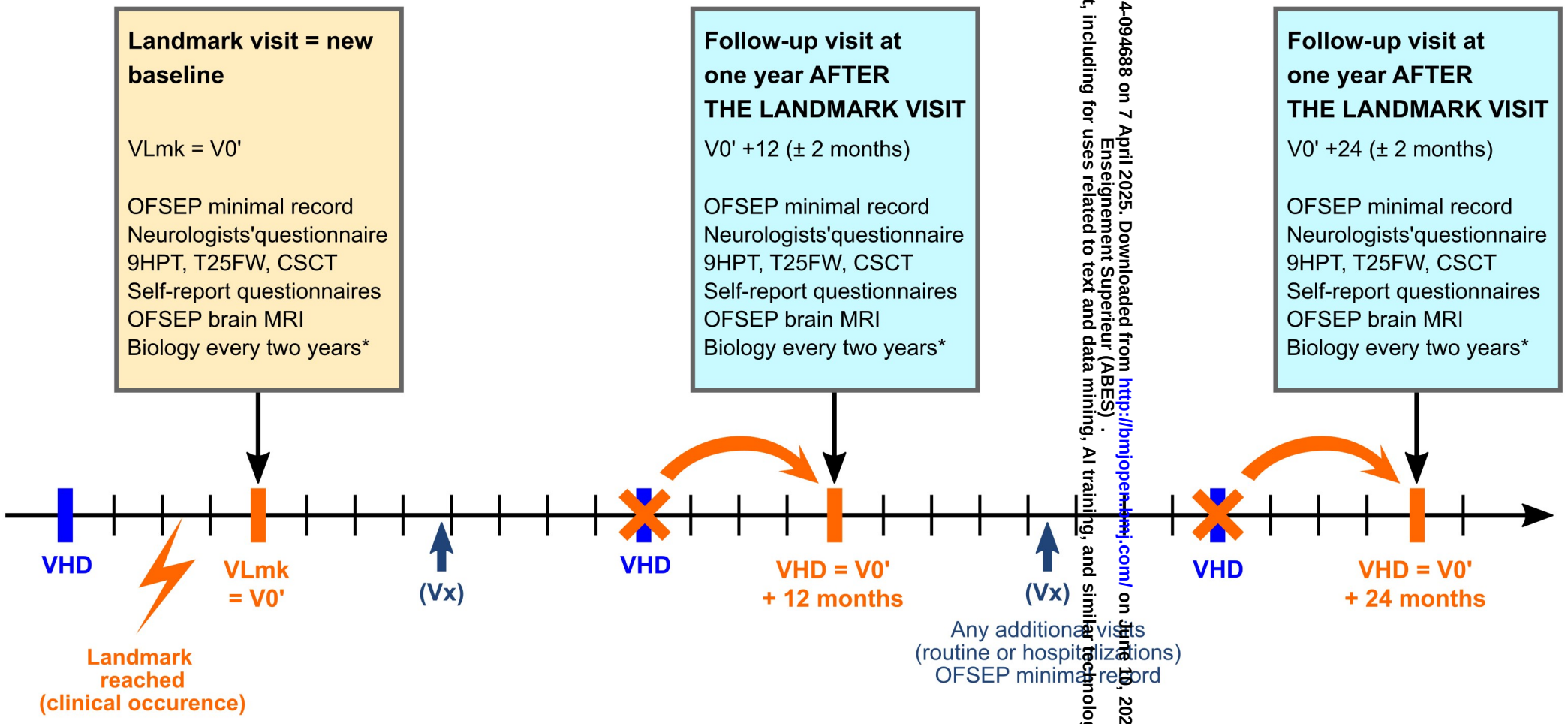
Figure 1. OFSEP-HD cohort recruitment flow diagram



*at the end of the recruitment period

Study schedule

(when a "recent disease activity" landmark visit occurs)



VLmk - VLandmark visits = new baseline V0'

