Universitat de Girona
Facultat de Medicina

BENEFITS OF YOGA FOR REDUCE FATIGUE IN MULTIPLE SCLEROSIS

CLINICAL TRIAL

FINAL DEGREE PROJECT

Sandra Ramis Pozuelo :Author
Lluís Ramió i Torrentà, PhD :Clinical tutor
Xavier Castells Cervello, PhD :Methodological tutor

Girona, January 2022

“Vull agrair tot el suport que he rebut per part del meu tutor el Dr. Lluís Ramió i Torrentà, a més de formar-me al llarg de les pràctiques d’estiu com a futura metgessa”

“Estic molt agraïda amb el meu tutor metodològic en Xavier Castells, és el primer record que tenc quan vaig arribar a aquesta Universitat de trasllat d’expedient i ara formarà part dels darrers records també”

“Finalment vull agrair la implicació del meu voltant, totes les persones que fan que cada dia m’aixequi un poc més il·lusionada i que han estat allà en els moments més difícils”

ABSTRACT

BACKGROUND: Multiple sclerosis (MS) is a chronic autoimmune demyelinating disease of the central nervous system. It is the leading cause of non-traumatic disability in adults. There are multiple factors involved in the disease, despite numerous investigations, the pathophysiology today remains uncertain. Fatigue in MS is one of the most disabling symptoms on a day-to-day basis, it can affect up to 80% of patients. As with MS, the pathophysiological processes underlying fatigue remain uncertain. Given the lack of knowledge about fatigue, there is no completely effective treatment to reduce it, which is why we propose an approach through yoga, since it has been shown that aerobic exercise is beneficial in reducing this symptom.

OBJECTIVE: The main objective of this study is to determine if the practice of yoga in MS patients reduces fatigue. In addition, secondarily we will study its possible influence on: quality of life, kinesiophobia, sleep quality, gait speed, balance, depression, sexual function and relapses.

DESIGN: controlled, randomized, prospective, single-blind, single-center clinical trial.

PARTICIPANTS: 88 patients aged 18 to 65 years diagnosed with MS according to the McDonald 2017 criteria under follow-up at the Neuroimmunology and Multiple Sclerosis Unit of the Santa Caterina Hospital, who also presented fatigue characterized by a score >38p on the MFIS scale.

INTERVENTION: Participants will be randomly assigned into two groups of equal size (1:1/44:44). The members of the intervention group will attend yoga classes twice a week for 1 hour, for 6-months. Both groups, at the beginning and at the end of the study, will complete the scales that we want to evaluate with the nursing team (blinded). In addition, controls will be carried out with the neurologist to assess the evolution.

KEY WORDS: · Multiple Sclerosis · Yoga · MFIS · Fatigue ·

ABBREVIATIONS

2CdA	2-Clhoro deoxy-Adenosine
APC	Activating antigen presenting cells
BBB	Blood brain barrier
BDI	Beck Depression Inventory
BOC	Oligoclonal bands
Ca	Calcium
CAM	Complementary and Alternative Medicine
CAM	Complementary and Alternative Medicine
CDK	Deoxy Cytidine Kinase
CDMS	Clinically defined multiple sclerosis
CI	Confidence interval
CIS	Isolated clinical syndrome
CNS	Central nervous system
DIS	Diffusion in space
DIT	Diffusion over time
EDSS	Expanded Disability Status Scale
FIS	Fatigue Impact Scale
FSS	Fatigue Severity Scale
Gd	Gadolinium
HLA	Human Leukocyte Antigens
IC	Information Consent
IFN-ß	Interferon beta
IL	InterLeukin
K	Potassium
mAbs	Monoclonal antibodies
MFIS	The Modified Fatigue Impact Scale
MHC	Major histocompatibility complex
MOG	Oligodendrocyte myelin glycoprotein
MP	Methyl prednisolone
MRI	Magnetic resonance imaging

MS	Multiple sclerosis
Na	Sodium
NFF2	Nucleation factor transcription pathway
NfL	Neurofilaments
NO	Optic neuritis
PBM	Myelin Basic Protein
PI	Principal Investigator
PNMT	Phenyl-etanhol-N-Metyhyl-Transferasa
PPMS	Primary progressive MS
QoL	Quality of Life
RIS	Isolated radiological syndrome
RRMS	Relapsing Remitting MS
SF-36	Health Status Questionnaire
SPMS	Secondary Progressive MS
SPSS	Statistical Package for the Social Sciences (SPSS)
SSS	Sexual satisfaction Scale
Th1 CD4 +	T-helper 1
Th2 CD4 +	T-helper 2
TNF	Tumor necrosis factor

INDEX OF FIGURES

INDEX OF TABLES

INDEX OF CONTENTS

1. MULTIPLE SCLEROSIS

1.1. INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system (CNS) characterized by inflammation, demyelination, axonal loss, and gliosis. It is the disabled, non-traumatic neurological disorder most common in young adults. Diagnosis is currently clinical, based on criteria based mainly on the concepts of **dissemination in space** (DIS) and **dissemination in time** (DIT) of CNS lesions.

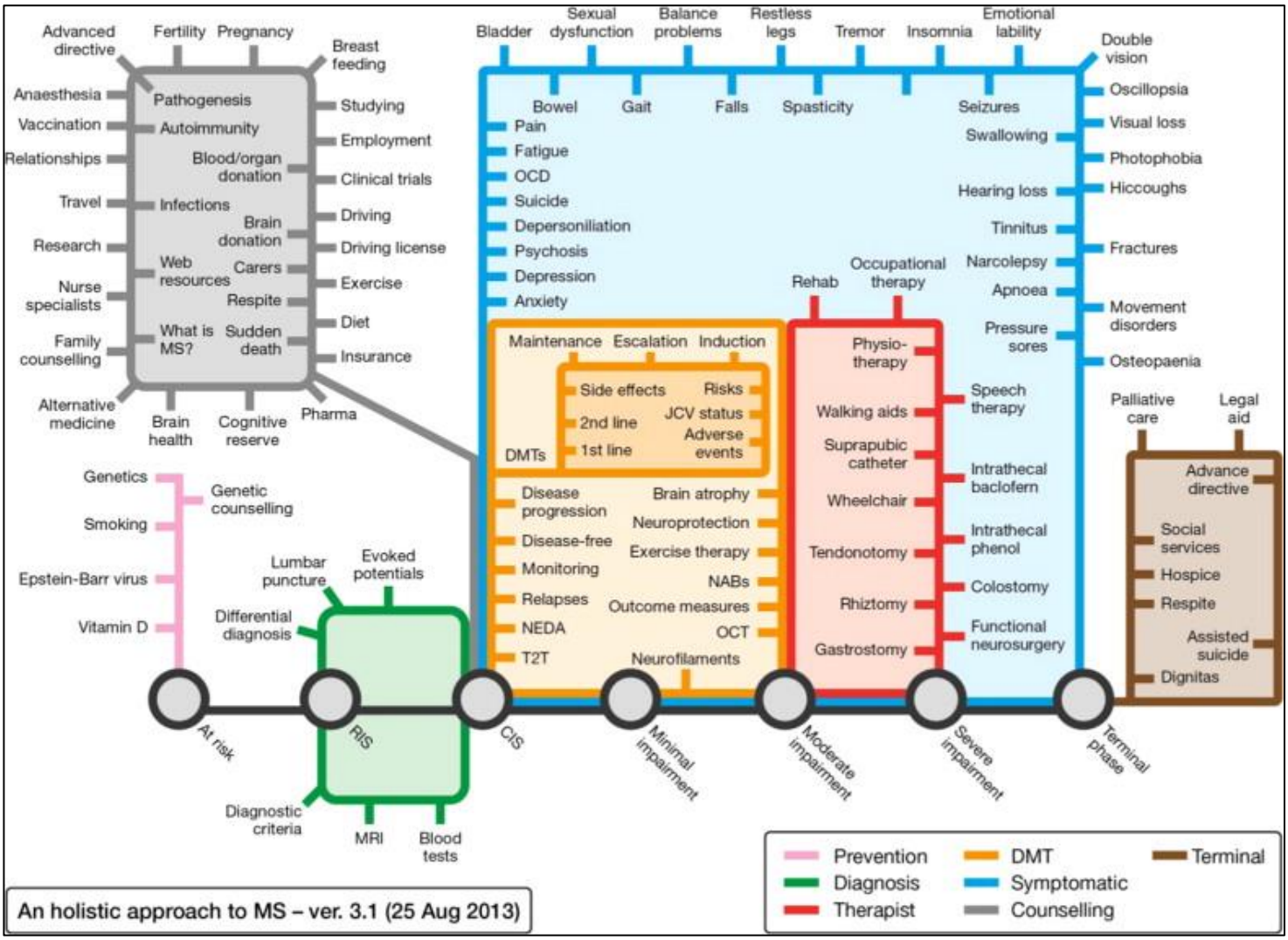


Figure 1: Holistic approach to MS.

Data from (1)

In the new reviews, it is tried to improve the sensitivity and precocity of the diagnosis of the MS. In 2001 **the McDonald criteria** (along with the 2005 revision) incorporated the magnetic resonance imaging (MRI) criteria for DIS and DIT and allowed the diagnosis of MS after a single clinical relapse, if in an MRI of subsequent control targeted new injuries (also complying with DIT). In 2010 the McDonald review simplifies the DIT and DIS criteria, along with the earliest diagnosis of MS, only with a clinical relapse if MRI meets specific DIT and DIS criteria. The latest modification (McDonald 2017) is only applied to isolated clinical syndrome (CIS) and clinical demonstration or MRI of DIS, the presence of specific oligoclonal bands in CSF allows the diagnosis of MS (2).

1.2. EPIDEMIOLOGY

Recent prevalence studies indicate that the frequency of the disease has increased worldwide in recent decades due to improved health care and widespread availability of diagnostic tests (MRI). This increase is shown mainly by women with remittance forms affecting around the age of 25-30. We find classically high-risk MS regions (southern Canada, northern US, British Isles and Scandinavia) have documented the highest **prevalences** in the world, with 248 cases/100,000 inhabitants. In other regions considered classically of medium prevalence at present they are considered of medium-high risk prevalence (Spain, Italy) around 100/100,000 inhabitants, explaining why the latitudinal gradient of the **incidence** of the disease is attenuating (3,4).

Nowadays we have 2,5M of people affected by MS all over the world and 700.00 of them in Europe, these numbers show social and sanity impact of the disease which also is reflected economically. World trends exemplified that the incidence is increasing in southern areas of the planet while northern Europe and North America remains stable according to the classic latitudinal gradient described by Kurtzke. The reduction in **mortality** and the improvement in survival seem to justify the high prevalences despite the fact that the incidence does not continue to increase (3,6). The incidence data in **Spain** have been obtained based on retrospective studies from cross-sectional prevalence studies, the mean incidence of the eight prospective studies is 4.2 cases per

100,000 inhabitants. Analyzing the region of Spain we observe higher prevalences in higher latitudes (3).

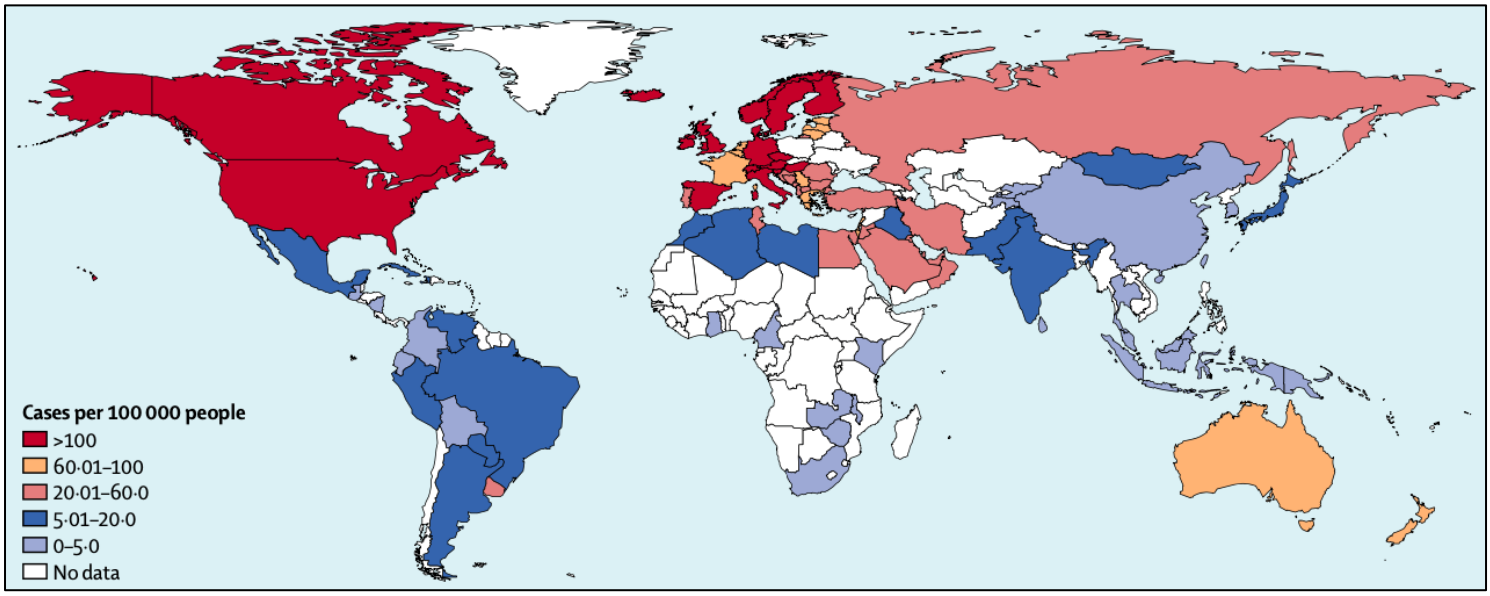


Figure 2: Global prevalence of MS.

Data from *(5)*

1.3. RISC FACTORS

Among the **risk factors** identified for MS we find viral infections, especially by the Epstein-Barr virus, female sex, little exposure to sunlight (vitamin D deficiency), smoking, family / genetic history, living in high latitudes, being born in May and high body mass index during adolescence. Among these, tobacco and vitamin D can also influence the course of MS (3,7). About the **Epstein-Barr virus**, recent studies demonstrates a high association (8–10).

Women have a higher risk of presenting MS like other autoimmune diseases, likewise, women have a different clinical course: they are mainly RRMS forms, therefore they are more likely to start early, to develop MS after a CIS, to have more lesions inflammatory on MRI and more flare-ups than men. On the other hand, **men** tend to present progressive forms as well as a worse prognosis (3). It has been seen that **pregnancy** can act as a protective factor, specifically during the third trimester, reducing relapses and the severity of these related to an increase of up to 20 times the levels of

progestogens and estrogens. However, although there is no increase in disability or lesions of the white matter by MRI during pregnancy, in the postpartum there are usually relapses, in relation to the normalization of hormonal values and the autoimmune response (7,11).

Regarding **genetics**, it explains 30% of the etiology of the disease, of which 10% is explained by the HLA DRB1 1501 gene on the short arm of chromosome 6, although the implication of this gene and many others is unknown (3,12,13).

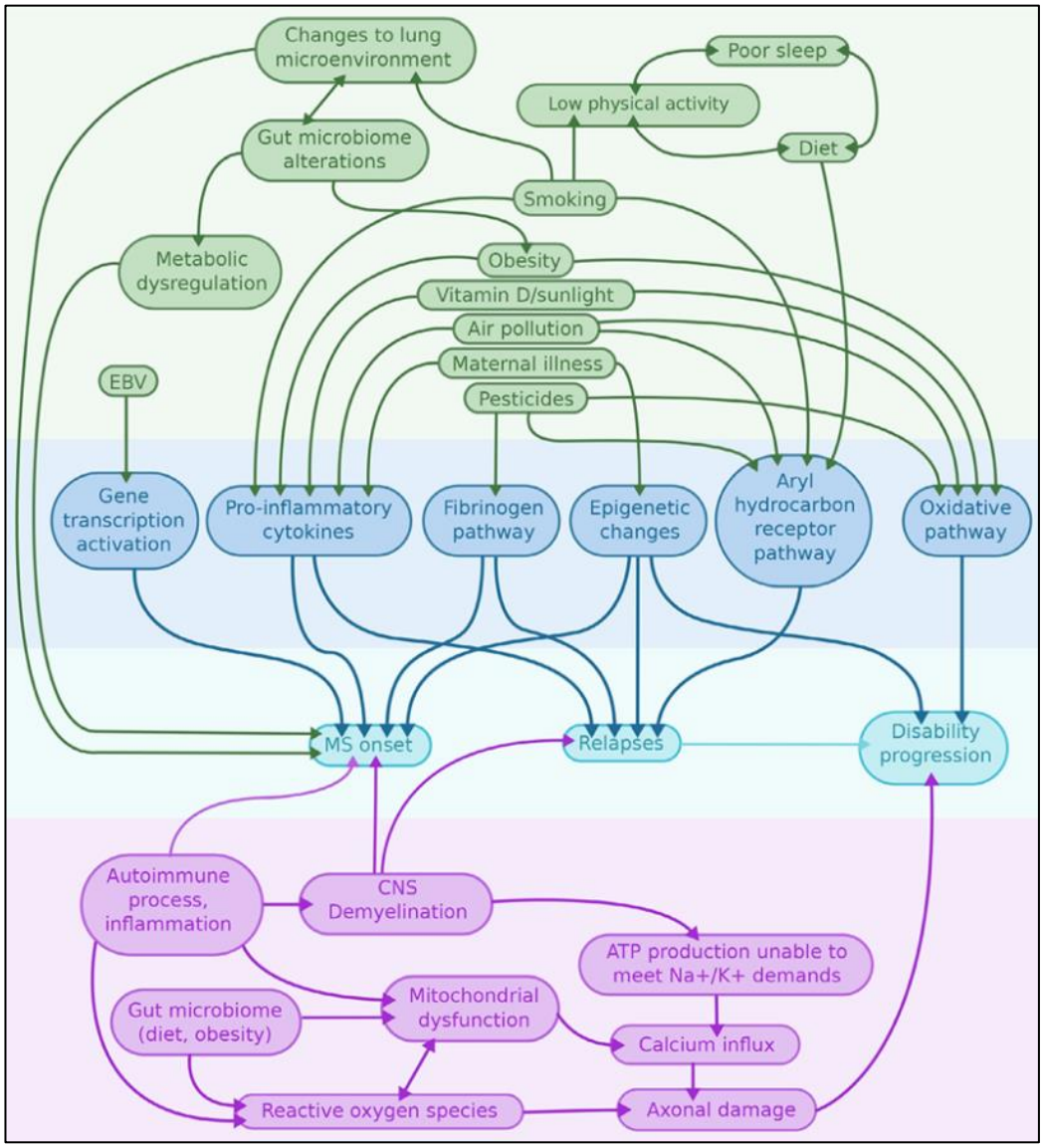


Figure 3: environmental contributions to MS risk.

Data from *(14)*

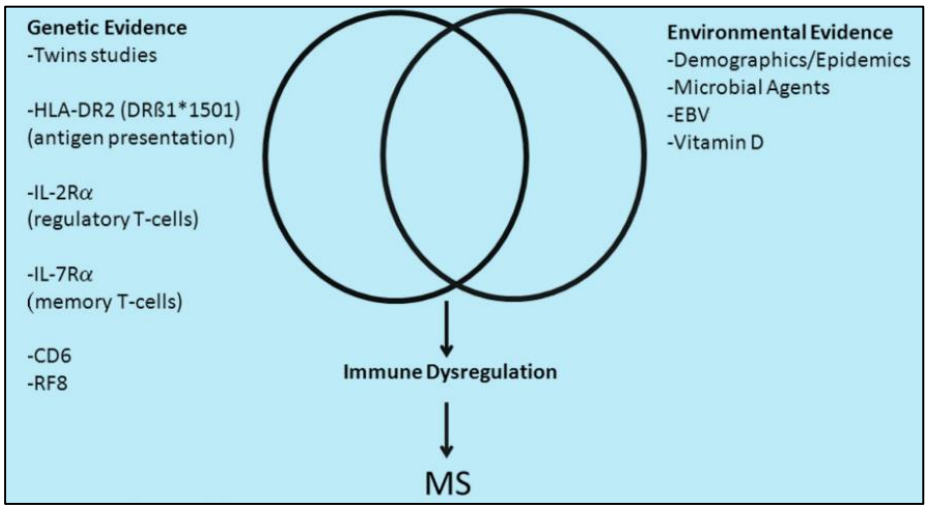


Figure 4: Immunogenic disease led to immune dysregulation.

Data from *(15)*

1.4. PATHOPHYSIOLOGY

MS is a disease mediated by the immune system, in which we find 3 aspects: **perivenous inflammation**, **demyelination** and **gliosis**; causing demyelination plaques of the white matter of the CNS, well defined, with few cells, loss of myelin and a relative preservation of axons and gliosis. It has a greater predilection for the optic nerve, periventricular white matter, brainstem, cerebellum, and spinal cord (16,17).

Immune response:

Myelin is made up of multiple proteins (myelin basic protein, myelin proteolipid, myelin oligodendrocytic glycoprotein or myelin-associated glycoprotein), these are released when myelin is destroyed, for example, in the course of an infection (7). Subsequently, these proteins are recognized by the major histocompatibility complex type II (MHCII) that activates the receptor complex of T lymphocytes. It is necessary for the pathogenesis that these T lymphocytes belong to an abnormal population with **immunological dysregulation** that allows them to react to autoantigens, they are autoreactive. T lymphocytes cross the blood-brain barrier (BBB) due to the expression of integrins that allow endothelial adhesion (16). Once inside the CNS, 2 types of

responses can be generated (TH1 and TH2), each with its production of cytokines and consequently different effector mechanism (5,10):

- **The TH1 type response** produces pro-inflammatory cytokines such as IL2, TNF and INF, activating antigen presenting cells (APCs), promoting differentiation towards a TH1 response and inhibiting the TH2 type response.
- On the other hand, **the TH2 response** produces anti-inflammatory cytokines such as IL4, IL5, IL-6, IL-10 and IL-13, thus regulating humoral immunity, while reducing local inflammation, promoting differentiation towards TH2 and inhibiting the TH1 response.

Therefore, in MS the type of response observed is **TH1**. Lymphocytes CD4-TH1 release pro-inflammatory cytokines by activating macrophages, cells that initiate lesions in MS, phagocytizing myelin, promoting active demyelination by secretion of cytokines, oxygen free radicals, and proteolytic enzymes (such as metalloproteases). Among the **cytokines** we find: IL-10, IL-2, g-INF and a-TNF, generating a (15,16):

- Inhibition of IL-12 by mononuclear leukocytes in peripheral blood.
- Increased receptors for certain cytokines in the cell membrane of immune cells such as CCR5 and CXCR3, their expression being more important in the affected areas.
- Receptors for alpha-cytokines (IP-10 and Mig) are predominantly expressed on macrophages and reactive astrocytes within active lesions.
- There is also a greater range of migration mediated by cytokines (RANTES and MIP-1a).