"Recent disease activity" landmark visit occurs at **the first patient visit** showing recent disease activity defined by:

- **a relapse in the past 3 months, or**
- **a gadolinium-enhancing lesion in the past 3 months (and up to 3 months after the annual visit)**

Initial schedule

Re-schedule after a landmark visit occurs

*Biology performed every two years, during the closest-to-target HD visit with:
[Target date = inclusion date + multiple of 2 years], within the frame:
[Target date - 6 months ; Target date + 1 year]

Table S1. Characteristics of the MS subjects at inclusion in the OFSEP-HD cohort (n=2842)*

			Number	%
	Socio-demographic			
Age at inclusion (years)				
	mean (SD)		42.7 (11.6)	
median (Q1-Q3)			42.0 [34.0-51.0]	
Sex	male		757	*26.6*
	Female		2085	*73.4*
Level of education		university > 3yrs	529	*19.6*
		university ≤ 3yrs	843	*31.3*
		college	1324	*49.1*
		missing	*146*	
Occupation	employed		1731	63.6
	sick leave		443	16.4
	retired		175	6.4
	student		109	4.0
	unemployed		261	9.6
	missing		*123*	
	Lifestyle			
Tobacco	never smoker		1025	38.4
	former smoker		857	32.2
	current smoker		781	29.4
	missing		*179*	
Alcohol	≥ once a week		972	35.3
	2-3 times a month		548	19.9
	≤ once a month		577	20.9
	non consumer		249	11.3
	never over lifetime		339	12.3
	missing		*157*	
	Clinical			
Age at disease onset (years)				
mean (SD)			31.7 (10.2)	
median (Q1-Q3)			30.4 [24.3-38.3]	
Age at diagnosis (years)				

mean (SD)		35.0 (10.7)	
median (Q1-Q3)		34.1 |27.0-42.1]	
MS phenotype	unique episode	409	14.4
	relapsing remitting	1925	67.7
	secondary progressive	337	11.9
	primary progressive	171	6.0
EDSS (0-10)			
mean (SD)		2.4 (1.9)	
median (Q1-Q3)		2.0 [1.0-4.0]	
Annual relapse rate in the past 2 years [CI 95]		0.98 [0.80-1.19]	
Comorbidity	number**		
mean (SD)		0.46 (1.07)	
median (Q1-Q3)		0.0 (0-1)	
	Groll index	1.82 (1.23)	
	Charlson index	0.46 (0.85)	
BMI (kg/m²)			
mean (SD)		24.6 (5.1)	
median (Q1-Q3)		23.5 [21.0-27.1]	
Disease activity			
Episode in the past 3 months		191	6.7
Episode in the past 12 months		558	19.6
MRI activity in the past 3 months		561	19.7
	missing	*369*	
MRI activity in the past 12 months		951	33.5
	missing	*203*	
Remission (NEDA 3) in the past 12 months		850	29.9
	missing	*399*	
Landmarks at inclusion			
MS diagnosis for less than 6 months		124	4.4
MS progression in the past 12 months		38	1.3
Relapse or MRI activity in the past 3 months		631	25.4
	missing	*360*	
Remission (NEDA 3) in the past 5 years		305	10.7
	missing	*34*	

MS past monitoring			
Brain MRI density (nbr per year) [CI 95]	0.54 [0.41-0.70]		
Spinal cord MRI density (nbr per year) [CI 95]	0.23 [0.15-0.34]		
Disease modifying treatment			
Naive		182	6.4
No treatment		355	12.5
Highly effective therapy		1429	50.3
Moderately effective therapy		872	30.7
Off label therapy or clinical trial		4	0.1
Quality of life			
SF12*** physical component (0-100)	59.7 (27.0)		
missing		*242*	
mental component (0-100)	54.9 (31.4)		
missing		*242*	
Global score (0-100)	53.6 (22.5)		
missing		*242*	
MusiQol index (0-100)	70.5 (16.1)		
missing		*354*	
EQ-5D-5L (0-1)	0.867 (0.169)		
missing		*191*	