The large TH1 response and the inhibition of TH2 leads to a greater action of the CD8 lymphocytes, in relation to CD4 activity, which is correlated with more severe axonal damage. It is argued that TH2 cells also contribute to myelin damage mediated by antibodies against myelin basic protein (PBM) and oligodendrocyte myelin glycoprotein (MOG), which are the main targets of the immune response in MS. All of this has also effects on the BBB, making it more permeable. An interesting fact is that lymphocytes are not always found in active lesions, but rather they are more abundant

in the periphery of the lesions and in the unaffected white matter, finding data that the immune response can contribute to the repair of myelin. The axonal damage that occurs in MS is not well defined and remains a paradigm (15,16).

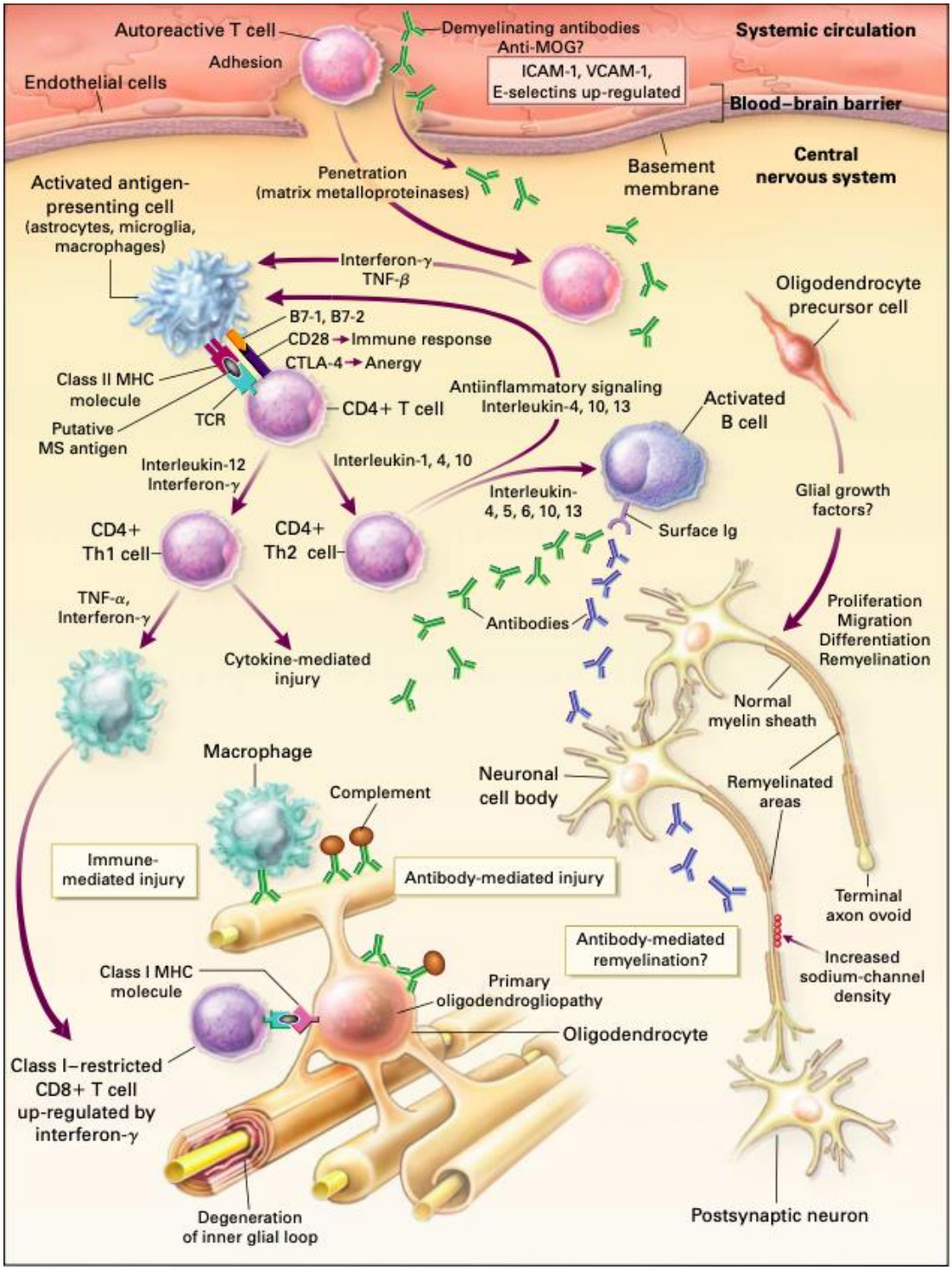


Figure 5: Possible Mechanisms of Injury and Repair in Multiple Sclerosis.

Data from *(17)*

1.5. CLINICAL COURSE

MS manifests itself mainly in young adults between 20-40 years of age with a predominance of the female gender (17). Depending on the form of onset, patients are classified into relapsing-remitting MS RRMS (85% of cases) or primary-progressive MS (15% of cases)(16).

Relapse

- **Definition**

The flare is the hallmark manifestation of RRMS patients, although less frequently in progressive MS they may experience relapses. The **relapse** (recurrence or exacerbation) is a clinical concept, it is considered relapse those symptoms that the patient refers that can be objectified, typical of an acute inflammatory lesion in the central nervous system, with a minimum duration of 24 hours and in the absence of fever or infection. To accept the existence of 2 relapses, these must be separated by at least one month from the beginning of the symptoms of the first until the beginning of the symptoms of the second. We must distinguish relapse from the concept of **pseudo-relapse**, this is the exacerbation of previous symptoms and its onset and resolution coincide with a triggering situation, mainly the increase in temperature. But if the duration of the pseudo-relapse exceeds in time the situation that triggers it, it will be considered a relapse. The cause of pseudo-relapses is due to blockages in axonal conduction (18).

- **Natural evolution**

The most typical relapse affects the optic nerve, the spinal cord or the brainstem and cerebellum. They can affect several locations at the same time (polytopic relapse). In the natural evolution of the relapse, the onset is acute or subacute with initial progressive worsening until the borderline of **disability**, the symptoms last 1-2 weeks at their maximum intensity and usually remit for 2-4 more weeks. Incomplete resolution of symptoms is attributed to accumulation of disability. The **intensity** of the relapse has

been investigated according to the degree of disability reached by the patient on the EDSS scale (18):

- Mild: increase in EDSS <1 point
- Moderate: increase in EDSS between 1-2.5 points
- Severe: ≥3 points increase

- **Relapse and MRI**

We have two forms of activity: **clinical** and **radiological**. Within radiology it is defined by the appearance of lesions on MRI. However, we know that there is no correlation between these and that patients may present relapses without radiological activity. We detect **radiological** activity in 2 ways: **appearance of gadolinium-binding lesions in T1 sequences (T1 + Gd)** and the **appearance or increase of lesions in T2**.

We know that we can have an inflamed area at the time of the relapse and that clinically it is perceived as monosymptomatic, this incongruity can be explained by the involvement of non-eloquent areas of the brain where neuroplasticity manages to mask the lesional damage or also the real functional affectation that It is not perceived by the doctor, such as mild cognitive impairment or **fatigue** (18).

Phenotypes

Among the different manifestations of multiple sclerosis, there are different **phenotypes**:

- **MS with relapses** (2)**:**

a. Isolated clinical syndrome (CIS): first demyelinating and inflammatory clinical manifestation that may be MS. By definition, it has to be isolated in time (monophasic) and is usually isolated in space (monofocal). Symptoms usually affect the optic nerve, brain stem or cerebellum and/or spinal cord.

b. Recurrent remitting multiple sclerosis (RRMS): evolution in the form of flare-ups followed by periods of recovery or remission in which the presence of DIS and DIT

has been demonstrated. In this way, a CIS, if the presence of DIS and DIT is demonstrated by MRI, can now be diagnosed with RRMS.

- **MS with progressive course** (2)**:**

a. Primary progressive multiple sclerosis (PPMS): it is characterized by the appearance of neurological symptoms (usually gait disorders) of insidious onset and progressive course from the beginning.

b. Secondary progressive multiple sclerosis (SPMS): appearance of a progressive worsening of neurological symptoms after an initial phase characterized by relapses that occurs independently of these. Currently we do not have the clinical means or the image to establish the transition point between RRMS and SPMS, therefore the diagnosis is usually carried out retrospectively.

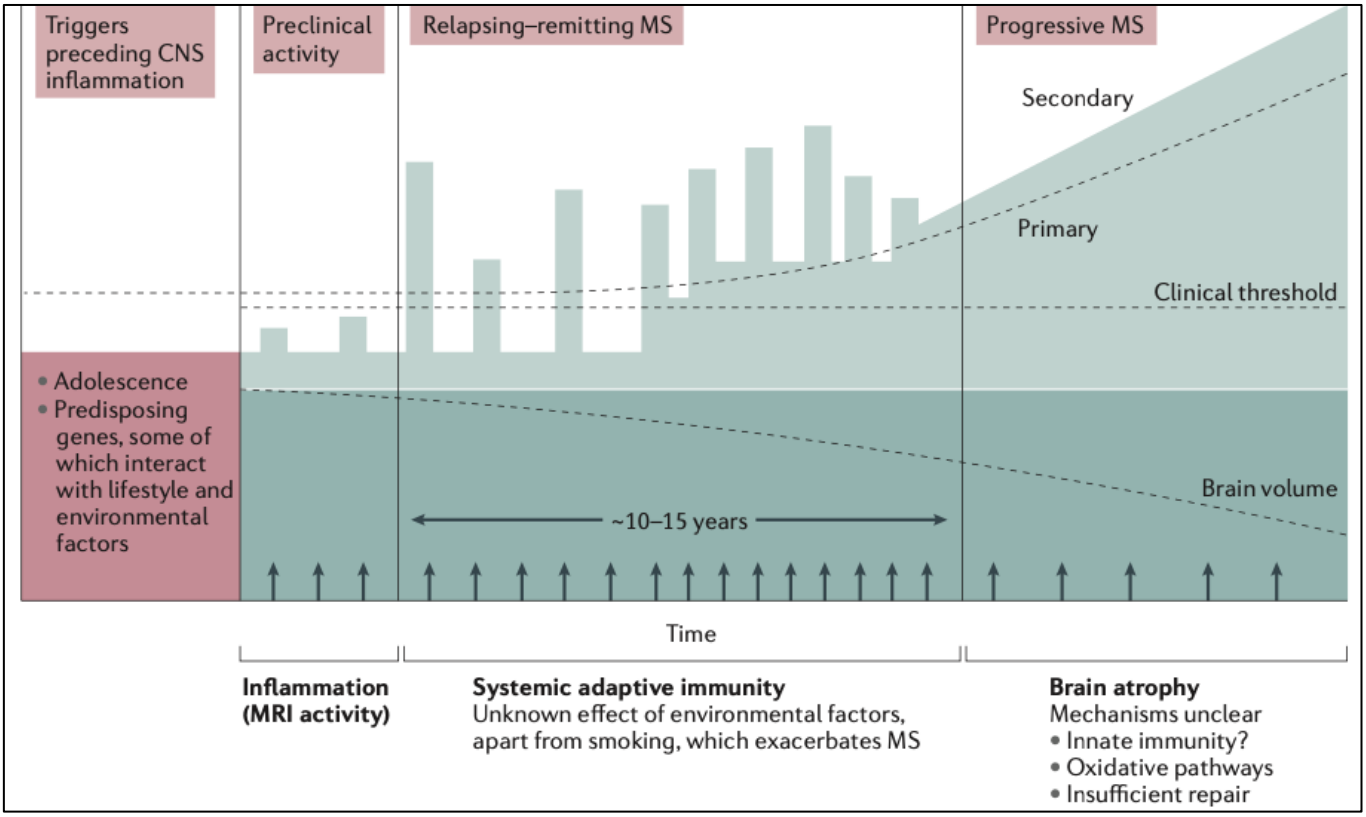


Figure 6: Evolution of multiple sclerosis.

Data from *(19)*

Among other aspects, it is worth highlighting the **isolated radiological syndrome (RIS)** that should not be considered as a phenotype of the disease since by definition these patients have not presented symptoms derived from MS. Up to 30% of these patients can develop CIS in 5 years and subsequently convert to clinically defined multiple sclerosis (CDMS) (20,21).

Gait

Regarding the gait of MS patients, there is a concept called **kinesiophobia**, it is the fear of pain related to movement, in patients with musculoskeletal pain (low back pain). This can influence the degree of disability of the EDSS, requiring more support while walking (22,23).

1.6. CLINICAL EVALUATION

MS is a disease with an unpredictable course with a great variety of **motor, sensory** and **cerebellar symptoms**, which makes the comprehensive assessment of the patient difficult and may even be inaccurate, although it is necessary to be able to compare the evolution of patients objectively and conclude with the clinical assessment (17). For this, we have the scales of neurological deterioration produced by the disease and of the personal, family and social consequences, of these the most used is **the expanded disability status scale (EDSS)** (Annex B). Developed by Kurtzke in 1983, it quantifies the involvement of 8 functional systems (pyramidal, cerebellar, brain stem, sensitivity, intestine and bladder, visual, mental and others). The main problem with this scale is interobserver variability. The aspects to assess the response to treatment and thus the evolution of the patient are (7):

- **Number of relapses.**
- **Expanded Disability Status Scale (EDSS).**
- **Evidence of changes on magnetic resonance imaging (MRI).**

1.7. DIAGNOSIS

The diagnosis of MS continues to be a challenge, there is a small balance between reaching an early diagnosis and a misdiagnosis, therefore an exhaustive medical history, a good neurological examination and the realization of a correct differential diagnosis, especially in front of patients with red flags, continue to be fundamental pillars (5).

The recently **revised diagnostic criteria in MS are McDonald 2017**, through a clinical and paraclinical approach, emphasizing the need to demonstrate dissemination in time (DIT) and space (DIS). The main contributions of the new criteria are (2):

- Simplification of the DIS and DIT criteria to be able to include symptomatic lesions of the spinal cord or brainstem.
- Inclusion of a new topography to demonstrate the presence of DIS.
- Possibility of using LCR to establish the diagnosis of MS.

Dissemination in space

DIS is considered to be the presence of at least 1 lesion in 2 of the 4 typical areas of MS (periventricular, cortico-juxtacortical, infratentorial and medullary) (24). The presence of symptomatic lesions in the aforementioned areas has been shown to confer an increased risk of developing a second flare during MS follow-up (2,25,26).

Dissemination in time

Among the new criteria, the demonstration of DIT is based on: the simultaneous presence of lesions with and without enhancement after the administration of gadolinium in the same MRI (5), or by the appearance of at least one new lesion (with or without enhancement of gadolinium) on a follow-up MRI after a previous one (27). Furthermore, the presence of oligoclonal bands (BOC) in the CSF may replace the requirement to comply with DIT in patients with a typical CIS and demonstration of DIS in the absence of a diagnostic alternative (2,28).

Table 1: The 2017 McDonald criteria for diagnosis of MS in patients with an attack onset.

Data from *(24)*

	Number of lesions with objective clinical evidence	Additional data needed for a diagnosis of multiple sclerosis
≥2 clinical attacks	≥2	None*
≥2 clinical attacks	1 (as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location†)	None*
≥2 clinical attacks	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI‡
1 clinical attack	≥2	Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of CSF-specific oligoclonal bands¶
1 clinical attack	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI‡ AND Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of CSF-specific oligoclonal bands¶

1.8. IMAGE FEATURES

MRI is the most sensitive paraclinical technique in the identification of demyelinating lesions that characterize MS. It is not only essential to establish an early diagnosis but also contributes to **prognosis**, both in the prediction of clinical recurrences and the progression to disability. It also acquires an important role in the **monitoring** of the different treatments and the prediction of their efficacy. In the follow-up of the natural history of MS with MRI we observed a slight correlation with the clinical evolution, the origin of this clinical-radiological dissociation reflects the limitations of the clinical measurement scales (EDSS) as well as the parameters used in MRI (24,29).

Features

Typically, the lesions visible on MRI are multiple and small (<20mm), although they may become larger due to the confluence of many or the existence of pseudo-tumoral lesions. Regarding the **morphology**, they are nodular and ovoid, mainly the demyelinating plaques are **located** in the periventricular white matter, corpus callosum, juxtacortical white matter and in the infratentorial parenchyma (preferably the cisternal surfaces of the pons, the intrapontine path of the trigeminal nerves, the median and superior cerebellar peduncles, and the floor of the IV ventricle).

Different **sequences** are found in MRI for the study of MS (29,30):

- T2 potentiated
- Potentiated in T1
- T1-weighted with gadolinium (Gd)

In addition, different changes are observed in the CNS:

- **Cerebral atrophy**, being able to use cerebral volumetry as an indicator (29,31).
- **Involvement of the spinal cord**, they adopt an ovoid morphology with their major axis oriented craniocaudally and are located centrally, anteriorly and posteriorly, with a predisposition for the posterior and lateral cord with or without involvement of the central grey matter (29,32).
- **Optic neuritis (ON)**, is often the first manifestation of MS that can be visualized on MRI, however, it is not a diagnostic requirement in clinically typical ON (29,33).

MRI images (29)

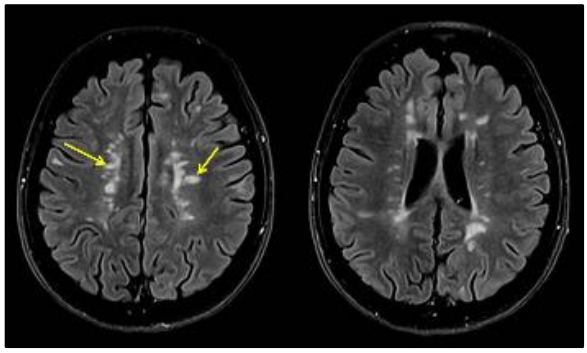


Figure 7: MRI T2-FLAIR periventricular region.

Hyperintense images in a periventricular situation, some ovoid (arrows) with their long axis perpendicular to the ventricular walls.

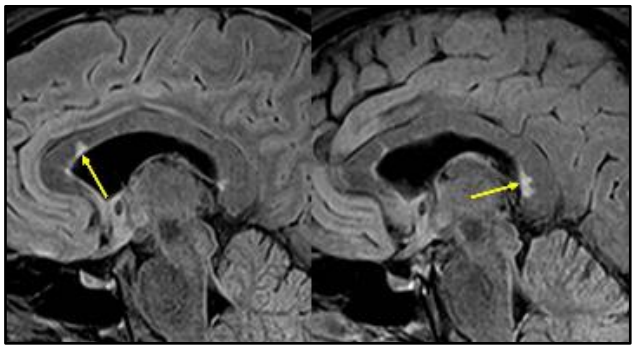


Figure 8: MRI T2-FLAIR corpus callosum region.

Typical image on the lower margin of the corpus callosum.

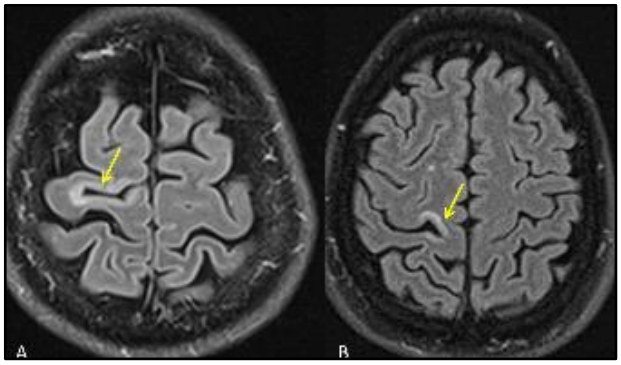


Figure 9: MRI infratentorial region.

T2-FLAIR: A) right prefrontal lesion and B) right perirolandic juxtacortical lesion.

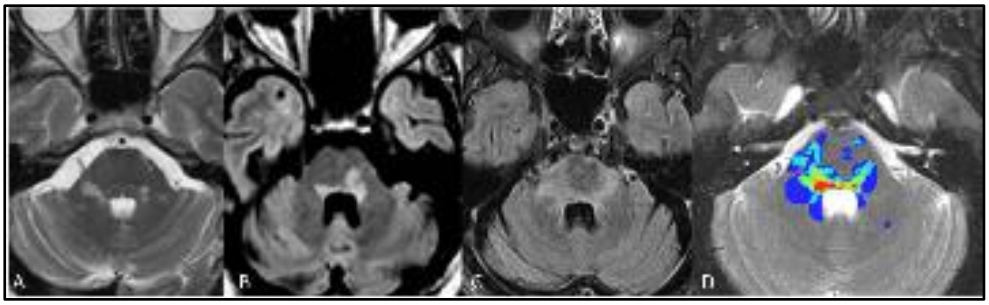


Figure 10: MRI Topography demyelinating lesions of the brainstem.

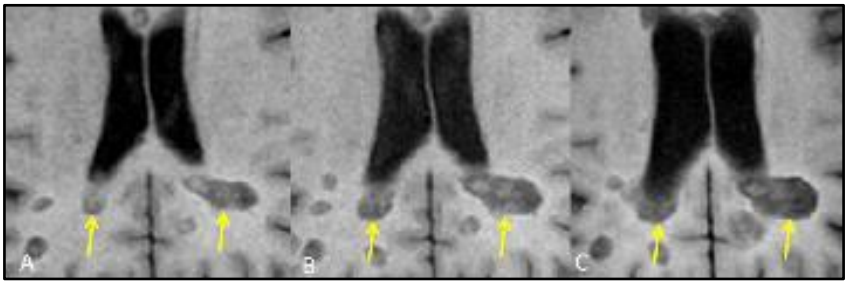


Figure 11: MRI T1 slowly expanding lesions.

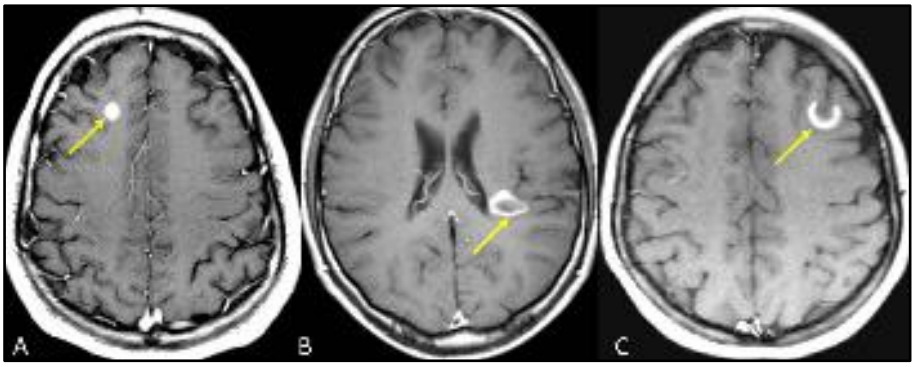


Figure 12: MRI T1 + Gd.

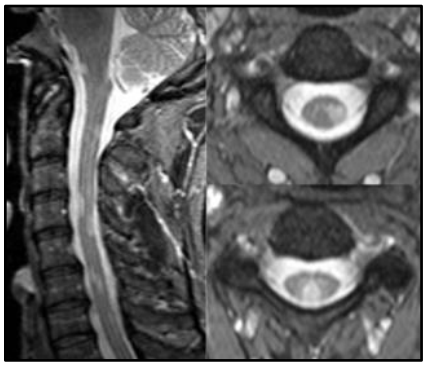


Figure 13: MRI Cervical region (STIR image).

Typical lesions affecting the posterior and lateral cord that do not exceed two vertebral bodies in craniocaudal extension.

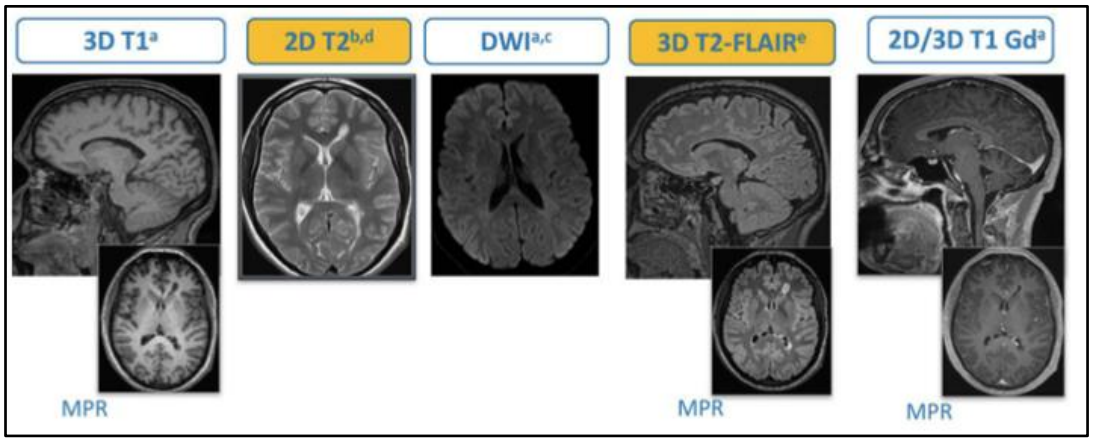


Figure 14.MRI: Basic protocol of brain MRI in the diagnosis and follow-up of MS.

a) Optional sequences.
b) 2D T2. If you have 3D T2-FLAIR sequences of high quality, skip this sequence.
c) Per differential diagnosis.
d) If you have high-quality 3D T2-FLAIR sequences, you can ignore the T2 sequences in the monitoring studies.

1.9. CSF DIAGNOSTIC STUDY

The method used is lumbar puncture for sample collection. A series of basic tests are carried out: **cell count** (normal or mild lymphocytic pleocytosis), **evaluation of the integrity of the BBB** (determination of the CSF albumin / serum albumin ratio), serologies for differential diagnosis, **quantitative assessment of the increase of IgG synthesis**.

In addition, certain biomarkers are studied (34):

- **Demonstration of oligoclonal bands in CSF**

The most sensitive method (95%) and the only biomarker used in clinical practice. Its absence has a high negative predictive value for the development of MS. The band pattern remains constant in the same individual throughout life and does not change with corticosteroid treatment. The drawback is that they are not specific to MS, and therefore we can find them in other neurological diseases of immunological

pathogenesis. The presence of bands may be conditioned by genetics since it has been associated with an HLADRB1 * 15 allele. We also determined the bands in serum since a pattern called "in mirror" has been observed where we have the same number of bands in serum and in CSF, this is observed in systemic diseases with CNS involvement. As we have already mentioned previously, the presence of BOC can help to confirm the diagnosis in patients who do not have dissemination in time (DIT).

- **Light chain neurofilaments (NfL)**

This biomarker is not yet used in clinical practice, it reflects **axonal damage**, therefore it is not specific for MS and is observed in other situations such as cranioencephalic trauma, ALS and Alzheimer's. It is considered a good predictor of a first relapse in patients with CIS.

- **Protein 1 similar to chitinase 3**

It is an indicator of **glial activation**. Elevated levels are associated with the conversion of CIS to MS, the rapid accumulation of disability, cognitive deterioration in the initial phases, and more lesions on MRI.

1.10. TREATMENT

MS is a chronic disease of variable semiology that directly and indirectly affects various systems, for which the approach must be **multidisciplinary**, therefore we must not only consider functional and structural problems but also activity, participation and environmental factors. Due to the scarce evidence within the various treatments, we must individualize each one and carry out periodic monitoring of each patient according to the different objectives (35).

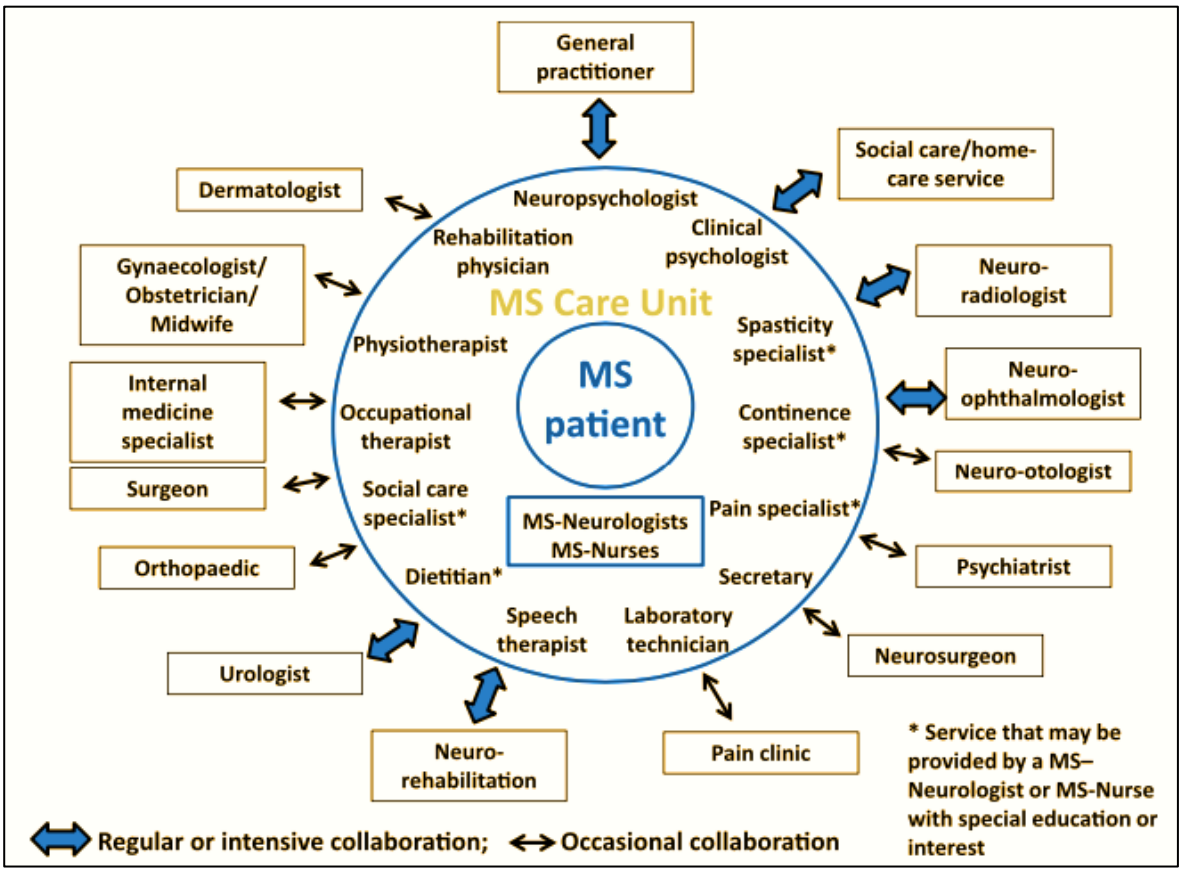


Figure 15: Multidisciplinary treatment

Data from*(36)*

Relapse treatment

We have **3 goals** in treating the relapse:

1. Reduce the severity of the relapse
2. Accelerate recovery
3. Reduce residual disability after the relapse

- **Pharmacotherapy**

The drug we use are **corticosteroids**, specifically methylprednisolone (MP) at high doses. The NICE7 guideline advises administering no less than 500mg of MP orally / 24h for 5 consecutive days or as an alternative oral MP 1g / 24h for 3-5 days. There is no indication for descending corticosteroid therapy after megadose either oral or

intravenous. Treatment is advised early. It should be clarified that corticosteroid treatment reduces the duration of the relapse and its intensity, but not the residual disability that it may entail (18).

- **Non-pharmacological treatment**

A comprehensive and multidisciplinary approach that integrates psychological support, functional rehabilitation treatment (including rehabilitators, physiotherapists, occupational therapy, speech therapists and specialists in cognitive rehabilitation) is essential for the correct treatment of the relapse (18).

Immunomodulatory treatment (own creation, sources in the table)

Table 2: Immunomodulatory treatment in MS

Medicines	Mechanism of action and dosage	Effectiveness	Adverse effects	Usage indication
Interferon-ß (AVONEX®,PLEGRID®, BETAFERON®,REBIF®)(36)	Modulating cytosine immune response, specific mechanism unknown. Subcutaneous injection 250µg every other day.	↓ the annual relapse rate by 34%, lengthens the time between relapses and reduces serious ones.	Erythema, lipoatrophy, skin necrosis, flu sd, lymphopenia, anemia and thrombocytopenia, ↑ transaminases.	CIS, RRMS and SPMS (with clinical or radiological activity).
Glatiramer acetate (COPAXONE®/GLATIRAMER ACETATE MYLAN®) (36)	It acts on the interaction of the MHC and the L-T receptor, induces an L-TH2 response and suppressive cytokines. Subcutaneous injection 3 days/week.	↓ the rate of relapse, decreases the progression of disability	Local reactions, with erythema, induration and lipodystrophy, transient post-injection reaction with palpitations and anxiety.	CIS, RRMS and SPMS (with clinical or radiological activity).
Teriflunomide (AUBAGIO®) (37)	Oral inhibitor of the dihydroorate dehydrogenase, interferes with novo synthesis of pyrimidines, antiproliferative, immunomodulatory.	↓ 31% annual relapse rate, ↓ 29% in disability (not significant p=0.03), ↓ 67% in lesion volume.	Teratogen in studies (avoid pregnancy and lactation), ↑ transaminases, flu sd, weight loss, hair loss and diarrhea.	First-line adult MS: 1 or more Gd+ lesions or 2 or more lesions in the last 2 years, or 1 relapse with sequelae in the last year (> 1p EDSS at 3 months).
Dimethylfumarate (TECFIDERA®) (38)	Double: inhibits proinflammatory cytokines and ↓oxidative stress by activating the nucleation factor transcription pathway (Nff2).	↓ the number of Gd uptake lesions (90-70%) and new lesions in T2 (85-74%).	Hot flashes, gastrointestinal discomfort, itching, proteinuria, ↑ transaminases, lymphopenia and infections.	RRMS (> 18y): first relapse or active MS (2 relapses in the last 2 years or 1 relapse in the last year that > 1p EDSS/or has radiological activity).
Natalizumab (TYSABRI®) (39)	Recombinant humanized monoclonal antibody (mAb) IgG4, inhibits the alpha-4ß-1 integrin of mononuclear leukocytes with its analog receptor VCAM1 present in the BBB endothelium. 300 mg intravenously every 4 weeks.	↓ 68% in the annual rate of relapses, ↓ in disability of 42-24%, ↓ in the number of new lesions or increases in size by 83%.	Headache, dizziness, vomiting, nausea, arthralgia, urinary tract infections, nasopharyngitis, tremors, fever, fatigue, urticaria, hypersensitivity, and progressive multifocal leukoencephalopathy.	RRMS: non-responders to the 1st line (recurrence in the previous year and >9 hyperintense lesions on T2 MRI or 1+ Gd enhancement) or severe, rapidly evolving RRMS (2 recurrences in the last year+ new activity on MRI).

Fingolimod (GILENYA®) (40)	Sphingosine 1-phosphate (S-1-P) related to 5 receptors: lymphocyte recirculation, neurogenesis, endothelial function, vasoregulation and cardiovascular development. It retains lymphocytes in the lymph nodes. Oral 0.5 mg/day.	↓ the severity of relapses, the need for hospitalization, and concomitant medication in addition to demonstrating a significant ↓ in the annualized rate of relapses.	Upper respiratory tract infection, headache, hypertension, and lymphopenia	Very active RRMS with recurrence the previous year in 1st line treatment and >9 hyperintense lesions on T2 MRI or 1 with Gd enhancement; o Severe RRMS, rapid evolution (2 relapses in the last year and new activity on MRI).
Anti-CD20 therapies (38)	The mAb binds CD20 on pre-B and mature B. Selective and transient but long-lasting depletion of L-B CD20+, preserving the pre-existing humoral response, innate immunity and L-T. Therapies: rituximab (1000 mg 2 doses separated by 15 days every 6 months), ocrelizumab, ofatumumab.	**Rituximab,** RRMS+PFMT = ↓ annual relapse rate, ↓ Gd lesions and T2/PPMS lesion volume= does not change progression (except <51 years). **Ocrelizumab,** RRMS=↓ number of new lesions and annual relapse rate/PPMS= ↓ progression, worst 55-step test, ↓ volume of the lesion in T2).	Infusion reactions (headache, sore throat, pyrexia, and hypertension), infections, neoplasms, hypogammaglobulinemia, and hypersensitivity reactions.	**Recurrent forms**: severe with rapid evolution ≥2 relapses in the last year and ≥1 Gd+ lesions or ≥2 new lesions in T2; that responds to the 1st or 2nd line and also: relapse >1p EDSS at 3 months or ↑ in the lesion load ≥ 2 T2 lesions or new spinal or posterior fossa lesions. **PPMS** if baseline EDSS ≤ 6.5 and one condition: if <10 years from symptom onset or 10-15 years with ↑ EDSS +/- relapses.
Cladribine (MAVENCLAD®) (42)	2-chloro-deoxy-adenosine (2CdA), a synthetic analogue of adenosine resistant to degradation by deoxycytidine kinase (CDK). It induces apoptosis of dividing lymphocytes by inhibiting key enzymes for DNA synthesis and repair. Oral 3.5mg/Kg.	EMRR, ↓ 57.6% relative in annual relapse rate, ↓33% in progression to disability	Lymphopenia, infections, neoplasms	Rapidly evolving severe relapsing MS (≥2 relapses last year+ ≥1 Gd+ lesions or ≥2 new T2 lesions). Active relapsing MS with treatment and ≥1: relapse +sequel >1p EDSS at 3 months or ↑ lesion load ≥2 T2 lesions or new spinal/ post-fossa lesions.
Alemtuzumab (LEMTRADA®) (43)	A Humanized anti-CD52 IgG1 kappa mAb, lysis against L-T and L-B by complement or antibodies and subsequent repopulation. 12 mg/day intravenously 5 days, with a second course of 12 mg/day intravenously 3 days one year later.	↓ of the annual rate of relapses, without statistically significant differences regarding the reduction of disability.	Infusion reaction (headache, rash, pyrexia), infections, stroke and cervical-cephalic arterial dissection, neutropenia and autoimmune hepatitis.	Very active RRMS: who have received an adequate full cycle of at least one disease-modifying treatment, or severe RRMS defined by ≥2 relapses in a year with ≥1Gd + lesions or increased T2 lesions.

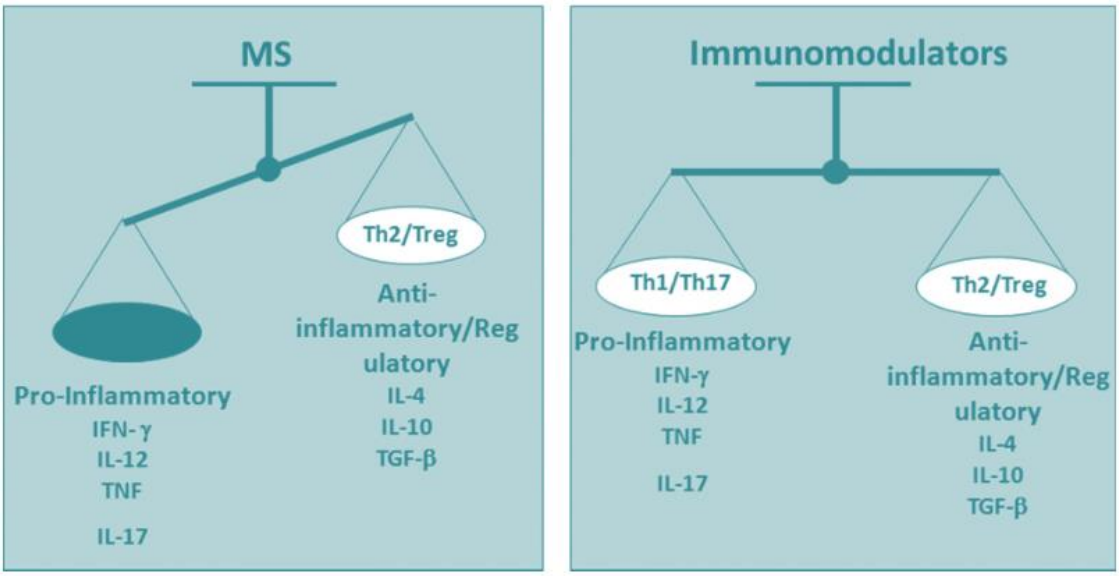


Figure 16. Cytokine imbalance in MS.

Data from *(15)*

Symptomatic and rehabilitative treatment

- **Rehabilitation**

The patient's approach must be **multidisciplinary**, directed by an expert neurologist, evaluated by the rehabilitation physician after the relapse and periodically in progressive phases, in addition to integrating occupational therapy and activities of daily living (35).

- **Motor disturbances**

  - Rehabilitation treatment:

The **motor deficit** must be treated by means of exercises of muscular empowerment, resistance to the effort and improvement of the motor activities. **Physiotherapy** and mobilizations have a role in the management of spasticity, transcranial magnetic stimulation is also recommended in some studies.

Physical exercise can have a positive effect on fatigue, improved functionality, muscle strength, aerobic capacity, and improved quality of life. Regarding ataxia, it is

speculated that lumbar stabilization exercises can improve some aspects of ataxia and instability of the disease.

If the patient has **impaired walking**, the use of an **orthosis** is recommended to facilitate it (crutch, cane, wheelchair) (35).

- Pharmacological treatment of spasticity:

There are different **drugs** available for the treatment of **spasticity**, but we must monitor the side effects (sedation, muscle weakness, ataxia and mental confusion): baclofen, tizanidine and tetrahydrocannabinol (THC) + cannabidiol (35).

- Treatment of the deambulation

Fampridine is the only one authorized to improve **gait** in adults with MS. It improves walking speed along with other symptoms such as fatigue, paraesthesia, spasticity and instability. Its mechanism of action is by blocking K + channels, increasing the conduction of action potentials in demyelinated axons. It is indicated in patients with an EDSS between 4 and 7. Among the adverse effects are described: urinary infection, insomnia, headache, dizziness, asthenia, nausea and paraesthesia (35).

- Treatment of tremor

The **tremor** is usually resistant to drug treatment; therefore, it is advisable to add physiotherapy to improve postural stability and try techniques and strategies to alleviate the tremor and stress management. There are a number of **drugs** that can be tried that have not been shown to be effective: propanolol, primidone, clonazepam, and ondasteron (35).

- **Fatigue**

There is no pharmacological treatment that has demonstrated a high degree of evidence regarding its effectiveness. The strongest evidence is **aerobic exercise**. In addition to non-pharmacological guidelines on conserving energy, aggravating factors must also be corrected: sleep disturbances, overweight, infections, intercurrent illnesses

and depression. For intercurrent treatment of **fatigue and depression**, fluoxetine is recommended. The **drugs** most used empirically to improve fatigue are: amantadine and modafinil (35).

To consider that there are some drugs that can cause fatigue as a side effect: baclofen, carbamazepine, tricyclic antidepressants, diazepam and interferon.

- **The pain**

It can be classified into:

1. Neuropathic or primary: caused by inflammation or demyelization of the CNS. Typical trigeminal neuralgia and Lhermitte. Can be treated with: carbamazepine, gabapentin, pregabalin.
2. Secondary or musculoskeletal pain. This pain is treated with anti-inflammatories, physical therapy and orthotics. Tricyclic antidepressants and serotonin and norepinephrine reuptake inhibitors can be tried for dysesthesias.

Although the sensitization of the inner and peripheral areas of pain is increasingly being demonstrated and therefore many studies recommend non-pharmacological treatment such as: aquatic exercises, yoga and more specifically neuromodulation techniques with transcutaneous electrical nerve stimulation (TENS) or transcranial stimulation by direct current (EMT) (35).

- **Paroxysmal symptoms**

It is important to avoid triggers (heat, exercise, neck flexion). If they require pharmacological treatment: carbamazepine, oxcarbazepine and gabapentin (35).

- **Swallowing, speech and language disorders**

We must consider speech therapy treatment. In addition, if we suspect swallowing problems, risk of aspiration or suffer from recurrent respiratory infections, we should carry out a study using video-fluoroscopy to establish an accurate diagnosis (35).

- **Cognitive disturbances**

The positive effect of neuropsychological treatment has been seen, although it only has a slight degree of evidence, mainly in relation to memory capacity, working memory and attention. It is recommended at the request of the patient and especially when it affects her functional, social or work activity. We did not find pharmacological treatment in this area (35).

- **Psychiatric disorders**

We must not underestimate the psychological and psychiatric problems of MS patients and they must be cared for appropriately. For mood disorders, selective serotonin and norepinephrine reuptake inhibitors are recommended along with psychological intervention with a cognitive-behavioural approach (35).

- **Involvement of bladder and sphincter function**

If they present urinary alterations, they should frequently be evaluated by a urologist with knowledge in neurology, requiring a urodynamic study to make the correct diagnosis. The use of sacral neuromodulation or the posterior tibial nerve has a control effect of the hyperactive buffet, on the other hand, in cases of incontinence, pelvic floor exercises are recommended. From the pharmacological point of view:

- **Spastic buffet:** the spasticity of the detrusor prevents the storage of urine leading to incontinence, we will give anticholinergic drugs to relax the muscle (tolterodine, oxybutynin, solifenacin).
- **Urinary retention sd:** relaxation deficit of the bladder sphincter or detrusor contraction deficit. An alpha-blocker such as tamsulosin can be used.
- **Mixed sd or detrusor dyssynergia:** coexistence of alterations of both spastic buffer and retention. They must be evaluated by the urologist; they can benefit from botulinum toxin (even sphincterectomy in severe cases).