* missing values are indicated where applicable; **reported by the neurologist;

Comparison of included (n=2847) vs not included (16239) among 19086 eligible MS individuals according to inclusion criteria

Table S2. Adjusted odds ratios to be included in OFSEP-HD cohort among 19086 eligible MS individuals

	aOR*	95% CI	p-value
MRI activity at +/- 3 months from baseline			
Yes	0.86	0.75-0.98	0.026
No	1		
Missing	0.11	0.10-0.13	<0.001
MS diagnosis for more than 6 months			
Yes	0.29	0.24-0.37	<0.001
No	1		
EDSS (+/- 1 month)			
[0.0-3.5]	1		
[4.0-5.5]	0.91	0.79-1.03	0.145
[6.0-7.0]	0.69	0.58-0.81	<0.001
Remission (NEDA 3) over the past 5 years			
Yes	1		
No	0.90	0.79-1.02	0.107
Missing	0.74	0.63-0.86	<0.001
Disease modifying treatment at baseline			
Naïve	0.26	0.21-0.31	<0.001
No treatment	0.51	0.44-0.59	<0.001
Highly effective therapy	1		
Moderate effective therapy	0.58	0.52-0.64	<0.001
Off label therapy or clinical trial	0.51	0.20-1.30	0.158
Time from MS onset to first clinic visit (yrs)	0.97	0.96-0.97	<0.001

*Logistic regression model with center as a random effect (AIC= 11995), with significant likelihood ratio (p<0.001) compared to model with center as a fixed effect (AIC = 12680).

Comparing included (n=2847) vs not included (16239) among 19086 eligible MS individuals according to inclusion criteria, those included have less MRI activity in the past 3 months, a MS diagnosis for more than 6 months, a moderate EDSS, and receive more highly effective therapy, with a significant heterogeneity of recruitment across MS centers.

Comparison of patients with missing data vs no-missing data in the OFSEP-HD cohort

Table S3. Baseline characteristics of patients with missing data on landmarks

	Missing data (n|%)		No missing data (n|%)		p value
Total	**383**	**13.5**	**2459**	**86.5**	
Age at baseline					
Median [Q1-Q3]	45.4 [36.3-54.7]		41.5 [33.7-50.4]		<0.001
Age at MS onset					
Median [Q1-Q3]	31.2 [24.0-40.0]		30.4 [24.3-37.9]		0.129
Age at MS diagnosis					
Median [Q1-Q3]	35.2 [27.3-45.4]		34.0 [27.0-41.7]		0.016
Sex					0.805
Men	104	27.1	653	26.6	
Women	279	72.9	1806	73.4	
Level of education					0.257
University > 3yrs	62	16.2	467	19.0	
University ≤ 3 yrs	105	27.4	738	30.0	
College	194	50.7	1130	46.0	
Missing	22	5.7	124	5.0	
MS phenotype					<0.001
Unique episode	50	13.0	359	14.6	
Relapsing remitting	225	58.8	1700	69.1	
Secondary progressive	76	19.8	261	10.6	
Primary progressive	32	8.4	139	5.7	
EDSS					
Median [Q1-Q3]	2.5 [1.5-4.0]		2.0 [1.0-4.0]		<0.001
ARR* in the past 2 years [95%CI]	0.83 [0.77-0.90]		1.00 [0.97-1.03]		<0.001**
Comorbidity number					
Median [Q1-Q3]	0 [0-1]		0 [0-1]		0.511
Disease Modifying treatment					<0.001
Naïve	28	7.3	154	6.2	
No treatment	70	18.3	285	11.6	
Highly effective therapy	150	39.2	1279	52.0	
Moderate effective therapy	135	35.2	737	30.0	
Off label therapy or clinical trial	0	0.0	4	0.2	