We can also have intestinal alterations, for which we could recommend glycerine suppositories or microenemas, but for problems of difficult control or incontinence they should be evaluated by the specialist (35).

- **Sexual dysfunction**

In men we find erectile and ejaculation dysfunction and in women vaginal dryness, together they can present decreased libido and hypo or anorgasmia. We must consider the whole of the patient: neurological, emotional and pharmacological factors.

Pharmacologically, phosphodiesterase type 5 inhibitor drugs (vadernafil, sidernafil, tadalafil) are used in erectile dysfunction. If it is not effective, we can try intracavernous or intraurethral prostaglandin E1. For vaginal dryness they recommend lubricants for local use with estrogens at low doses (35).

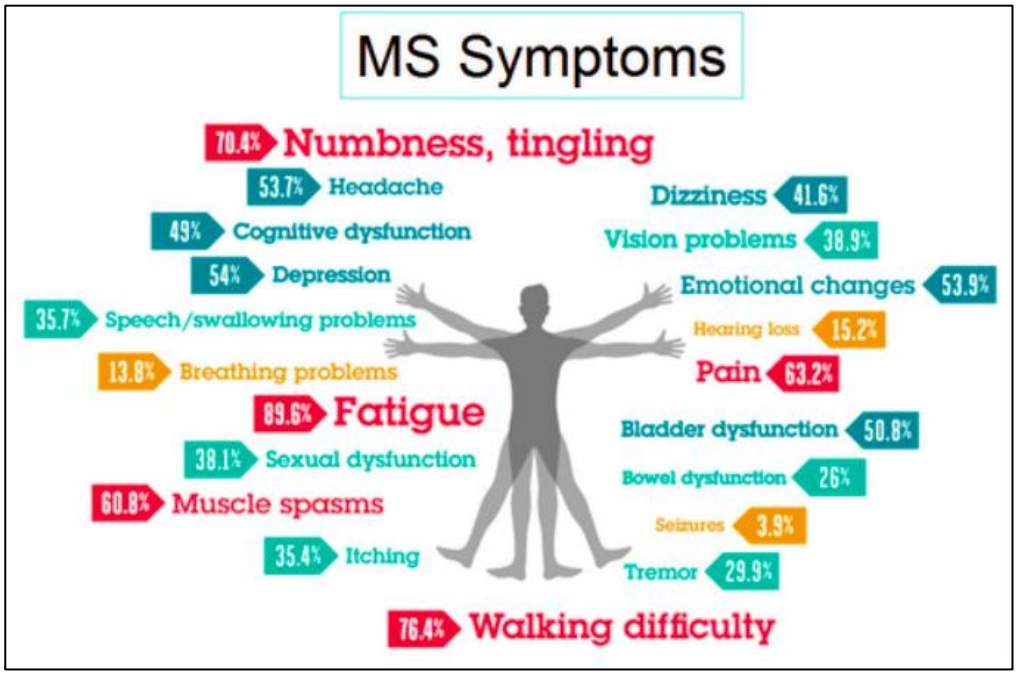


Figure 17: MS symptoms.

Data from *(45)*

1.11. PROGNOSIS

The prognosis of the disease depends on the clinical phenotype, the treatment of choice, the environment and the aggravating factors. Survival in MS patients after the onset of the disease is on average 35 years, with the peak of mortality being 55 and 64 years (46). In 50% of the cases, we found severe physical disability that prevents ambulation 15 years after the onset of the disease. The disease reduces life expectancy by 7 years compared to the general population. Regarding the age of onset, it has been observed that late onset tends to have a better outcome than early onset in younger patients (47).

Table 3. Prognosis indicators.

Data from *(47)*

FAVORABLE FEATURES	UNFAVORABLE FEATURES
○ Late age of presentation	○ First symptom at an early age
○ Female gender	○ Male gender
○ Optic neuritis as a presenting episode	○ Progressive course from presentation
○ Sensory symptoms as a presenting episode	○ Frequent exacerbations
○ Acute onset of symptoms	○ Poor recovery from exacerbations
○ Minimal residual disability after each exacerbation (excellent recovery)	○ Involvement of cerebellar or motor functions
○ Long interexacerbation period	○ Progressive form
	○ A high number of T2 lesions, infratentorial, Gd-enhancing

2. FATIGUE AND MS

2.1. INTRODUCTION

Fatigue in MS is extremely common. It may affect up to **80%** of the people with MS and can be severe in over 65-70% of the people. Nowadays there is no consensus for the definition of fatigue, nevertheless Lapierre and Hum recently defined it as subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual or desired. The pathological processes underlying MS-related fatigue are not yet well known (48).

2.2. PATHOPHYSIOLOGY OF FATIGUE

Myelin is important for the conduction and protection of the axon, which its destruction causes slowing or blocking of nerve conduction due to the disappearance of the saltatory conduction and exposure of K from the axon membrane, causing a prolongation of the refractory period and explains the fatigue of patients during exercise. Rapid recovery can be induced by resolution of edema and inflammation, however late recovery is attributed to the use of alternative axonal pathways, remyelination, or increased internodal Na channels. In the long run, the abnormal proliferation of Na channels in the membrane with entry of Na exchanged with Ca can cause **axonal damage** causing **degeneration**. Consequently, cumulative axonal damage is correlated with irreversible disability (7,13).

Fatigue

We found two types of MS-related fatigue: **peripheral** and **central**, with different mechanisms related to each one (49). Although the cause of MS-related fatigue still blur (50,51).

Table 4: Differing characteristics between central and peripheral fatigue.

Data from *(52)*

Fatigue type	Key Features	Physiological	Psychological	Neurochemicals Released
Central	Presence of both physical and mental fatigue, failure to sustain sustained mental tasks (e.g. mental arithmetic, remembering).	Impaired brain function Sleep problems Altered thought processes Brain atrophy Autonomous response (altered heart rate) during cognitive challenge.	Lassitude Inability to concentrate	↑ Cytokines (e.g. IL-6; IFN-alpha) ↑ hypocretin-1 ↓melatonin ↓HPA axis function
Peripheral	Failure to achieve motor and muscle activation and voluntary strength for maximum muscle force	Motor Weakness Reduced strength and endurance		↑ATP ↑TNF a ↑Interleukin 6 ↓acetylcholine

2.3. CLINICAL FEATURES

Fatigue is strongly related to the impact of MS. Relation to other clinical variables:

- Fatigue is worse in those with progressive disease and clearly worsens once ambulation is affected. It is a cause of **morbidity** even in non-ambulant patients.
- Exists a weak correlation in between with **anxiety and depression**
- **No** relation is found disease duration or patient age.
- **Sleep** is closely related to higher levels of fatigue, by excess or by default. The optimal would be 7.5 hours of sleep.

More work is needed to understand the causality behind the demonstrated associations (53).

2.4. SCALES

Fatigue vs fatigability, the term "**fatigue**" refers to perceived fatigue, as defined by a person's subjective experience using structured questionnaires directed at that experience. In contrast, **fatigability** is defined as a deterioration in the performance of

a task, generally due to the loss of resistance (54). Several scales have been developed to assess the level of fatigue in general populations and in those with MS:

- Fatige Impact Scale (FIS) was created in order to measure the impact of fatigue on the quality of life in chronic illnesses (55).
- The Modified Fatigue Impact Scale (MFIS) was created shortening the 40-item FIS. This resulted in a 21 item scale with nine “physical” items, 10 “cognitive items” and two “psychosocial” items (56).
- Fatigue Severity Scale (FSS) is a multidimensional scale that assesses psychosocial and generic aspects. It consists of 9 items with 7 possible values (57).

3. YOGA

The ancient practice of **yoga** started in India over 5000 years ago, it combines these elements with a philosophy of mind-body awareness (58). The term *yoga* is derived from the Sanskrit word *yukti*, meaning "union of body, mind, and spirit" (59), is classified by the National Institutes of Health as a form of Complementary and Alternative Medicine (**CAM**). Four basic principles are found on its practice and teaching (60):

1. [The] human body is a holistic entity comprised of various interrelated dimensions inseparable from one another and the health or illness of one dimension affects the other dimensions.
2. [individuals] and their needs are unique and therefore must be approached in a way that acknowledges this individuality and their practice must be tailored accordingly.
3. [yoga] is self-empowering; the student is his or her own healer.
4. [the] quality and state of an individual's mind is crucial to healing.

The practice consists of the union balance, strengthening, stretching, aerobic exercises and the consciousness of mind and body through breathing, postures and relaxation. There are different subtypes of yoga (61):

- **Hatha** and **Kundalini**, softer and focused on breath and poses
- **Iyengar** with focus on poses and the use of accessories
- **Ashtanga** and **vinyasa** typically more physically demanding
- **Bikram yoga**, which is taught in a hot environment, such practice is the least recommended in MS due to the sensitivity to heat.

Like meditation, the practice of yoga cultivates a way of being rather than performing a task.

3.1. BENEFITS OF YOGA

Different studies have been published in the last years investigating the effect of yoga in MS. As a review these studies have shown the benefits of yoga in multiple areas:

- **Chronic pain** reduction (59,60,62).
- Improvement of **quality of life (QoL)**: including depression, cognition and mental fatigue. To consider that depression can affect cognition, will to treatment and suicidal intention (60–66).
- **Body fatigue**, although the level of improvement was not significantly different from that of a conventional aerobic exercise regimen (60,61,64–71). **Step length, walking speed** and **balance** (56,59).
- **Urological improvement**: neurogenic dysfunction of the bladder, reduces post-mictional urine volume, miction frequency, incontinence and improvements in self-perception of urogenital disorder (59,61,74).
- Improves **sexual function** (75). **Eating disorders** (76)
- Improve **nervous, immune, and cognitive systems** (62). Improved **hippocampal volume, connectivity and memory** (77). **Autism spectrum disorder**, **Alzheimer's disease, epilepsy, fibromyalgia, peripheral nervous system disorders**, **chronic insomnia**(60)**, neuromuscular function** and **flexibility** (59).
- Improve **lower blood pressure** (59,60), **heart attack** and **stroke** (60).
- Improved **physical** and **emotional functioning**, including stress reduction, increased social interaction, increased body awareness, increased motivation, and shifts in attitude and life focus (59,60).

Yoga should be considered as a complementary therapy for medical treatment. This discipline offers people a timeless and holistic model of health and healing and, although it may not result in the complete elimination of physical illnesses and/or adverse conditions from the body, it offers a holistic path of healing. There is an indisputable connection between a person's overall physical and mental health and the inner peace and well-being that yoga is designed to achieve. Yoga suspends the fluctuations of the mind and by acting consciously we live better and suffer less (60).

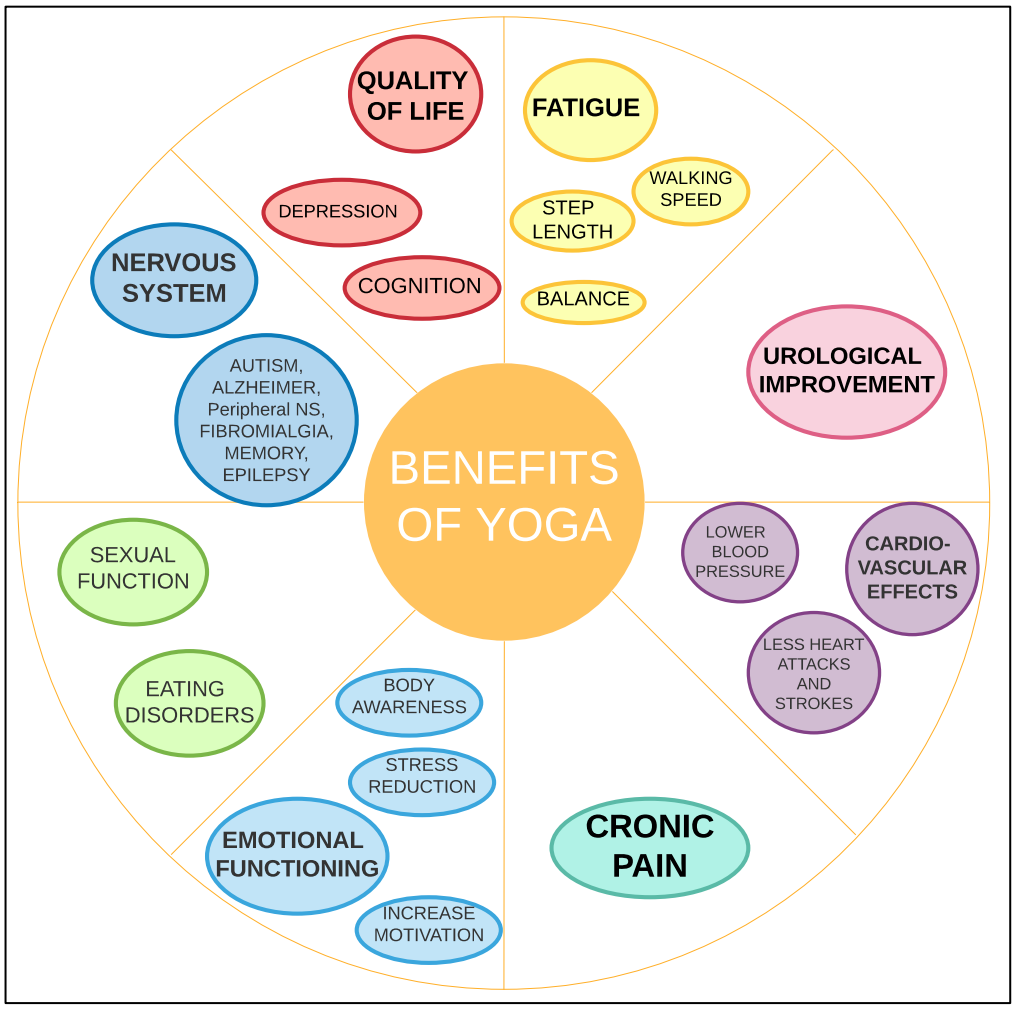


Figure 18: Benefits of yoga

(Own creation)

3.2. YOGA PRACTICE

The philosophy and practice of yoga were first described by Patanjali in the classical text **Yoga Sutras**. Within the 196 sutras we find components of yoga including mindful breathing, meditation, changes in lifestyle and diet, visualization and use of sound, among many others. We also find the **asanas** (physical practice), but we must not forget the rest, Patanjali describes an eightfold path to consciousness and enlightenment.

The practice is **personalized** and there are no guidelines regarding the frequency and duration, although the more you practice the greater. You must perform wisely and modify according to personal needs and goals. At the beginning, the highest possible frequency is crucial, the duration of the induction phase varies according to the physical condition and the state of health. The more difficult yoga is for someone at the beginning, the more their body needs (60).

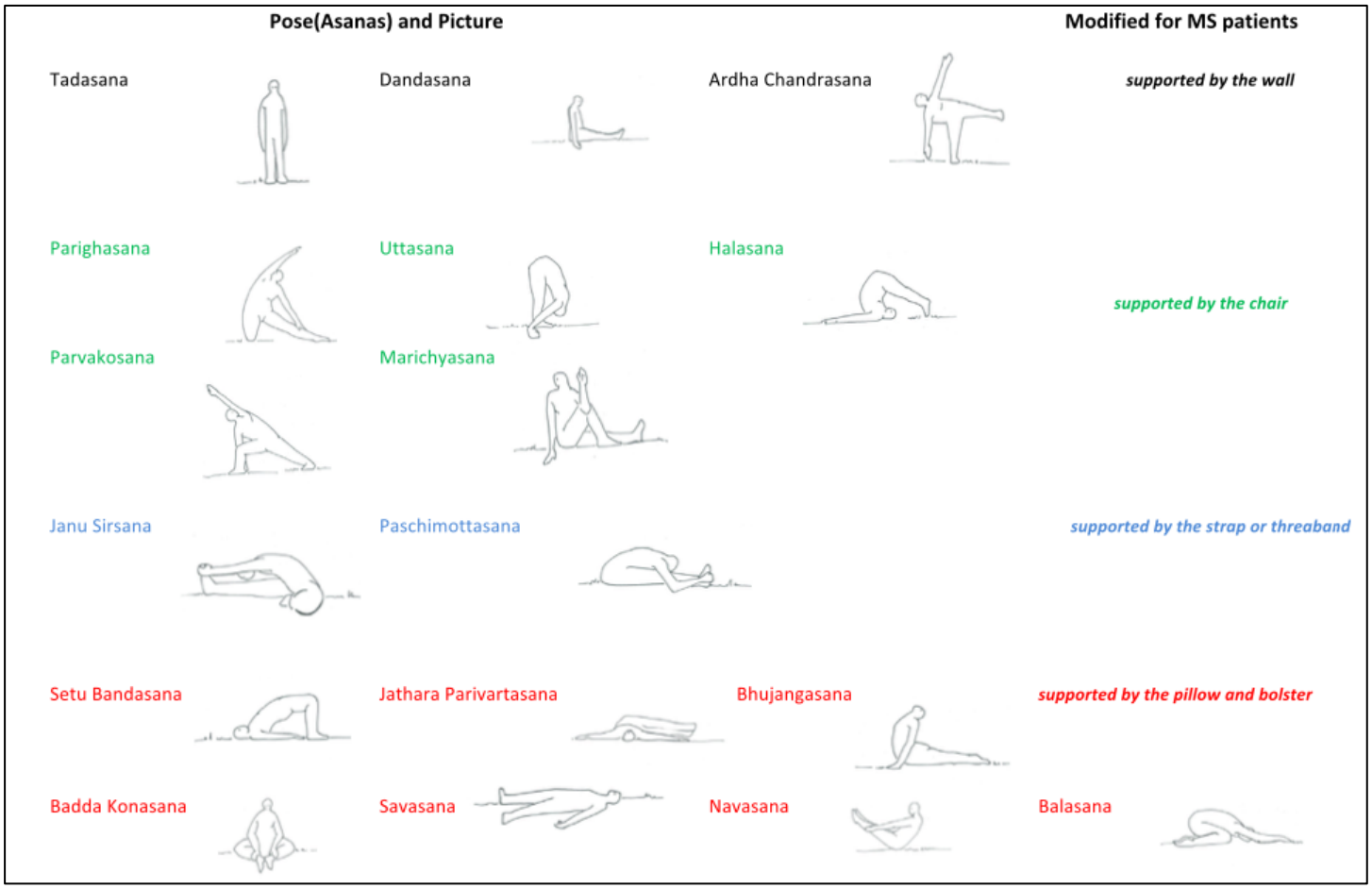


Figure 19. Pose -asanas- and pictures, modified for MS patients.

Data from *(72)*

Table 5. Yoga postures -asanas-

Data from *(72)*

Asanas	Poses	Possible and claimed benefits
Tadasana	Mountain Pose	Establishes well-aligned posture, strengthens thighs, knees, and ankles, firms abdomen and buttocks, reduces flat feet
Dandasana	Staff Pose	Strengthens the back muscles, stretches the shoulders and chest, improves posture
Savasana	Corpse Pose	Relaxes, calms the brain and helps relieve stress and mild depression, reduces headache, fatigue, and insomnia, helps to lower blood pressure
Uttanasana	Standing Forward Bend	Stretches thoracic and lumbar spines, hamstrings, calves, and hips, strengthens the thighs and knees, reduces fatigue and anxiety
Trikonasana	Triangle Pose	Strengthens and stretches the legs, hips, and spine, stimulates the abdominal organs, helps relieve stress
Baddha Konasana	Cobbler's Pose	Stretches the adductor muscles, improve hip mobility, and coordinate these with foot eversion, stimulates abdominal organs, ovaries and prostate gland, bladder, and kidneys, Stimulates the heart and improves general circulation, helps relieve mild depression, anxiety and fatigue
Halasana	Plow Pose	Calms the brain, stimulates the abdominal organs and the thyroid gland, stretches the shoulders and spine, reduces stress and fatigue
Bhujangasana	Cobra Pose	Strengthens and extends the upper back and neck.
Setu Bandhasana	Bridge Pose	Extends and strengthens the back of the body and open the chest and shoulder, extends the spinal range, stimulates abdominal organs, lungs, and thyroid, reduces anxiety, fatigue, backache, headache, and insomnia
Parighasana	Gate Pose	Laterally stretches the torso and one leg, improves lateral flexion, stretches hamstrings, opens the shoulders, stimulates abdominal organs and lungs.
Jathara Parivartanasana	Revolved Abdomen Pose	Mobilize the joints of the spine, strengthens transverse and oblique abdominal muscles, stretches the front of the shoulder.
Janu Sirsasana	Head to Knee Pose	Calms the brain and helps relieve mild depression, stretches the spine, shoulders, hamstrings, stimulates the liver and kidneys, relieves anxiety, fatigue, headache, menstrual discomfort
Balasana	Child's Pose	Passively flexes the lumbar and extends the thoracic spine and flexes the hips, calms the brain and helps relieve stress and fatigue
Navasana	Boat Pose	Strengthens the abdomen, hip flexors, and spine, stimulates the kidneys, thyroid and prostate glands, and intestines, helps relieving stress.
Marichyasana	Marichi's Pose	Uses the leverage of the arms and legs to align the sacroiliac joint, stretches the spine and shoulders, stimulates abdominal organs like the liver and kidneys
Parsvakonasana	Extended Side Angle Pose	Strengthens and stretches the legs, knees, and ankles, stretches the groins, spine, waist, chest and lungs, and shoulders, stimulates abdominal organs
Paschimottanasana	Seated Forward Bend Pose	Strengthens the back and legs, calms the brain and helps relieve stress and mild depression, stretches the spine, shoulders, hamstrings, stimulates the liver, kidneys, ovaries, and uterus, soothes headache and anxiety and reduces fatigue
Ardha Chandrasana	Half Moon Pose	Strengthens the abdomen, ankles, thighs, buttocks, and spine, stretches the groins, hamstrings and calves, shoulders, chest, and spine, improves coordination and sense of balance, helps relieving stress

3.3. YOGA AND FATIGUE

Years ago it was thought that **exercise** worsened MS fatigue and overheating problems, today it is recognized as a **beneficial therapy** (70). **Fatigue** is one of the most

common and worrisome symptoms of MS, unfortunately drug treatment provides limited relief. That is why the ban is open to mind and body techniques that have a calming effect on the autonomic nervous system. There is no complete review that evidences the pathophysiology of said benefit, although there is **no** evidence that indicates that they are **harmful** (61).