*ARR=annual relapse rate

**from negative binomial regression

Table S4. Baseline characteristics of patients with missing data on clinical outcomes

	Missing data (n|%)		No missing data (n|%)		p value
Total	**637**	**22.4**	**2205**	**77.6**	
Age at baseline					
Median [Q1-Q3]	44.2 [36.3-54.2]		41.2 [33.5-50.0]		<0.001
Age at MS onset					
Median [Q1-Q3]	31.5 [24.5-39.5]		30.1 [24.2-37.8]		0.017
Age at MS diagnosis					
Median [Q1-Q3]	35.5 [27.9-44.9]		33.7 [26.9-41.6]		0.001
Sex					0.035
Men	149	23.4	608	27.6	
Women	488	76.6	1597	72.4	
Level of education					0.049
University > 3yrs	103	16.2	426	19.3	
University ≤ 3 yrs	175	27.5	668	30.3	
College	320	50.2	1004	45.5	
Missing	39	6.1	107	4.9	
MS phenotype					0.492
Unique episode	85	13.3	324	14.7	
Relapsing remitting	443	69.5	1482	67.2	
Secondary progressive	77	12.1	260	11.8	
Primary progressive	32	5.0	139	6.3	
EDSS					
Median [Q1-Q3]	2.0 [1.5-4.0]		2.0 [1.0-4.0]		<0.001
ARR* in the past 2 years [95%CI]	0.93 [0.88-0.99]		0.99 [0.96-1.02]		0.053**
Comorbidity number					
Median [Q1-Q3]	0 [0-1]		0 [0-1]		0.017
Disease Modifying treatment					0.034
Naïve	41	6.4	141	6.4	
No treatment	100	15.7	255	11.6	
Highly effective therapy	296	46.5	1133	51.4	
Moderate effective therapy	200	31.4	672	30.5	
Off label therapy or clinical trial	0	0.0	4	0.2	

*ARR=annual relapse rate

**from negative binomial regression

Table S5. Baseline characteristics of patients with missing data on patient reported outcomes

	Missing data (n|%)		No missing data (n|%)		p value
Total	**546**	**19.2**	**2296**	**80.8**	
Age at baseline					
Median [Q1-Q3]	45.9 [36.7-54.9]		40.9 [33.6-49.8]		<0.001
Age at MS onset					
Median [Q1-Q3]	32.7 [25.2-41.5]		29.9 [24.0-37.3]		<0.001
Age at MS diagnosis					
Median [Q1-Q3]	37.2 [27.9-45.9]		33.4 [26.8-41.3]		<0.001
Sex					0.415
Men	153	28.0	604	26.3	
Women	393	72.0	1692	73.7	
Level of education					<0.001
University > 3yrs	66	12.1	463	20.2	
University ≤ 3 yrs	123	22.5	720	31.4	
College	262	48.0	1062	46.2	
Missing	95	17.4	51	2.2	
MS phenotype					<0.001
Unique episode	53	9.7	356	15.5	
Relapsing remitting	351	64.3	1574	68.6	
Secondary progressive	84	15.4	253	11.0	
Primary progressive	58	10.6	113	4.9	
EDSS					
Median [Q1-Q3]	2.5 [1.5-4.0]		2.0 [1.0-3.5]		<0.001
ARR* in the past 2 years [95%CI]	0.93 [0.87-0.99]		0.99 [0.96-1.02]		0.084**
Comorbidity number					
Median [Q1-Q3]	0 [0-1]		0 [0-1]		0.471
Disease Modifying treatment					0.115
Naïve	46	8.4	136	5.9	
No treatment	69	12.6	286	12.5	
Highly effective therapy	280	51.3	1149	50.0	
Moderate effective therapy	151	27.7	721	31.4	
Off label therapy or clinical trial	0	0.0	4	0.2	

*ARR=annual relapse rate

**from negative binomial regression