Possible pathophysiology on the benefit of exercise

As for the pathophysiology of the effects of yoga in patients with multiple sclerosis, it is unknown. Although yoga is considered an aerobic sport and there is literature regarding the possible benefits of aerobic exercise in MS patients for the improvement of fatigue. We use the term possible since we are dealing with different hypotheses and therefore, we cannot clarify that it is the definitive mechanism, although it is worth reviewing it. Hypothesis on the relationship between the benefit of exercise on fatigue in MS (78):

- **Cytokines.**

Regarding the process of demyelination and axonal damage, we found a wide participation of the cytokines **IL-6, TNF-α and INF-γ** (79). Elevated concentrations of these proinflammatory **Th1** cytokines can contribute to neurodegeneration and disability (80). Exercise can help **reestablish the imbalance** as it provides an increase in **Th2** anti-inflammatory cytokines (such **as IL-4 and IL-10**) (81). Regarding this theory, we know that a clear pattern of responses has not been found, but we can affirm that a single exercise session influences inflammatory cytokines and that chronic changes occur in the concentration of various cytokines at rest after a training period (78).

- **Neurotrophic factors.**

Proteins that prevent neuronal death and promote the process of neuronal recovery, regeneration and remyelination throughout life (82). Among the most studied we find: **brain-derived neurotrophic factor** (BDNF) and **nerve growth factor** (NGF) (81). Studies have been found on the effects of exercise on trophic factors (83).

However, it should be emphasized that it cannot be clearly established whether exercise has a disease-modifying effect or not in patients with MS, but there are studies that indicate that this is the case (78).

- **Relationship of stress and the immune system.**

The neuroendocrine changes and the resulting immune responses associated with stress and the possible mechanism of action of Yoga. In the image: solid lines indicate a stimulating effect and dotted lines indicate an inhibitory effect (84):

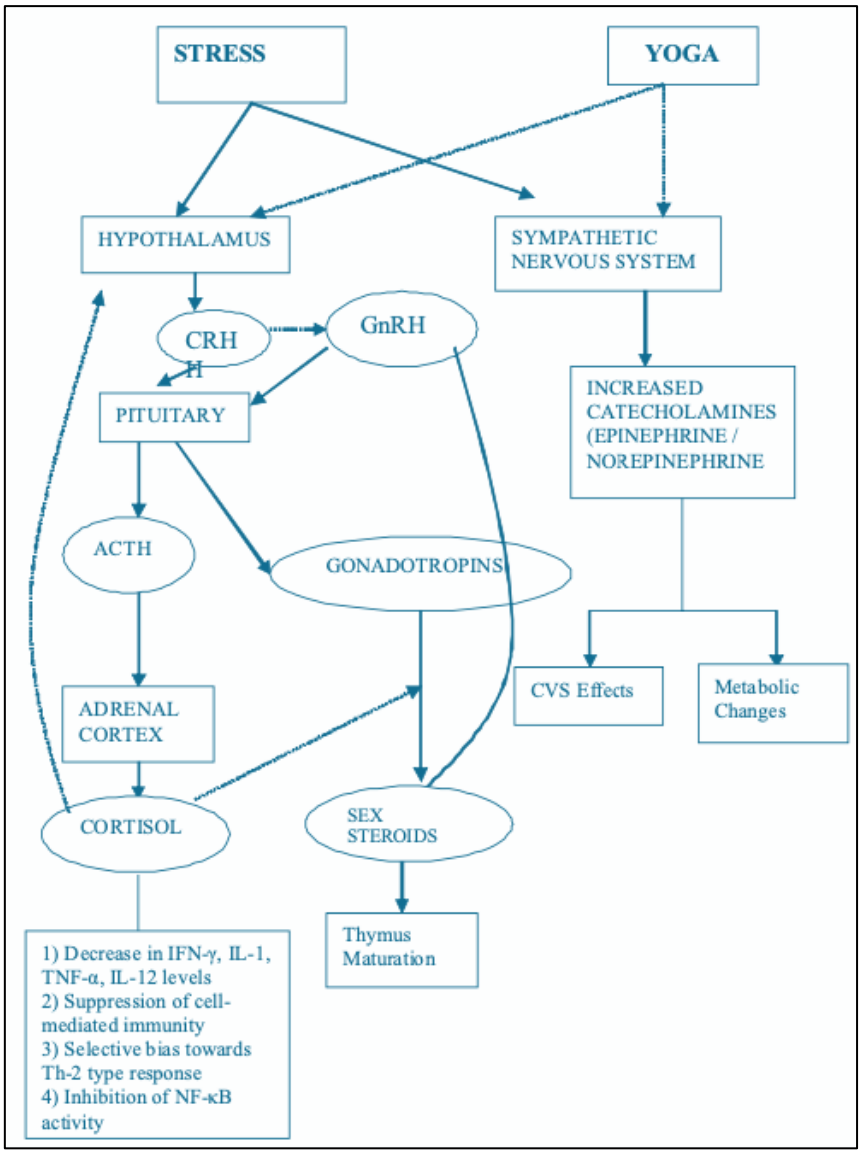


Figure 20: Modulation of immune responses in stress by yoga.

Data from *(84)*

- **Inhibits** the posterior or **sympathetic** area of the hypothalamus optimizing sympathetic responses and restoring autonomic reflexes associated with stress. The parasympathetic may or may not be affected.
- Hypothalamus and limbic system (in charge of emotional expression) is modulated through yogic practice, **inhibiting** areas responsible for fear, aggressiveness, and anger and **stimulating** gratifying centers of the middle forebrain and other areas, a fact that provides a state **of happiness and pleasure**. As a **result**: lower anxiety, heart and respiratory rate, blood pressure, and cardiac output.
- There is also the inhibition of the paraventricular nuclei of the hypothalamus, consequently affecting the anterior pituitary gland by **reducing** the production of ACTH, causing a decrease in cortisol and PNMT (phenyl-ethanolamine-N-methyl transferase) at the level of the adrenal glands. Consequently, the reduction of steroids and catecholamines reduces stress. All this leads to a **decrease** in INF-γ, IL-1, IL-12 and TNF-α, a suppression of cell-mediated immunity, selective bias towards the **Th-2 type response**, inhibition of NF-Kß activity.

3.4. LITERATURE REVIEW

Regarding MS and yoga, we find varied literature, in which the benefit of yoga is found in relation to the improvement of fatigue.

Although there are certain limitations regarding these studies (60,61,64–71):

- The mechanism of action by which yoga improves fatigue in MS has not been found. We also know that both aerobic exercise and yoga have shown statistically significant improvement in fatigue (61). This is the reason why none intervention is more recommended than the other, despite the fact that yoga obtains more significant results.
- The sample size, generally in the different yoga studies that we found, is small, ranging from 11 to 76 patients, with studies with a low number of patients predominating, a fact that limits its reliability.
- Regarding the duration of the studies, we found short-term studies (less than 4 weeks) to mid-term studies (no longer than 6-months)

- About the duration, there is an article of 6 weeks (short term) that has not shown significant differences (85).
- Furthermore, in most of the articles the MS phenotype was not specified despite its importance in the person's disability.
- Some determine that some benefits could be conferred through social interactions during group exercise.
- We ran into some studies with lack of random sampling.
- We found absence of a control group in some studies.
- Some studies have a high percentage of dropouts, observing up to 33%.
- The sample of the different studies is not homogeneous for sex and therefore the results are not generalized to both sexes.

4. JUSTIFICATION

Multiple sclerosis is a **chronic autoimmune demyelinating** disease of the **CNS**, the presentation is **early** and there is a **progressive potential** of the disease. Regarding the complete understanding of the pathophysiology, nowadays it is still unknown fact that makes it more difficult to treat correctly.

Fatigue is one of the most disabling symptoms of these patients and the most prevalent of the disease, occurring in up to 80% of them. We know the effect of the demyelination of the disease that leads to a defective transmission that can be the cause of said fatigue, but we do not have any pharmacological treatment that has demonstrated a high level of evidence regarding its efficacy.

Considering the early presentation of this disease, with life expectancy close to the general population, research **efforts** should focus on knowing the mechanism that triggers the disease, its pathophysiology, how to slow down its evolution and **improve the quality of the day** as much as possible.

In this study we analyze the effect of **yoga** to improve **fatigue** in MS, since it has been seen that it can be beneficial in alleviating fatigue in patients with MS, beyond other **multiple benefits**. That is why we consider yoga as the main promoter to alleviate fatigue and not only aerobic exercise, given the multiple benefits described that we can obtain.

For this reason, the intention is to carry out a **protocol** that mitigates the limitations of the studies published today, in order to be able to recommend to our patients a **complementary technique** to the usual treatment.

5. HYPOTHESIS

Main hypothesis

The performance of the practice of **yoga** leads to an improvement of **fatigue** in multiple sclerosis.

Secundary hypothesis

- Yoga determines an improvement in the **quality of life** in patients with multiple sclerosis.
- Yoga leads to an improvement in **gait speed** and **balance**.
- Yoga provides a decrease in **kinesiophobia**.
- Yoga leads to an improvement in the **quality of sleep**.
- Yoga leads to decreased **depression** and improved mood.
- Yoga leads to an improvement in **sexual function.**
- Yoga leads to a reduction in **relapses** of MS patients.

6. OBJECTIVES

Main objectives

The main objective of this study is to compare the improvement in **fatigue** between two groups: an intervention group that will perform **yoga** and another, the **control group**, that will carry out their activities of ordinary life.

Secondary objectives

- To determine an improvement in the **quality of life** in the yoga intervention group compared to the control group.
- To analyze the improvement in **gait speed** and **balance** in patients who carry out yoga practice compared to the control group.
- To examine the decrease in **kinesiophobia** due to yoga compared to the control group.
- To observe the improvement in the **quality of sleep** in patients who perform yoga practice compared to the control group.
- To establish a decrease in **depression** and an improvement in mood in patients who practice yoga compared to the control group.
- To specify the improvement of **sexual function** in the group that practices yoga compared to the control group.
- To detect a decrease in **relapses** in patients who practice yoga compared to the control group.

7. MATERIALS AND METHODS

7.1. STUDY DESIGN

The study will be an **analytical, randomized, prospective, controlled, single blind clinical trial**. The patients will be randomly assigning two groups with a 1:1 ratio: first one, intervention group, will carry out the yoga sessions and the second group, control, will carry out the ordinary activities of daily living. Due to the impossibility to blind the intervention group, it will be a single-blind study. The study will last **6-months**.

Table 6: Study design summary.

STUDY TYPE	Interventional: clinical trial
HEALTH CARE CENTER	Single-center: Hospital Santa Caterina (Girona)
ALLOCATION	Randomized 1:1 ratio
CONTROL TYPE	Ordinary activities of daily living
INTERVENTION MODEL	Yoga practice
MASKING	Single blinded, due to the impossibility to blind the intervention group
PRIMARY PURPOSE	Intervention

7.2. STUDY POPULATION

The study population will be patients between **18 and 65 years of age**, diagnosed with MS in accordance with **the McDonald criteria 2017** who carry out their **follow-up** in the multiple sclerosis unit of the Santa Caterina Hospital in Girona. The neurologists of this unit will propose to the patients to participate in this **6-month** clinical trial as long as they meet the inclusion criteria and none of the exclusion criteria.

Inclusion criteria

- To be diagnosed with **MS** for at least 6-months (any phenotype), with an **age** between 18 and 65 years old.

- Presents **fatigue** assessed by the neurologist and scaled by MFIS, knowing that >38p on the scale is considered fatigue (57).
- Expanded Disability Status Scale (**EDSS**) score of between one and seven.
- To be residing in the city of **Girona** or have a means of transportation to get to the Santa Caterina hospital.
- **Relapse-free** period of 6-months prior to the study.
- **Willingness** to participate in the study and signature of **IC**.
- Commit not to make changes in the **diet**, and not have made any changes in the last month.
- Patients who take **medication for fatigue**, to participate in the study **must have taken it for at least 6-months** and still have fatigue, since the effects of these medications may take time to take effect.

Exclusion criteria

- Patients with **terminal disease** or another disease that could interfere in the study.
- The need for **major surgery** during the study period.
- **Unwillingness** for cooperation.
- A **relapse** during the study.
- **Pregnant** women.

Withdrawal criteria

- The patient meets the exclusion criteria or ceases to meet the inclusion criteria at some point in the clinical trial (either recently developed or previously unrecognized).

Participants are free to withdraw from participation in the study at any time. He/she should tell the research team that he/she intends to withdraw.

7.3. SAMPLE

Sample size

Accepting an **alpha risk** of 0.05 and a **beta risk** of less than 0.2 in a bilateral contrast, 44 subjects in the first group and 44 in the second are needed to detect a difference equal to or greater than 1.9 units. The common **standard deviation** is assumed to be 2.9. A **follow-up loss rate** of 15% has been estimated (86). **GRANMO** sample size calculator has been used to calculate the sample. The data used for the calculation of the sample are collected in the following article (67).

Sample selection

The non-probabilistic consecutive sampling method will be carried out until 88 subjects are obtained.

Potential patients who meet the **inclusion criteria** will be recruited, **randomly selected**, and invited to participate by phone. People who wish to participate will be asked to attend personally where they will be given all the information regarding the study, both verbal and written (Annex C), as well as the possible risks and complications. All participants who were finally willing to participate had to read and sign the informed consent (IC) (Annex D). Only if these steps are done correctly will the individual participate in the study.

7.4. VARIABLES

Independent variables

The independent variable in our study is **yoga**. Since we want to observe how yoga affects fatigue. It is a dichotomous nominal qualitative variable, expressed by yes or no, depending on whether you participate in the intervention group or not.

Hatha techniques, among the different types of yoga, have shown benefits in other symptomatology beyond fatigue, in modifying physical pain and quality of life for example, that is why we will use this modality in the study (62).

Dependent variables

- **Main dependent variable:**

The main dependent variable is the reduction in **fatigue**. It is a continuous quantitative variable. To assess this symptomatology, we have the Modified Fatigue Impact Scale (**MFIS**) (Annex E). The scale questionnaire consists of a self-report of 21 items recommended by the Multiple Sclerosis Council for Clinical Practice Guidelines (40,76,77):

- Physical subscale: this scale can range from 0 to 36. It is calculated by adding the raw scores of the following elements: 4+6+7+10+13+14+17+20+21.

- Cognitive subscale: this scale can range from 0 to 40. It is calculated by adding the raw scores of the following items: 1+2+3+5+11+12+15+16+18+19.

- Psychosocial subscale: this scale can vary from 0-8. It is calculated by adding raw scores in the following elements: 8+9

- MFIS total score: the MFIS total score can range from 0 to 84. It is calculated by adding scores on the Physical + Cognitive + Psychosocial subscales, in which we find that scores greater than 38 points are considered fatigue.

- **Secondary dependent variables:**

- Quality of life

It is a quantitative, discrete, continuous variable. To assess health-related quality of life we have the **short form-36** (SF-36) (Annex F), Health Status Questionnaire. This instrument addresses health concepts that are relevant to MS patients from the patient's perspective. There is no single global score for the SF-36, but it does generate 8 subscales and two summary scores. The 8 subscales are: physical functioning, role limitations due to physical problems, bodily pain, general perceptions of health, vitality, social functioning, role limitations due to emotional problems and mental health. The two summary scores are the physical component summary and the mental component summary.

The scales are set up so that a higher score indicates better health. To achieve this, 10-item responses are recoded before being added to other items on the same scale. The raw scale scores are then transformed to a 0-100 scale (87).

- Gait speed

It is a continuous quantitative variable. **The 25-foot timed walk** (T25-FW) (Annex G) is a quantitative test of performance of leg function and mobility based on a 25-foot timed walk, this test is consistent in evaluating improvement in gait speed. It is the first component of the MSFC that is administered at each visit. The patient is directed to the end of a clearly marked 25 foot path and instructed to walk 25 feet as quickly as possible, but safely. The time is calculated from the start of the instruction to begin and ends when the patient has reached the 25 foot mark. The task is re-administered immediately by having the patient walk back the same distance. Patients can use assistive devices when performing this task (88).

- Balance

It is a quantitative, discrete, continuous variable, which is assessed using the **Brief Test of Equilibrium Assessment Systems** (Annex H): the eight test items cover the six equilibrium subsystems, and the administration time is less than 10 minutes, making it more feasible in daily clinical practice. The 8-item Brief-BEST test was the main measure of interest. Each individual item was rated on an ordinal scale from 0 to 3, yielding a maximum possible score of 24. Higher scores indicate better balance performance (89).

- Kinesiophobia

It is a quantitative, discrete, continuous variable. **Tampa Scale for Kinesiophobia** (Annex I) is a self-report measure developed to assess "fear of movement-related pain" in patients with musculoskeletal pain. Total scores vary between 11 and 44 (22).

- Quality of sleep

It is a quantitative, discrete, continuous variable. We can assess sleep quality using the **Pittsburgh Sleep Quality Index** (PSQI) (Annex J) assesses 19 items that are grouped into seven component scores, each equally weighted on an 0-3 scale. The scores for the seven components are then added together to produce an overall PSQI score, which has a range of 0-2I; higher scores indicate poorer quality of sleep (90).

- Depression

It is a quantitative, discrete, continuous variable, which we measure using the **Beck Depression Inventory** (BDI) (Annex K) of 21 items. It is one of the most popular measures of depressive symptoms worldwide. The BDI takes approximately 10 minutes to complete (91).

- Sexual function

It is a quantitative, discrete, continuous variable. Changes in sexual functioning and intercourse are also common in MS, although health professionals are often unaware of these problems because many patients are reluctant to mention them, the **Sexual Satisfaction Scale** (SSS) (Annex L) is a good methodology for evaluate this area. The raw scores for the 4 sexual satisfaction items (Items 2-5) are added together to create a total score. Therefore, this scale can range from 4 to 24. Higher scores indicate greater problems with sexual satisfaction (87).

- Presence of relapses

Since we want to observe the reduction of these events in our intervention group, with respect to the control group. It is a dichotomous nominal qualitative variable, expressed by yes or no.

Covariates

- **Age**: is a variable that can affect the time of fatigue that a person can have. Measuring it in years it is a discrete quantitative variable.
- **Sex**: female or male, is a dichotomous qualitative variable, to be taken into account in our study design, given the high prevalence of this disease on the female sex.
- **Beliefs**: the variable will be classified as qualitative dichotomous, depending on whether it has beliefs or not. We will ask our patient if he is religious, if he/she answers yes, we classify him in the section of beliefs YES. In the case that the answer is no, we must ask if he has any belief beyond the religious one that moves him on a daily basis (Mother Nature, love, incompressible forces), if the answer is yes, we classify in the YES section.
- **EDSS**: in our study we intend to encompass a wide range of disability of the EDSS compared to other designs, knowing that yoga is a practice that can be done sitting down, although it may need help to enter certain postures depending on the degree of mobility, we have the advantage of an instructor, and we can take advantage of it. It is a discrete quantitative variable since a numerical value is established for the degree of physical disability (Annex B).
- **MS Phenotype**: it is a polytomous qualitative variable (if we include RRMS, PPMS and SPMS). It is not a mystery that there is different clinical affectation in MS depending on the phenotype and therefore the symptomatology can be more or less affected.
- **Physical activity**: since we have a control group that will continue to carry out their activities of ordinary life, it would be convenient to divide it into physically active or not, since it could alter the results. It will be a dichotomous qualitative variable. We will consider physically active to that person who carries out physical activity 1 hour at least two days a week.
- **Employment status:** we are interested in knowing if the patient has a mentally active life, therefore, knowing his occupation (if he studies, works or, on the contrary, is unemployed). Qualitative polytomic variable.

- **Receives treatment for MS**: dichotomous qualitative variable, since we are interested in knowing whether or not they receive disease-modifying treatment.
- **Treatment for MS**: in the event that you receive disease-modifying treatment, it will be necessary to specify which one. Therefore, it is a polytomous qualitative variable.

Table 7: Variable's summary

	Variable	Description of the variable	Measure instruments	Categories or Values
Independent variable	**Yoga**	Dichotomous, nominal qualitative	Case report form	Yes / No
Dependent variable	**Fatigue**	Continuous, quantitative, discrete	MFIS scale	0-84
	Quality of Life	Continuous, quantitative, discrete	SF-36	0-100
	Gait speed	Continuous, quantitative, discrete	T25-FW	seconds
	Balance	Continuous, quantitative, discrete	The 8-item Brief-BEST	0-24
	Kinesiophobia	Continuous, quantitative, discrete	Tampa Scale for Kinesiophobia	11-44
	Quality of sleep	Continuous, quantitative, discrete	PSQI	0-21

	Depression	Continuous, quantitative, discrete	BDI	0-62
	Sexual function	Continuous, quantitative, discrete	SSS	4-24
	Presence of relapses	Dichotomous, nominal qualitative	Case report form	Yes / No
Covariates	Age	Continuous, quantitative, discrete	Medical history	Years
	Sex	Dichotomous qualitative	Medical history	Male/female
	Beliefs	Dichotomous qualitative	Medical history / case report form	Yes / No
	EDSS	Continuous, quantitative, discrete	Medical history / case report form	0-10
	MS phenotym	Polytomic qualitative	Medical history / case report form	RRMS / PPMS / SPMS
	Physical activity	Dichotomous qualitative	Medical history / case report form	physically active / not physically active
	Employment status	Polytomic qualitative	Medical history / case report form	Studies/work/ unemployed

	Receives treatment	Dichotomous qualitative	Medical history / case report form	Yes / No
	Treatment for MS	Polytomic qualitative	Medical history / case report form	Medicine the patient takes

7.5. PROCEDURES

Once the sample has been recruited in accordance with the inclusion and exclusion criteria, the patients will be asked to sign an informed consent in which they agree to participate in the 6-months study. Subsequently:

- **The intervention group**: will meet twice a week to carry out the yoga practice that will last 1 hour. It will take place at the Santa Caterina Hospital, at the afternoons.
- **Both groups**:
  - They will have 3 visits with the **neurologist**: the first recognition, in the middle of the study (the third month) of follow-up and the last one at 6-months from the beginning.
  - In addition, they will meet with **nursing** at the beginning and at the end of the study, this team will be the **blinded**, and therefore the one in charge of the different scales.

Many of the scales used in our study can be performed in the waiting room of the MS unit of Hospital Santa Caterina. For this we would need an electronic device such as a tablet that would facilitate filling the scales

Objectives per week

Each week of the study will have a defined objective, since the practice will not be the same throughout the 6-months:

- July:
    - 1st: learn to control the breath and the different types of breaths.
    - 2nd: lead the breath with the practice of the asanas
    - 3rd: know the different techniques of meditation, relaxation and visualization, to be able to put them into daily practice at home, inducing a state of spiritual consciousness (integrating body, mind and spirit).
    - 4th: begin the practice of flexibility, opening of the hips.
- August:
    - 1st: improve attention and concentration.
    - 2nd: start spinal twists, learn to develop your own intention for each practice.
    - 3rd: strengthen the lower body and learn to channel emotions.
    - 4th: Strengthen the upper body, start inverted postures and develop body awareness.
- September:
    - 1st: practice balances together with the control of the own body during the asanas.
    - 2nd: strengthen the lower body and increase the ability to concentrate.
    - 3rd: spinal twists and detachment lessons.
    - 4th: strengthen upper body, continuation of inverted postures and stimulate our nervous system.
- October:
    - 1st: reinforce flexibility, continuation of balance and develop respect and sensitivity towards our body.
    - 2nd: strengthening of the lower body, balance and learning to relax our body and focus our attention.
    - 3rd: upper body strengthening, continuation of inverted postures and boosting self-esteem.
    - 4th: strengthening of the posterior muscles of the back together with turns of the spine and deepening of the breath.
- November:

- 1st: upper body practice together with inverted postures, development of inner peace and stillness.
- 2nd: lower body practice along with balances, bring attention to postures.
- 3rd: reinforce flexibility and continuation of balance, improve coordination.
- 4th: strengthening of the posterior muscles of the back together with turns of the spine, strengthening of relaxation techniques.

- December:
  - 1st: reinforce flexibility, continuation of balances and emphasize self-esteem.
  - 2nd: lower body practice along with balances and improving self-control.
  - 3rd: upper body practice together with inverted postures, anxiety control.
  - 4th: Posterior back musculature strengthening along with spinal twists and practicing gratitude.

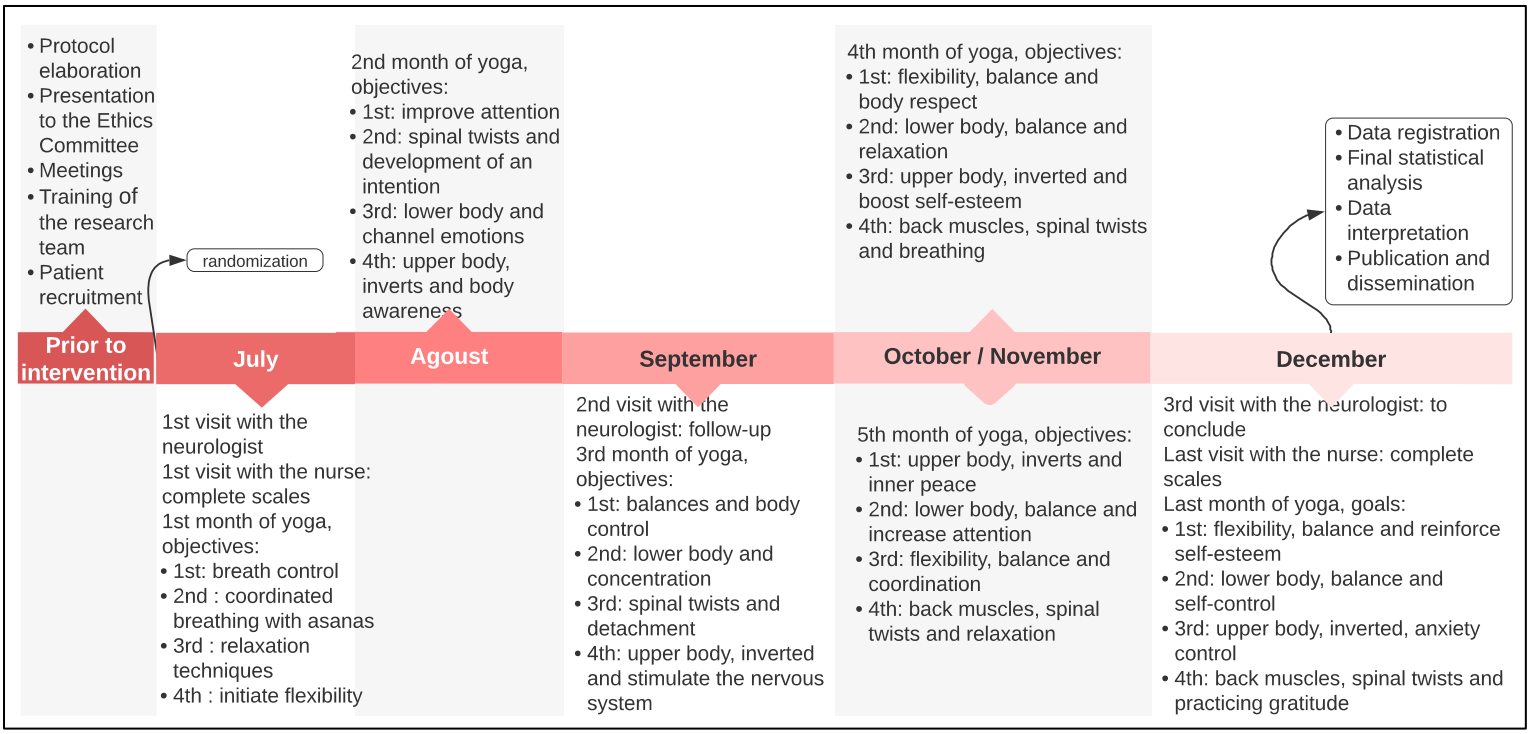


Figure 21: Summary yoga purposes per week.

Yoga program:

The **hatha** yoga practice is a 1-hour manual class. Among the 44 people who will be part of the intervention group, they will be divided into two subgroups so that the yoga classes are for 22 people, a smaller group.

- *Instructors*

Our **instructors** will conduct a guided practice that includes acknowledging the validity of participants' pain and fatigue and gently challenging them to try a new way of coping; discuss and model acceptance of one's own physical abilities; frequently demonstrate and encourage mindful attention to the present moment; emphasize breathing in each part of the class; and teach the class at a slow pace.

All **participants** will start sitting on a chair along with their respective blocks and mats. The teachers will adapt the practice to the physical capacities of each participant; therefore, some participants continued to use the chair for balance during class, while others did not. That is why we are going to need **two yoga teachers** so that one of them helps those who have more difficulties to enter the asanas (92). In each session, three aspects are practiced: mind control, breath control, and slow body movement (61).

- *Breathing*

Throughout the entire practice, "**prāṇāyāma**" breathing is practiced, a term that derives from the Sanskrit that designates the breathing exercises of yoga that lead to the concentration and control of prana (energy contained in the body's breathing), therefore when we control prana, we control vital energy. Within breathing we find different modalities (92):

- Bhastrikā: rapid and powerful inhalations and exhalations by means of the force of the diaphragm, letting the air sound when exhaling.
- Nāḍī Śoḍhana: from Sanskrit, "nadi" means 'to channel' and "shodhana" means 'purify, cleanse'.
    - **Hand position** "Mrigi mudra": It consists of flexing the index and ring fingers of the hand.
    - **Breathing**: Gently close the right nostril with the thumb, inhale through the left, then close the left nostril with the ring and little

fingers and exhale slowly through the right. Keeping your right nostril open, inhale, close it, and slowly open and exhale through the left. This is a cycle. Repeat 3-5 times and then release the hand mudra and return to normal breathing.

Figure 22: Mrigi mudra.

Data from *(93)*

- *Practice*

All the **sessions** throughout the weeks will follow this script, except for point 4 in which we will find different postures "asanas" throughout the different sessions (92).

1. Greeting and discussion of practice at home.
2. Focus the awareness on the body and on the breath followed by a sound tone "mantra" typically the "Om".
3. Warm-up movements including cat-cow, a side stretch, shoulder rolls, and neck lengthening with neck release.
4. A sequence of asanas depending on the objective of each practice, modified by a chair for those patients with disabilities.

   Each pose will be held for approximately 5 breaths with rest periods between poses. Patients should be encouraged to respect their individual limits and appropriate modifications should be taught for those with reduced ability (67).
5. Then the final relaxation posture "Śavāsana", progressive relaxation techniques, visualization and meditation.
6. Finally final sitting meditation and discussion of the practice at home.

- *Asanas*

The Sanskrit "asanas" means seat as it was the posture in which yoga practitioners meditated. Today we use it to refer to the different postures that we can carry out, below I present a series of postures with and without modification, **adapting them to patients with MS**:

- **Heating:** cow stretch, cat stretch, sun salutation.
- **Upper body:** Adho Mukha Svanasana, Chaturanga Dandasana, Raja Bhujangasana sospesa, vasisthasana, Makara Adho Mukha Svanasana, Ardha Pincha Mayurasana, Pada Adho Mukha Svanasana, Balasana.
- **lower body:** Garudasana or eagle posture, Virabhadrasana I or Warrior Posture I, Virabhadrasana II or Warrior Posture II, Utkatasana, strong pose or chair pose.
- **Posterior back muscles:** Bhujangasana or cobra pose, Setu Bandha Sarvangasana or half bridge pose, Balasana or child pose, Salamba Bhujangasana or sphinx pose.
- **Spinal twist:** Parswa Halasana, Parivrtta Janu Sirsasana, Jathara Parivartanasana or reclining pose with twist, Ardha Matsyendrasana or seated half twist pose.
- **Balances:** Virabhadrasana III or Warrior Posture III, Bakasana or crow pose, Ardha Chandrasana or half-moon pose, Natarajasana or dancer's pose.
- **Flexibility:** Hanumanasana or split pose, Paschimottanasana or clamp pose, Kapotasana or pigeon pose, Baddha Konasana or throne pose.
- **Inverted postures:** Sirsasana, Halasana, Urdhvadhanurasana or wheel pose, Salamba Sirsasana or tripod pose.

Figure 23: sun salutation with and without chair.

Data from *(94,95)*

Figure 24: Variation of asanas on a chair.

Data from *(96)*.

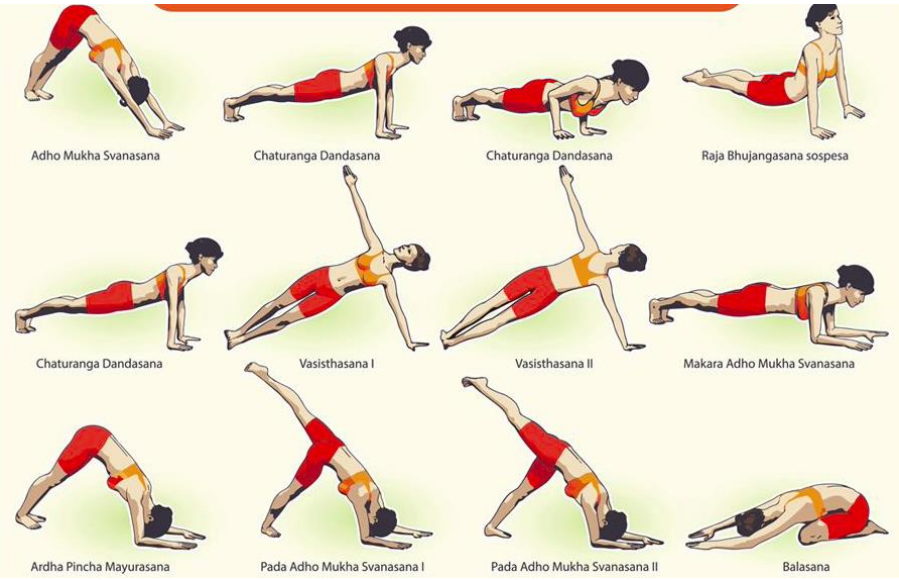


Figure 25: Upper body asanas.

Data from *(97)*

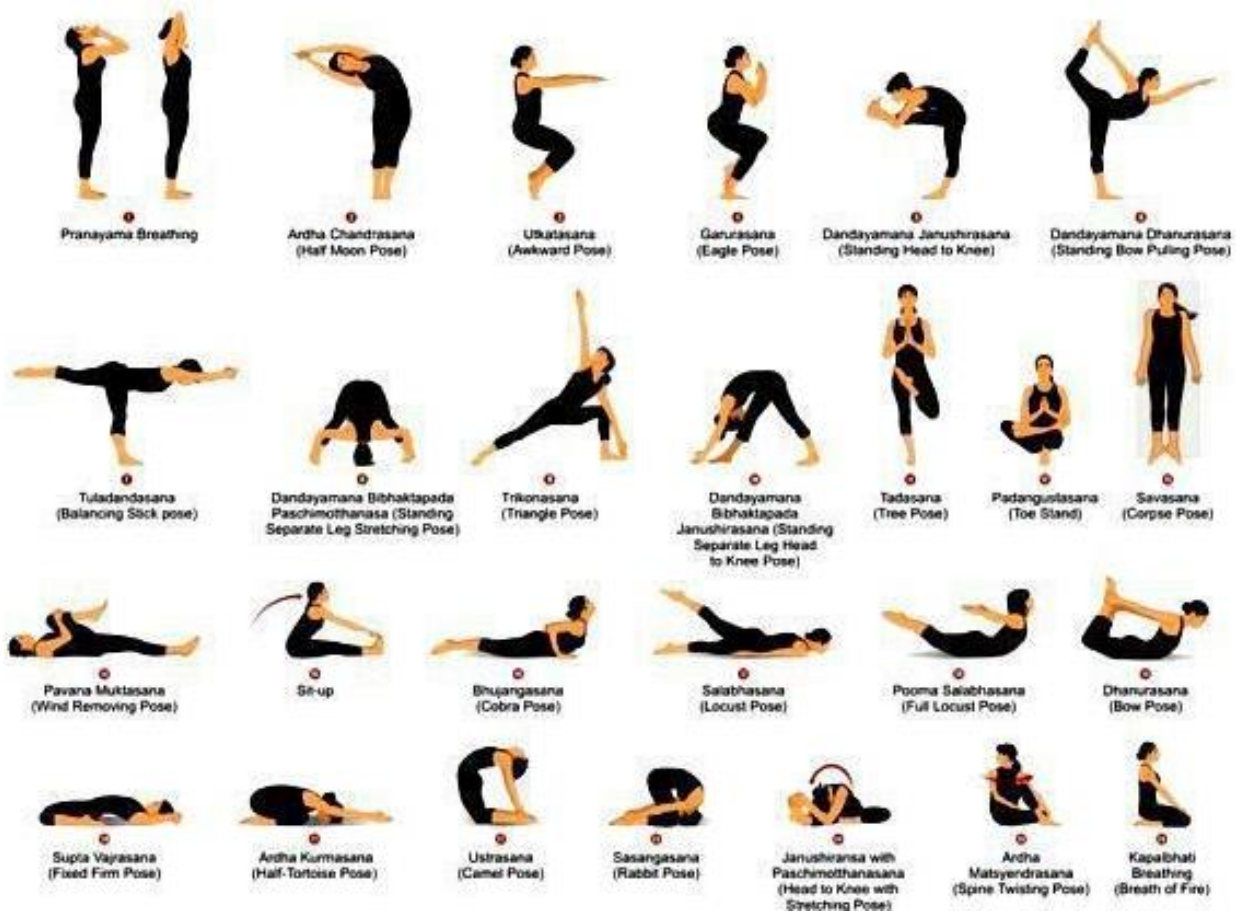


Figure 26: Yoga asanas.

Data from *(98)*

8. STATISTICAL ANALYSIS

Descriptive analysis

We will group the quantitative variables (Fatigue, Quality of Life, Gait speed, Balance, Kinesiophobia, Quality of sleep, Depression, Sexual function) using the mean, the standard deviation, the medians, the interquartile range (IQR), stratified again by the intervention and control group.

We group the qualitative variables in proportions stratified by intervention and control group.

This statistical study will be accompanied by different **graphs** such as the bar graph for quantitative variables and the box plot for quantitative variables.

We will repeat these analyzes, stratifying by intervention. This last analysis will be stratified by the covariates. The quantitative variables will be duly categorized.

Bivariate indifference

The difference of means and medians with respect to the quantitative variables will be analyzed using the student's t-test and the Mann-Whitney U, respectively, the latter will be used in which case our sample does not follow a normal distribution.

The difference in proportions of the qualitative variable between intervention and control will be analyzed by calculating the relative risk and its 95% confidence interval (CI).

In the case of the quantitative variables (Fatigue, Quality of life, Gait speed, Balance, Kinesiophobia, Sleep quality, Depression, Sexual function), the effect of yoga practice will be evaluated using Poisson regression, adjusting for the same covariates as before. In the case of the existence of relapses during the study, it will be analyzed using logistic error controlling the covariates.

These analyzes will be stratified by covariates. The quantitative variables will be duly categorized.

Multivariate analysis

Since it is a **randomized study** no between-patient baseline differences are expected. Nevertheless, if differences on baseline characteristics are observed we will handle the possibility of confusion bias by carrying out a multivariate regression analysis

All the statistical analysis of the variables will be carried out using the Statistical Package for the Social Sciences (**SPSS**) program. In the analysis of the statistical results, the values of $p < 0.05$ will be considered significant and the values of $p < 0.001$ highly significant.

9. WORK PLAN

Research team

The **principal investigator** (PI) of the study will be a neurologist from the Santa Caterina Hospital, in charge of coordinating the entire project, with the help of the participants as required. In addition, they will oversee participating in the follow-up of the patients, as well as interpreting the statistical analysis to be able to write the final work and present the results.

During the follow-up of the patients, we will have the first part that will be about filling the scales to study, which will be carried out by the **nursing team** (blinded). Subsequently, they will be attended by the neurologist to carry out the follow-up, who will not be blinded so that the patient can comment on any questions or need for change that may arise throughout the study.

For the study to work, all the personnel of the Multiple Sclerosis Unit of the Hospital Santa Caterina must know how the study works. Both nurses, receptionists, neurologists and statisticians.

The qualified statistician will carry out the analysis of the results, available from the University of Girona.

Study stages

Stage 0. Study design (December 2021 – January 2022)

1. First meeting (December 2021): the development of this project was agreed upon by Dr. Lluís Ramió i Torrentà (Principal Coordinator) and Sandra Ramis (Principal Investigator).
2. Protocol elaboration (December 2021-January 2022): the protocol has been developed during December (2021) -January (2022) 2021. A bibliographic search has been carried out and the objectives, hypotheses and methodology have been established.

The study coordinator and principal investigator will be primarily responsible.

Stage 1. Ethical evaluation of the protocol (January 2022)

1. Presentation and approval by the Ethics Committee (January 2022- February 2022): the protocol will be presented to the research ethics committee (CEIC) of the Santa Caterina Hospital. Any necessary protocol modifications will be made to achieve CEIC conditions.

   The study coordinator and principal investigator will be primarily responsible.

Stage 2. Coordination (March 2022)

1. First meeting of the research team (March 2022): we will hold the first meeting in order to know how to distribute and organize tasks, as well as for the team that will be part of it to get to know each other. It should be noted that the team is also made up of the two yoga instructors, who will participate in the training of the rest of the group regarding the practice of yoga.
2. Training (March 2022): the entire research team will receive information about the study protocol. It will be taught to collect and record the data and to give the information to the patient. All this will avoid differences when recruiting patients and will ensure the necessary homogeneity to obtain representative conclusions.

   The entire team will be responsible.

Stage 3. Intervention and follow-up visits (April 2022 – November 2022)

1. Recruitment of patients (April 2022 – June 2022): calls will be made to potential patients who are interested and later a consultation will be held with the neurologist to make sure that they meet the inclusion criteria, that there have no exclusion criteria and that the patient is willing to participate by signing the informed consent and providing them the information sheet. In addition, in this first visit, the nurses will carry out the scales for the first time to the participants. Once we have our sample (n=88) the patients will be randomized into two groups.

2. Intervention and follow-up (July 2022 – December 2022): the intervention group that will carry out the yoga practice will meet twice a week in the rehabilitation center of the MS unit of the Santa Caterina hospital. Both groups will be checked by the neurologist after three months (August) and at the end of six months (November). In addition, in November the nursing team will pass the scales again to be able to compare them with the initial results.
3. Data registration (July 2022 – December 2022): the statisticians will record in the database all the scales and information collected from the different patients. The investigation team will be the main responsible.

During this stage, the entire team will meet every three months to assess whether there is proper compliance with the protocol. In the event that something did not work, the necessary decisions would be made to solve it.

Stage 4. Data analysis and interpretation (January 2023 – April 2023)

1. Final statistical analysis (January 2022 – February 2023)
2. Data interpretation (March 2023- April 2023): the data will be interpreted by the principal investigator and the study coordinator. Subsequently, a discussion and a conclusion will be elaborated.

The statistician and the principal investigator will be primarily responsible.

Stage 5. Publication of results (May 2023 – June 2023)

1. Publication and dissemination of the results (May 2023 – June 2023): the final article will be published in a neurology journal in order to properly disseminate the results of the study. In addition, the results will be presented at national and international conferences of specialists.

The main investigator and the coordinator of the study will be the main responsible.

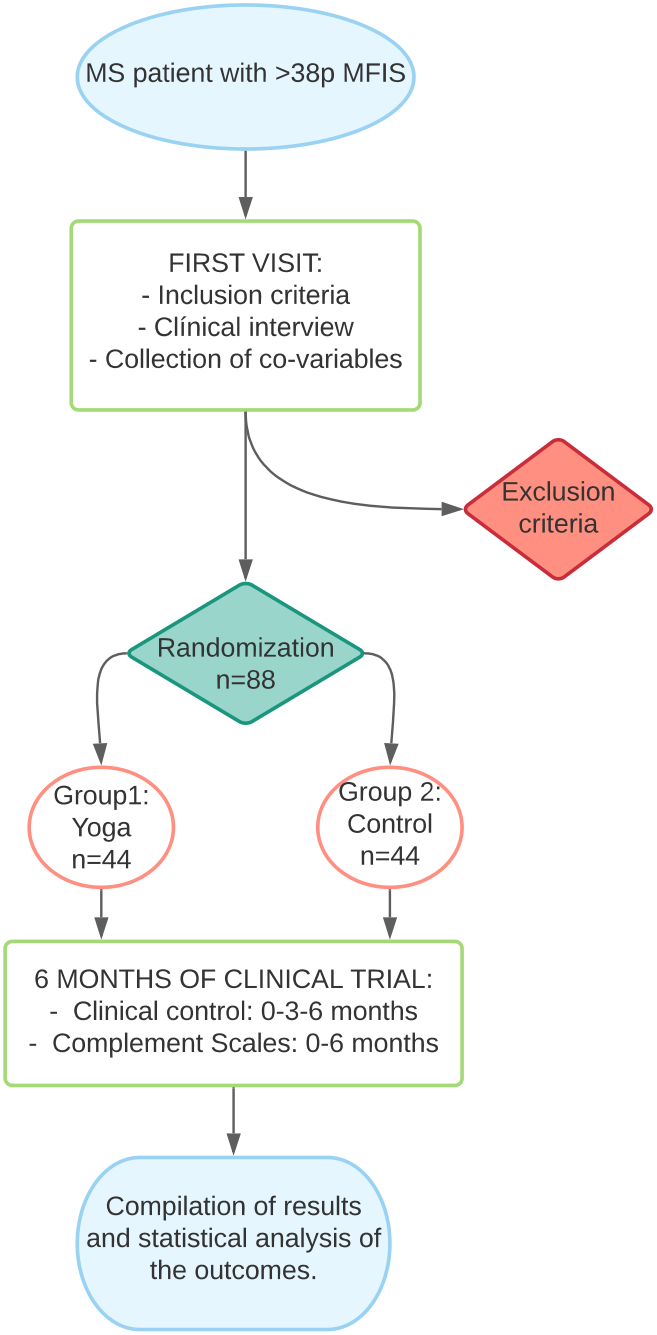


Figure 27: Methods of data collection diagram

(Own creation)

Chronogram

STAGE	TASK	PERSONNEL	PERIOD																		
			21	2022												2023					
			Dec	Jan	Feb	Mar	Apr	My	Jun	Jul	Ago	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	My	Jun
Stage 0 Study design	First meeting	PI + study coordinator																			
	Protocol elaboration	Principal investigator																			
Stage 1 ethical evaluation	Presentation to the Ethics Committee	PI + study coordinator + CEIC																			
Stage 2 Coordination	First meeting of research team	All team																			
	Training of the research team	All team																			
Stage 3 Intervention and follow-up	Patient recruitment	Investigators and neurologist																			
	Follow up meetings	All team																			
	Follow-up visits	Neurologist and nurses																			
	Intervention	Yoga instructors																			
	Data registration	Investigators and nurses																			
Stage 4 Data analysis and interpretation	Final statistical analysis	Statistic																			
	Data interpretation	PI + study coordinator																			
Stage 5 Publication	Publication and dissemination	PI + study coordinator																			

Feasibility

Our study is possible since we have:

- A **location** where to carry out the yoga sessions, in the day hospital of the EM unit of the Santa Caterina Hospital.
- A suitable **sample** for our study. In the health region of Girona there are an estimated 1000 registered patients, of which 800 are interviewed periodically.
- Adequate **personnel** to carry out the study within the MS unit. We will have the statistics from the University of Girona. Finally, we will hire the yoga instructors in Girona as well.

10.ETHICAL CONSIDERATION

This protocol will be reviewed by the "Comité d'Ètica d'Investigació Clínica" (CEIC) of the Santa Caterina Hospital, the coordinating hospital of the study.

This study is designed in accordance with the "Declaration of the **Helsinki** World Medical Association on ethical principles for medical research involving human beings (2013)" to guarantee human rights and ethical considerations.

All medical ethical principles are respected in this study:

- The objective of this study is to improve fatigue through a non-pharmacological intervention, therefore, the quality of life of patients could be affected. Therefore, the study is based on the principle of **beneficence** given the intention of producing a benefit for the patients who participate.
- In which case our study is significant, and the practice of yoga is added for the non-pharmacological treatment of fatigue in patients with MS, it does not imply any prejudice for the patients since no negative effects of said practice have been reported, consequently the principle of **non-maleficiency** is respected.
- The study does not discriminate between the different members, following the principle of **justice**.
- In order to respect the **autonomy** of patients, according to *"Ley 41/2002, de 14 de noviembre, básica reguladora de la autonomía del paciente y de los derechos y obligaciones en materia de información y documentación clínica"*, patients will be informed of the protocol included in the study by means of an informative document where the study will be explained (Annex C).

The researcher(s) will make sure that the participants have understood all the information and will resolve any doubts. Then the patients will sign an informed consent authorizing access to the medical records (Annex D).

The personal data of the participants will be confidential, according to "*Reglamento (UE) 2016/679 del Parlamento Europeo y del Consejo, de 27 de abril de 2016, relativo a la protección de las personas físicas en lo que respecta al tratamiento de datos personales y a la libre circulación de estos datos*", and" *Ley Orgánica 3/2018,*

de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales".

Finally, the researchers will declare that they have **no conflicts of interest**.

11.STUDY STRENGHTS AND LIMITATIONS

Limitations

- **Selection bias**

In the study we used a non-probability sampling method, for this reason there are different opportunities in the selection, in which case we would be in front of a selection bias and the probability of having a non-representative sample. Despite this, the consecutive method has been chosen because it is a non-probabilistic method that minimizes said bias. In addition, when recruiting our patients, they will be included in accordance with the inclusion and exclusion criteria, a fact that will minimize the error.

- **Blinding**

It is impossible to blind participants to the intervention and, given that they are aware of the treatment, some may have an expectation of improvement, which could influence the results. That is why we will only perform a single blind since the statistician and nurse will be blinded to the intervention of the participants, trying to reduce said bias. The doctor will not be blinded since he will collect the clinical interview and will know which patients want to be part of one group or another of the study, that is why to create a blind, nursing will carry out the scales to the patients, in this way who collects the data, in our case nursing, will not know to which group each patient belongs.

- **Information bias**

A possible limitation is the Hawthorne effect, that is, the patient could change his behavior since he was being studied, without having to do with any type of intervention related to our study.

- **Confusion bias**

Since our trial accepts the possible existence of confounding factors that could influence the outcome of the study, we have tried to minimize them by randomizing the

patients in each group so that both have the same number of patients and avoiding it. But the known benefits of yoga go further because it is a technique that aims to find harmony between the body and the mind of our patients, which can induce possible confounding factors such as: change of diet, change of toxic habits, increased awareness of the present and respiration which leads to an improvement of the state of mind, some benefits could be conferred through social interactions during group exercise and the yoga instructor serving as an encouraging mentor

- **Dropouts**

Due to the lack of knowledge of the long-term effects of yoga, we are interested in our study having a considered duration, such as 6-months. But, due to the long duration we expose the possibility of losing some patients. To avoid this bias, it will be necessary to encourage patients about the possible long-term beneficial effects of our study in all its many aspects. According to other studies, the percentage of drops out that we expect to have is 15% (86).

- **Sex effect**

Due to the higher prevalence of women compared to men in multiple sclerosis, and that the sample is randomized, there is the possibility that our subjects are mostly women and therefore, depending on the final male/female ratio of our sample, it may not be possible. can generalize the results for men.

Strengths

- **Unicentric**

The fact of requiring a sample of 88 people means that we can carry out the study in Girona and that is why our study is single-center, which facilitates its performance. Also, to avoid the bias of obtaining information from different centers.

- **Budget**

The studio has an achievable budget.

- **No side effects**

No side effects have been described with yoga, although multiple beneficial effects in regard to it. Although the intervention will not be shown to be beneficial for fatigue, it would have multiple possible domains of patients' lives in which it could make an improvement.

- **Homogeneous procedure**

Since the patients will travel to the center to perform the yoga intervention, they will all receive the same class, along with the same teachers. Fact that makes possible the unification of the results.

Table 8: Summary strengths and limitations.

PROS	CONS
Unicentric	Selection bias
Budget	Confusion bias
No side effects	Blinding
Homogeneous procedure	Dropouts
	Infomation bias
	Sex effect

12.BUDGET

Many of the study activities do not generate any cost. For example, visits and procedures that are included in the normal clinical practice of neurologists and nurses do not need extra funding. In addition, the search of the bibliography and the protocol will be carried out without compensation.

Personnel

A qualified **statistician** from the University of Girona will be hired to periodically analyze and evaluate the data. We also consider expenses derived from **meetings**.

We will require **two yoga instructors**, since we will have some patients with a certain disability and help may be needed to get into certain postures, while the other instructor can guide the class.

Material

To carry out the different scales and to be able to analyze them at the moment, transferring them to the clinical history, we will need tablets, approximately **4 electronic devices**. An application capable of dumping patient data into the currently used support program is also required.

We will need the appropriate **material** for the **yoga classes**, which will include: 22 yoga mats, 22 blankets, 44 yoga blocks and 22 yoga belts. We will also need the space to carry out the classes, which fortunately will be free since the MS rehabilitation center of the Santa Caterina Hospital will be used, since it is available in the afternoons.

Publication and dissemination

The **publication** budget has been estimated, as well as the assistance of the research team to **conferences and congresses** (registration, transport and accommodation included).

Table 9: Budget

Type of cost	Description	Unit cost	Hours/ unit	Subtotal
Personnel expenses	Statistician	30€/hour	50h	1.500€
	Yoga instructors	30€/hour	2 people (6months/ 4 classes per week)	5.760€
	Coordination and meetings	3	150€	450€
Materials and services	Electronic device	80€	4	240€
	Yoga mats	24€	22	528€
	Blankets	10€	22	220€
	2 yoga blocks + 1 yoga belts	14€	22	308€
Study publication expenses	Open access publications. revision, editing, format, layout, design and elaboration of digital data	1.500 €	1	800 €
Study dissemination expences	Congresses (registration, travels, accommodation, diets)	3.000 €	2	2.800€
			TOTAL	14.906€

13.IMPACT

As far as I'm concerned, there are no evidence nor strong indications for yoga as a "complementary non-pharmacological therapy". It is not yet accurately reviewed for inclusion in protocols and indications for treating fatigue in patients with multiple sclerosis.

With this 6-month study we intend to demonstrate, with **a large sample** and a **mid-term study**, one of the many **benefits** of yoga as a non-pharmacological treatment, such as **fatigue**, which is one of the most common and difficult to treat symptoms of MS. If we achieve this, we will be able to change the lives of MS patients, as it is a very disabling symptom for these patients in their daily lives, and finally we will be able to introduce yoga in our **treatment guidelines**.

In addition, we may open the ban for **new lines of research** regarding yoga and thereby ensure that it is incorporated into the treatment indications for the **numerous pathologies** in which it can be beneficial.

14. BIBLIOGRAPHY

1. Researchgate.net [Internet]. Giovannoni Gavin Holistic approach to MS. London: Researshgate; 2021 [cited 2022 Jan 20]. p. 1. Available from: https://www.researchgate.net/figure/Multiple-sclerosis-tube-mapa-Redrawn-and-adapted-with-permission-of-Professor-Gavin_fig1_273390060
2. Vidal-Jordana A, Montalban X. Criteris diagnòstics d'Esclerosi Múltiple i formes clíniques. In: Blanco Y, Brieva L, Carmona O, editors. Diagnòstic i tractament de l'Esclerosi Múltiple [Internet]. Barcelona: Societat Catalana de Neurologia; 2021 [cited 2021 Jul 15]. p. 9–12. Available from: https://www.scneurologia.cat/wp-content/uploads/2021/03/Guia-Esclerosi-Multiple-Societat-Catalana-de-Neurologia-Societat-Catalana-de-Neurologia-2021.pdf
3. Pérez-Carmona N, Fernández-Jover E, Sempere ÁP. Epidemiology of multiple sclerosis in Spain. Rev Neurol [Internet]. 2019 [cited 2021 Jul 7];69(1):32–8. Available from: https://pubmed.ncbi.nlm.nih.gov/31236909
4. Alonso A, Hernán MA. Temporal trends in the incidence of multiple sclerosis: A systematic review. Neurology [Internet]. 2008 [cited 2021 Jul 13];71(2):129–35. Available from: https://pubmed.ncbi.nlm.nih.gov/18606967/
5. Thompson AJ, Baranzini SE, Geurts J, Hemmer B, Ciccarelli O. Multiple sclerosis. Lancet [Internet]. 2018 [cited 2021 Jul 15];391(10130):1622–36. Available from: http://dx.doi.org/10.1016/S0140-6736(18)30481-1
6. Rotstein DL, Chen H, Wilton AS, Kwong JC, Marrie RA, Gozdyra P, et al. Temporal trends in multiple sclerosis prevalence and incidence in a large population. Neurology [Internet]. 2018 [cited 2021 Jul 13];90(16):E1435–41. Available from: https://pubmed.ncbi.nlm.nih.gov/29549225/
7. Domínguez Moreno R, Morales Esponda M, Rossiere Echazarreta NL, Olan Triano R, Gutiérrez Morales JL. Esclerosis múltiple: revisión de la literatura médica. Rev la Fac Med [Internet]. 2012 [cited 2021 Dec 15];55(5):26–35. Available from: https://www.medigraphic.com/cgi-bin/new/resumen.cgi?IDARTICULO=36227
8. McClain MT, Heinlen LD, Dennis GJ, Roebuck J, Harley JB, James JA. Epstein-Barr virus and multiple sclerosis. Nat Med [Internet]. 2022 [cited 2022 Jan

19];11(1):85–9. Available from: https://pubmed.ncbi.nlm.nih.gov/33391262/

9. Henri. Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. Angew Chemie Int Ed 6(11), 951–952 [Internet]. 2022 [cited 2022 Jan 19];8222(January). Available from: https://pubmed.ncbi.nlm.nih.gov/35025605/

10. Robinson WH, Steinman L. Study of soldiers implicates common virus as MS trigger. Science (80-) [Internet]. 2022 [cited 2022 Jan 19];375(6577). Available from: https://pubmed.ncbi.nlm.nih.gov/35025651/

11. Confavreux C, Vukusic S. The clinical course of multiple sclerosis. Handb Clin Neurol [Internet]. 1st ed. 2014 [cited 2021 Dec 1];122:343–69. Available from: http://dx.doi.org/10.1016/B978-0-444-52001-2.00014-5

12. Ascherio A, Munger KL. Epidemiology of Multiple Sclerosis: From Risk Factors to Prevention--An Update. Semin Neurol [Internet]. 2016 [cited 2021 Dec 24];36(2):103–14. Available from: https://pubmed.ncbi.nlm.nih.gov/27116717/

13. Swanton J, Fernando K, Miller D. Early prognosis of multiple sclerosis. Handb Clin Neurol [Internet]. 1st ed. 2014 [cited 2021 Jul 16];122:371–91. Available from: http://dx.doi.org/10.1016/B978-0-444-52001-2.00015-7

14. Waubant E, Lucas R, Mowry E, Graves J, Olsson T, Alfredsson L, et al. Environmental and genetic risk factors for MS: an integrated review. Ann Clin Transl Neurol [Internet]. 2019 [cited 2022 Jan 4];6(9):1905–22. Available from: https://pubmed.ncbi.nlm.nih.gov/31392849/

15. Boppana S, Huang H, Ito K, Dhib-Jalbut S. Immunologic Aspects of Multiple Sclerosis Sridhar. Medicine (Baltimore) [Internet]. 2007 [cited 2021 Dec 8];78:207–220. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/msj.20249?casa_token=ImwWoiIGFisAAAAA:WfnXyhk0JU0CmONT0PA_ZOqgLjKn_3ehwKbZp6l787fWEomVS7PhxXNFvvfVvdmD0bqq7A9bIGR5oVM

16. Oroz N. Esclerosis múltiple. Rev Mex Neuroci [Internet]. 2007 [cited 2021 Dec 9];8(1):57–66. Available from: http://previous.revmexneurociencia.com/wp-content/uploads/2014/06/Nm071-10.pdf

17. Noseworthy JH, Uchinetti CL, Rodriguez M, Weinshenker BG. Clinical course and

diagnosis. 2004;

18. Hervás García DJV, Ramo Tello DC. Tractament del brot. In: Diagnòstic i tractament de l'Esclerosi Múltiple [Internet]. Barcelona: Societat Catalana de Neurologia; 2021 [cited 2021 Jul 20]. p. 59–64. Available from: https://www.scneurologia.cat/wp-content/uploads/2021/03/Guia-Esclerosi-Multiple-Societat-Catalana-de-Neurologia-Societat-Catalana-de-Neurologia-2021.pdf
19. Olsson T, Barcellos LF, Alfredsson L. Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis. Nat Rev Neurol [Internet]. 2016 [cited 2022 Jan 4];13(1):26–36. Available from: http://dx.doi.org/10.1038/nrneurol.2016.187
20. Moore F. Incidental mri anomalies suggestive of multiple sclerosis: The radiologically isolated syndrome. Neurology [Internet]. 2009;73(20):1714. Available from: https://pubmed.ncbi.nlm.nih.gov/19073949/
21. De Stefano N, Giorgio A, Tintoré M, Pia Amato M, Kappos L, Palace J, et al. Radiologically isolated syndrome or subclinical multiple sclerosis: MAGNIMS consensus recommendations. Mult Scler [Internet]. 2018 [cited 2022 Jan 4];24(2):214–21. Available from: https://pubmed.ncbi.nlm.nih.gov/29451440/
22. Weermeijer JD, Meulders A. Clinimetrics: Tampa Scale for Kinesiophobia. J Physiother [Internet]. 2018 [cited 2022 Jan 17];64(2):126. Available from: https://doi.org/10.1016/j.jphys.2018.01.001
23. Gómez L, López E, Ruiz T. Cuestionario Tsk-11Sv. J Pain [Internet]. 2011 [cited 2022 Jan 17];12(4):1. Available from: http://www.paininmotion.be/EN/sem-TSK11SVSpanish.pdf
24. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol [Internet]. 2018 [cited 2021 Dec 29];17(2):162–73. Available from: https://pubmed.ncbi.nlm.nih.gov/29275977/
25. Tintore M, Otero-Romero S, Río J, Arrambide G, Pujal B, Tur C, et al. Contribution of the symptomatic lesion in establishing MS diagnosis and prognosis. Neurology [Internet]. 2016 [cited 2022 Jan 14];87(13):1368–74. Available from:

https://pubmed.ncbi.nlm.nih.gov/27566747/

26. Brownlee WJ, Swanton JK, Miszkiel KA, Miller DH, Ciccarelli O. Should the symptomatic region be included in dissemination in space in MRI criteria for MS? Neurology [Internet]. 2016 [cited 2022 Jan 4];87(7):680–3. Available from: https://pubmed.ncbi.nlm.nih.gov/27421541/

27. Frohman EM, Racke MK, Raine CS. Multiple Sclerosis — The Plaque and Its Pathogenesis. N Engl J Med [Internet]. 2006 [cited 2022 Jan 4];354(9):942–55. Available from: https://pubmed.ncbi.nlm.nih.gov/16510748/

28. Huss AM, Halbgebauer S, Öckl P, Trebst C, Spreer A, Borisow N, et al. Importance of cerebrospinal fluid analysis in the era of McDonald 2010 criteria: a German–Austrian retrospective multicenter study in patients with a clinically isolated syndrome. J Neurol [Internet]. 2016 [cited 2021 Dec 1];263(12):2499–504. Available from: https://pubmed.ncbi.nlm.nih.gov/27730374/

29. Rovira DÀ, Auger DC. Ressonància magnètica en el diagnòstic i seguiment de l'Esclerosi Múltiple. In: Diagnòstic i tractament de l'Esclerosi Múltiple [Internet]. Barcelona: Societat Catalana de Neurologia; 2021 [cited 2021 Jul 6]. p. 18–54. Available from: https://www.scneurologia.cat/wp-content/uploads/2021/03/Guia-Esclerosi-Multiple-Societat-Catalana-de-Neurologia-Societat-Catalana-de-Neurologia-2021.pdf

30. Hemond CC, Bakshi R. Magnetic resonance imaging in multiple sclerosis. Cold Spring Harb Perspect Med [Internet]. 2018 [cited 2021 Jul 20];8(5):1–22. Available from: https://pubmed.ncbi.nlm.nih.gov/29358319/

31. Pérez-Miralles F, Sastre-Garriga J, Tintoré M, Arrambide G, Nos C, Perkal H, et al. Clinical impact of early brain atrophy in clinically isolated syndromes. Mult Scler J [Internet]. 2013 [cited 2021 Jul 15];19(14):1878–86. Available from: https://pubmed.ncbi.nlm.nih.gov/23652215/

32. Weier K, Mazraeh J, Naegelin Y, Thoeni A, Hirsch JG, Fabbro T, et al. Biplanar MRI for the assessment of the spinal cord in multiple sclerosis. Mult Scler J [Internet]. 2012 [cited 2021 Jul 16];18(11):1560–9. Available from: https://pubmed.ncbi.nlm.nih.gov/22539086/

33. Rocca MA, Hickman SJ, Bö L, Agosta F, Miller DH, Comi G, et al. Imaging the optic

nerve in multiple sclerosis. Mult Scler [Internet]. 2005 [cited 2022 Jan 4];11(5):537–41. Available from: https://pubmed.ncbi.nlm.nih.gov/16193891/

34. Robles DR. Estudi diagnòstic del líquid cefaloraquidi (LCR). In: Diagnòstic i tractament de l'Esclerosi Múltiple [Internet]. Barcelona: Societat Catalana de Neurologia; 2021 [cited 2021 Jul 15]. p. 55–8. Available from: https://www.scneurologia.cat/wp-content/uploads/2021/03/Guia-Esclerosi-Multiple-Societat-Catalana-de-Neurologia-Societat-Catalana-de-Neurologia-2021.pdf

35. Pelayo DR, Ramió i Torrentà DL, Pericot DI, Cano DA. Tractament simptomàtic i rehabilitador en l'Esclerosi Múltiple. In: Diagnòstic i tractament de l'Esclerosi Múltiple [Internet]. Barcelona: Societat Catalana de Neurologia; 2021 [cited 2021 May 15]. p. 139–47. Available from: https://www.scneurologia.cat/wp-content/uploads/2021/03/Guia-Esclerosi-Multiple-Societat-Catalana-de-Neurologia-Societat-Catalana-de-Neurologia-2021.pdf

36. Sorensen PS, Giovannoni G, Montalban X, Thalheim C, Zaratin P, Comi G. The Multiple Sclerosis Care Unit. 2019 [cited 2021 Jul 7];627–36. Available from: https://pubmed.ncbi.nlm.nih.gov/30351211/

37. Moral DE. Injectables en Esclerosi Múltiple. In: Diagnòstic i tractament de l'Esclerosi Múltiple [Internet]. Barcelona: Societat Catalana de Neurologia; 2021 [cited 2022 Jan 4]. p. 65–76. Available from: https://www.scneurologia.cat/wp-content/uploads/2021/03/Guia-Esclerosi-Multiple-Societat-Catalana-de-Neurologia-Societat-Catalana-de-Neurologia-2021.pdf

38. Sastre Garriga DJ. Teriflunomida en Esclerosi Múltiple. In: Diagnòstic i tractament de l'Esclerosi Múltiple [Internet]. Barcelona: Societat Catalana de Neurologia; 2021 [cited 2021 Jul 8]. p. 77–82. Available from: https://www.scneurologia.cat/wp-content/uploads/2021/03/Guia-Esclerosi-Multiple-Societat-Catalana-de-Neurologia-Societat-Catalana-de-Neurologia-2021.pdf

39. Carmona DO. Dimetilfumarat, BG-12 (Tecfidera®). In: Diagnòstic i tractament de l'Esclerosi Múltiple [Internet]. Barcelona: Societat Catalana de Neurologia; 2021 [cited 2021 Jul 20]. p. 83–7. Available from: https://www.scneurologia.cat/wp-

content/uploads/2021/03/Guia-Esclerosi-Multiple-Societat-Catalana-de-Neurologia-Societat-Catalana-de-Neurologia-2021.pdf

40. Brieva DL. Natalizumab. In: Diagnòstic i tractament de l'Esclerosi Múltiple [Internet]. Barcelona: Societat Catalana de Neurologia; 2021 [cited 2022 Jan 4]. p. 88–104. Available from: https://www.scneurologia.cat/wp-content/uploads/2021/03/Guia-Esclerosi-Multiple-Societat-Catalana-de-Neurologia-Societat-Catalana-de-Neurologia-2021.pdf
41. Sotoca DJ. Fingolimod i altres agonistes del receptor de l'esfingosina 1-fosfat. In: Diagnòstic i tractament de l'Esclerosi Múltiple [Internet]. Barcelona: Societat Catalana de Neurologia; 2021 [cited 2021 Jul 8]. p. 105–15. Available from: https://www.scneurologia.cat/wp-content/uploads/2021/03/Guia-Esclerosi-Multiple-Societat-Catalana-de-Neurologia-Societat-Catalana-de-Neurologia-2021.pdf
42. Martín DL, Pascual DE, Querol DL. Teràpies anti-CD20. In: Diagnòstic i tractament de l'Esclerosi Múltiple [Internet]. Barcelona: Societat Catalana de Neurologia; 2021 [cited 2021 Jul 20]. p. 116–25. Available from: https://www.scneurologia.cat/wp-content/uploads/2021/03/Guia-Esclerosi-Multiple-Societat-Catalana-de-Neurologia-Societat-Catalana-de-Neurologia-2021.pdf
43. Solà DN. Cladribina. In: Diagnòstic i tractament de l'Esclerosi Múltiple [Internet]. Barcelona: Societat Catalana de Neurologia; 2021 [cited 2021 Dec 1]. p. 126–32. Available from: https://www.scneurologia.cat/wp-content/uploads/2021/03/Guia-Esclerosi-Multiple-Societat-Catalana-de-Neurologia-Societat-Catalana-de-Neurologia-2021.pdf
44. Martinez Yélamos DS. Alemtuzumab. In: Diagnòstic i tractament de l'Esclerosi Múltiple [Internet]. Barcelona; 2021 [cited 2022 Jan 4]. p. 133–8. Available from: https://www.scneurologia.cat/wp-content/uploads/2021/03/Guia-Esclerosi-Multiple-Societat-Catalana-de-Neurologia-Societat-Catalana-de-Neurologia-2021.pdf
45. Kushh.ca [Internet]. MS symptoms. Toronto: Kushh; [cited 2022 Jan 18]. Available from: https://www.kushh.ca/living-multiple-sclerosis-marijuana/

46. Ragonese P, Aridon P, Salemi G, D'Amelio M, Savettieri G. Mortality in multiple sclerosis: A review. Eur J Neurol [Internet]. 2008 [cited 2021 Jul 8];15(2):123–7. Available from: https://pubmed.ncbi.nlm.nih.gov/18217882/

47. Rotstein D, Montalban X. Reaching an evidence-based prognosis for personalized treatment of multiple sclerosis. Nat Rev Neurol [Internet]. 2019 [cited 2021 Jul 21];15(5):287–300. Available from: http://dx.doi.org/10.1038/s41582-019-0170-8

48. Tur C. Fatigue Management in Multiple Sclerosis. Curr Treat Options Neurol [Internet]. 2016 [cited 2021 Dec 1];18(6). Available from: https://pubmed.ncbi.nlm.nih.gov/27087457/

49. Silverman M, Heim CM, Nater UM, Marques AH, Sternberg EM. Neuroendocrine and Immune Contributors to Fatigue. Bone [Internet]. 2011 [cited 2022 Jan 4];23(1):1–7. Available from: https://pubmed.ncbi.nlm.nih.gov/20656615/

50. Bol Y, Duits AA, Hupperts RMM, Verlinden I, Verhey FRJ. The impact of fatigue on cognitive functioning in patients with multiple sclerosis. Clin Rehabil [Internet]. 2010 [cited 2021 Jul 7];24(9):854–62. Available from: https://pubmed.ncbi.nlm.nih.gov/20576670/

51. lriarte J, Subirá ML, de Castro P. Modalities of fatigue in multiple sclerosis: correlation with clinical and biological factors. Mult Scler J [Internet]. 2000;6(2):124–30. Available from: https://pubmed.ncbi.nlm.nih.gov/10773859/

52. Newland P, Starkweather A, Sorenson M. Central fatigue in multiple sclerosis: a review of the literature. J Spinal Cord Med [Internet]. 2016 [cited 2021 Dec 1];39(4):386–99. Available from: https://pubmed.ncbi.nlm.nih.gov/27146427/

53. Mills RJ, Young CA. The relationship between fatigue and other clinical features of multiple sclerosis. Mult Scler J [Internet]. 2011 [cited 2021 Dec 3];17(5):604–12. Available from: https://pubmed.ncbi.nlm.nih.gov/21135018/

54. Multiple Sclerosis International Federation. La fatiga y la EM [Internet]. London: Multiple Sclerosis International Federation; 2012 [cited 2021 Jul 8]. Available from: https://www.msif.org/wp-content/uploads/2014/09/MS-in-focus-19-Fatigue-Spanish.pdf

55. Fisk JD, Ritvo PG, Ross L, Haase DA, Marrie TJ, Schlech WF. Measuring the

functional impact of fatigue: Initial validation of the fatigue impact scale. Clin Infect Dis [Internet]. 1994 [cited 2021 Dec 27];18:S79–83. Available from: https://pubmed.ncbi.nlm.nih.gov/8148458/

56. Mills RJ, Young CA, Pallant JF, Tennant A. Rasch analysis of the Modified Fatigue Impact Scale (MFIS) in multiple sclerosis. J Neurol Neurosurg Psychiatry [Internet]. 2010 [cited 2021 Dec 19];81(9):1049–51. Available from: https://pubmed.ncbi.nlm.nih.gov/20547635/

57. Castillo Cejas MD, Robles V, Borruel N, Torrejón A, Navarro E, Peláez A, et al. Cuestionarios de medida e impacto de la fatiga en la percepción de salud en la enfermedad inflamatoria intestinal. Rev Española Enfermedades Dig [Internet]. 2013 [cited 2021 Dec 13];105:144–53. Available from: http://scielo.isciii.es/pdf/diges/v105n3/es_original4.pdf

58. Frank R, Larimore J. Yoga as a method of symptom management in multiple sclerosis. Front Neurosci [Internet]. 2015 [cited 2022 Jan 12];9(APR):1–5. Available from: https://pubmed.ncbi.nlm.nih.gov/25983675/

59. Rogers KA, MacDonald M. Therapeutic Yoga: Symptom Management for Multiple Sclerosis. J Altern Complement Med [Internet]. 2015 [cited 2022 Jan 4];21(11):655–9. Available from: https://pubmed.ncbi.nlm.nih.gov/26270955/

60. Woodyard C. Exploring the therapeutic effects of yoga and its ability to increase quality of life. Int J Yoga [Internet]. 2011 [cited 2021 Dec 29];4(2):49–54. Available from: https://pubmed.ncbi.nlm.nih.gov/22022122/

61. Senders A, Wahbeh H, Spain R, Shinto L. Mind-body medicine for multiple sclerosis: A systematic review. Autoimmune Dis [Internet]. 2012 [cited 2022 Jan 12];1(1). Available from: https://pubmed.ncbi.nlm.nih.gov/23227313/

62. Doulatabad N, Tradit AJ, Altern C. The effects of pranayama, hatha and raja yoga on physical pain and the quality of life of women with multiple sclerosis. African J Tradit Complement Altern Med AJTCAM [Internet]. 2013 [cited 2022 Jan 3];10:49–52. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3746357/pdf/AJT1001-0049.pdf

63. Feinstein A, Rector N, Motl R. Exercising away the blues: Can it help multiple

sclerosis-related depression? Mult Scler J [Internet]. 2013 [cited 2022 Jan 12];19(14):1815–9. Available from: https://pubmed.ncbi.nlm.nih.gov/24126063/

64. Hassanpour-Dehkordi A, Jivad N. Comparison of regular aerobic and yoga on the quality of life in patients with multiple sclerosis. Med J Islam Repub Iran [Internet]. 2014 [cited 2021 Dec 30];28:1–7. Available from: https://pubmed.ncbi.nlm.nih.gov/25694999/

65. Dayapoğlu N, Tan M. Evaluation of the effect of progressive relaxation exercises on fatigue and sleep quality in patients with multiple sclerosis. J Altern Complement Med [Internet]. 2012 [cited 2022 Jan 10];18(10):983–7. Available from: https://pubmed.ncbi.nlm.nih.gov/22967281/

66. Kahraman T, Ozdogar AT, Yigit P, Hosgel I, Mehdiyev Z, Ertekin O, et al. Feasibility of a 6-Month Yoga Program to Improve the Physical and Psychosocial Status of Persons with Multiple Sclerosis and their Family Members. Explore [Internet]. 2018 [cited 2021 Dec 29];14(1):36–43. Available from: http://dx.doi.org/10.1016/j.explore.2017.07.006

67. Oken BS, Kishiyama S, Zajdel D, Bourdette D, Carlsen J, Haas M, et al. Randomized controlled trial of yoga and exercise in multiple sclerosis. Neurology [Internet]. 2004 [cited 2021 Dec 16];62(11):2058–64. Available from: https://pubmed.ncbi.nlm.nih.gov/15184614/

68. Cramer H, Lauche R, Azizi H, Dobos G, Langhorst J. Yoga for multiple sclerosis: A systematic review and meta-analysis. PLoS One [Internet]. 2014 [cited 2022 Jan 12];9(11):1–11. Available from: https://pubmed.ncbi.nlm.nih.gov/25390344/

69. Boehm K, Ostermann T, Milazzo S, Büssing A. Effects of yoga interventions on fatigue: A meta-analysis. Evidence-based Complement Altern Med [Internet]. 2012 [cited 2021 Dec 27];2012:1–9. Available from: https://pubmed.ncbi.nlm.nih.gov/22991569/

70. Ahmadi A, Arastoo AA, Nikbakht M, Zahednejad S, Rajabpour M. Comparison of the effect of 8 weeks aerobic and yoga training on ambulatory function, fatigue and mood status in MS patients. Iran Red Crescent Med J [Internet]. 2013 [cited 2022 Jan 12];15(6):449–54. Available from: https://pubmed.ncbi.nlm.nih.gov/24349740/

71. Frank R, Larimore J. Yoga as a method of symptom management in multiple sclerosis. Front Neurosci [Internet]. 2015 [cited 2021 Dec 13];9(APR):1–5. Available from: https://pubmed.ncbi.nlm.nih.gov/25983675/

72. Guner S, Inanici F. Yoga therapy and ambulatory multiple sclerosisAssessment of gait analysis parameters, fatigue and balance. J Bodyw Mov Ther [Internet]. 2015 [cited 2021 Dec 1];19(1):72–81. Available from: http://dx.doi.org/10.1016/j.jbmt.2014.04.004

73. Guner S, Inanici F. Yoga therapy and ambulatory multiple sclerosisAssessment of gait analysis parameters, fatigue and balance. J Bodyw Mov Ther [Internet]. 2015 [cited 2022 Jan 12];19(1):72–81. Available from: http://dx.doi.org/10.1016/j.jbmt.2014.04.004

74. Patil NJ, Nagaratna R, Garner C, Raghuram N V., Crisan R. Effect of integrated Yoga on neurogenic bladder dysfunction in patients with multiple sclerosis-A prospective observational case series. Complement Ther Med [Internet]. 2012 [cited 2021 Dec 27];20(6):424–30. Available from: https://pubmed.ncbi.nlm.nih.gov/23131373/

75. Najafidoulatabad S, Mohebbi Z. Yoga effects on physical activity and sexual satisfaction among iranian women with multiple sclerosis: a randomized controlled trial. African J Tradit Complement Altern Med AJTCAM [Internet]. 2014 [cited 2022 Jan 10];11:78–82. Available from: https://pubmed.ncbi.nlm.nih.gov/25395709/

76. Rain Carei T, L. Fyfe-Johnson A, Collette Breuner C, A. Marshall M. Randomized Controlled Clinical Trial of Yoga in the Treatment of Eating Disorders. Bone [Internet]. 2008 [cited 2022 Jan 12];23(1):1–7. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3624763/pdf/nihms412728.pdf

77. Leavitt VM, Cirnigliaro C, Cohen A, Farag A, Brooks M, Wecht JM, et al. Aerobic exercise increases hippocampal volume and improves memory in multiple sclerosis: Preliminary findings. Neurocase [Internet]. 2014 [cited 2022 Jan 4];20(6):695–7. Available from: https://pubmed.ncbi.nlm.nih.gov/24090098/

78. Dalgas U, Stenager E. Exercise and disease progression in multiple sclerosis: Can

exercise slow down the progression of multiple sclerosis? Ther Adv Neurol Disord [Internet]. 2012 [cited 2022 Dec 25];5(2):81–95. Available from: https://pubmed.ncbi.nlm.nih.gov/22435073/

79. Compston A, Coles A. Multiple sclerosis. Lancet [Internet]. 2008 [cited 2022 Jan 12];372(9648):1502–17. Available from: http://dx.doi.org/10.1016/S0140-6736(08)61620-7

80. Özenci V, Kouwenhoven M, Link H. Cytokines in multiple sclerosis: Methodological aspects and pathogenic implications. Mult Scler [Internet]. 2002 [cited 2021 Jul 15];8(5):396–404. Available from: https://pubmed.ncbi.nlm.nih.gov/12356206/

81. White LJ, Castellano V. Exercise and brain health - Implications for multiple sclerosis: Part II - Immune factors and stress hormones. Sport Med [Internet]. 2008 [cited 2022 Jan 10];38(3):179–86. Available from: https://pubmed.ncbi.nlm.nih.gov/18278981/

82. Ebadi M, Bashir RM, Heidrick ML, Hamada FM, Refaey HEL, Hamed A, et al. Neurotrophins and their receptors in nerve injury and repair. Neurochem Int [Internet]. 1997 [cited 2022 Jan 10];30(4–5):347–74. Available from: https://pubmed.ncbi.nlm.nih.gov/9106250/

83. Gold SM, Schulz KH, Hartmann S, Mladek M, Lang UE, Hellweg R, et al. Basal serum levels and reactivity of nerve growth factor and brain-derived neurotrophic factor to standardized acute exercise in multiple sclerosis and controls. J Neuroimmunol [Internet]. 2003 [cited 2021 Dec 3];138(1–2):99–105. Available from: https://pubmed.ncbi.nlm.nih.gov/12742659/

84. Rajagopalan A, Kumar SS, Johny M, Mukkadan JK. Modulation of immune responses in stress by yoga. Natl J Physiol Pharm Pharmacol [Internet]. 2017 [cited 2021 Dec 27];7(11):45–55. Available from: https://pubmed.ncbi.nlm.nih.gov/21829284/

85. Mostert S, Kesselring J. Effects of a short-term exercise training program on aerobic fitness, fatigue, health perception and activity level of subjects with multiple sclerosis. Mult Scler [Internet]. 2002 [cited 2021 Dec 1];8(2):161–8. Available from: https://pubmed.ncbi.nlm.nih.gov/11990874/

86. Cramer H, Haller H, Dobos G, Lauche R. A Systematic Review and Meta-Analysis Estimating the Expected Dropout Rates in Randomized Controlled Trials on Yoga Interventions. Evidence-based Complement Altern Med [Internet]. 2016 [cited 2022 Jan 3];2016. Available from: https://pubmed.ncbi.nlm.nih.gov/27413387/

87. Ritvo PG, Fischer JS, Miller DM, Andrews H, Paty DW, LaRocca NG. MSQLI Multiple Sclerosis Quality of Life Inventory: A User's Manual The Consortium of Multiple Sclerosis Centers Health Services Research Subcommittee [Internet]. New York: National Multiple Sclerosis Society; 1997 [cited 2021 Dec 3]. Available from: https://nmsscdn.azureedge.net/NationalMSSociety/media/MSNationalFiles/Brochures/MSQLI_-A-User-s-Manual.pdf

88. Fischer JS, Ph D, Jak AJ, Kniker JE, Rudick RA. Multiple sclerosis Functional composite (msfc). Noro Psikiyatr Ars [Internet]. 2001 [cited 2021 Dec 5];55(1):S46–8. Available from: https://pubmed.ncbi.nlm.nih.gov/24666846/

89. Huang M, Pang MYC. Psychometric properties of Brief-Balance Evaluation Systems Test (Brief-BESTest) in evaluating balance performance in individuals with chronic stroke. Brain Behav [Internet]. 2017 [cited 2022 Jan 15];7(3):1–10. Available from: https://pubmed.ncbi.nlm.nih.gov/28293482/

90. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: A New Instrument for Psychiatric Practice and Research. Psychiatry Res [Internet]. 1989 [cited 2022 Jan 10];28(2):193–213. Available from: https://pubmed.ncbi.nlm.nih.gov/2748771/

91. Wang YP, Gorenstein C. Psychometric properties of the Beck Depression Inventory-II: A comprehensive review. Rev Bras Psiquiatr [Internet]. 2013;35(4):416–31. Available from: https://pubmed.ncbi.nlm.nih.gov/24402217/

92. Germain ARD levine susan hanson maureen. A pilot study assessing acceptability and feasibility of hatha yoga for chronic pain in people receiving opioid agonist therapy for opioid use disorder. Physiol Behav [Internet]. 2017 [cited 2021 Dec 20];176(3):139–48. Available from: https://pubmed.ncbi.nlm.nih.gov/31443887/

93. Insayoga.com [Internet]. Insa Satorre N. Mrigi mudra. Valencia: Insayoga; 2021 [cited 2022 Jan 3]. p. 1. Available from: https://insayoga.com/nadi-sodhana-la-

respiracion-purificadora/

94. Bodyballet.es [Internet]. De Pedro Carolina El Saludo al Sol. Madrid: Bodyballet; 2021 [cited 2022 Jan 18]. p. 1. Available from: https://www.bodyballet.es/postura-de-yoga-el-saludo-al-sol/

95. hola.com [Internet]. Sánchez Carla Saludo al sol en la silla. Madrid: Hola; 2021 [cited 2022 Jan 18]. p. 1. Available from: https://www.hola.com/estar-bien/galeria/20201027178090/posturas-de-yoga-espalda-oficina/2/

96. Yogaenred.com [Internet]. Puscas Cris. Teruel: Yogaenred; 2021 [cited 2022 Jan 18]. p. 1. Available from: https://www.yogaenred.com/2019/01/11/liberate-del-estres-con-yoga-5-posturas-que-puedes-hacer-desde-tu-escritorio/

97. sportlife.es [Internet]. Vazquez Yolanda Yoga para fortalecer brazos, hombros, pecho y abdominales. Madrid: Sportlife; 2021 [cited 2022 Jan 3]. p. 1. Available from: https://www.sportlife.es/yoga-fit/para-deportistas/secuencia-yoga-para-fortalecer-brazos-hombros-espalda-pecho-y-abdominales_206838_102.html

98. klinicka.ru [Internet]. Posturas de yoga. Barcelona: klinicka; 2021 [cited 2022 Jan 15]. p. 1. Available from: http://klinicka.ru/nombres-de-posturas-de-yoga/

99. Piri Çinar B, Güven Yorgun Y. What we learned from the history of multiple sclerosis measurement: Expanded disability status scale. Noropsikiyatri Ars [Internet]. 2018 [cited 2022 Jan 10];55(Supplement 1):S69–75. Available from: https://pubmed.ncbi.nlm.nih.gov/30692861/

100. Lo MPhil CWT. Psychometric Properties of Brief-Balance Evaluation Systems Test Among Multiple Populations: A Systematic Review and Meta- analysis. Arch Phys Med Rehabil [Internet]. 2021 [cited 2022 Jan 14];S0003-9993(21):1–52. Available from: https://www.researchgate.net/publication/351675347_Psychometric_Properties_of_Brief-Balance_Evaluation_Systems_Test_Among_Multiple_Populations_A_Systematic_Review_and_Meta-analysis

101. Opapc.com [Internet]. PSQI. Míchigan: Oakland Psychiatric Associates; 2021 [cited 2022 Jan 13]. p. 1–6. Available from: http://www.opapc.com/uploads/documents/PSQI.pdf

102. Encyclopedia of Measurement and Statistics [Internet]. Salkin N. Beck Depression Inventory;2013. Worcester: American Psychological Association; 2021 [cited 2022 Jan 16]. p. 1–4. Available from: https://www.apa.org/pi/about/publications/caregivers/practice-settings/assessment/tools/beck-depression

15. ANNEXES

Annex A. The Disability Status Scale –functional systems

Data from (99).

1) Pyramidal Functions; 0. Normal. 1. Abnormal signs without disability. 2. Minimal disability. 3. Mild or moderate paraparesis or hemiparesis. 4. Marked paraparesis or hemiparesis; moderate quadriparesis; or monoplegia. 5. Paraplegia, hemiplegia, or marked tetraparesis. 6. Quadriplegia. *V. Unknown.*
2) Cerebellar Functions; 0. Normal. 1. Abnormal signs without disability. 2. Mild ataxia. 3. Moderate truncal or limb ataxia. 4. Severe ataxia, all limbs. 5. Unable to perform coordinated movements due to ataxia. *V. Unknown.* *X. Used throughout after each number when weakness (grade 3 or more on pyramidal) interferes with testing.*
3) Brain Stem Functions; 0. Normal. 1. Signs only. 2. Moderate nystagmus or other disability. 3. Severe nystagmus, marked extraocular weakness, or moderate disability of other cranial nerves. 4. Marked dysarthria or other marked disability. 5. Inability to swallow or speak. *V. Unknown.*
4) Sensory Function (revised in 1982); 0. Normal. 1. Vibration or figure-writing decrease only in one or two limbs. 2. Mild decrease in touch or pain or position sense, and/or moderate decrease in vibration in one or two limbs; or vibratory (c/s figure-writing decrease alone in three or four limbs. 3. Moderate decrease in touch or pain or position sense, and/or essentially lost vibration in one or two limbs; or mild decrease in touch or pain and/or moderate decrease in all proprioceptive tests in three or four limbs. 4. Marked decrease in touch or pain or loss of proprioception, alone or combined, in one or two limbs; or moderate decrease in touch or pain and/or severe proprioceptive decrease in more than two limbs. 5. Loss (essentially) of sensation in one or two limbs; or moderate decrease in touch or pain and/or loss of proprioceptive for most of the body below the head. 6. Sensation essentially lost below the head. *V. Unknown.*
5) Bladder-Bowel Functions (revised in 1982); 0. Normal. 1. Mild urinary hesitancy, urgency or retention. 2. Moderate hesitancy, urgency, retention of bladder or bowel, or rare urinary incontinence. 3. Frequent urinary incontinence. 4. In need of almost complete constant catheterization. 5. Loss of bladder and bowel function. *V. Unknown.*
6) Visual (Optical) Functions; 0. Normal. 1. Scotoma with visual acuity (corrected) better than 20/30.2. Worse eye with scotoma with maximal visual acuity (corrected) of 20/30 to 20/59.3. Worse eye with large scotoma, or moderate decrease in fields, but with maximal visual acuity (corrected) of 20–60 to 20–99 4. Worse eye with marked decrease in fields and maximal visual acuity (corrected) of 20/100–20/200; grade 3 plus maximal acuity of better eye 20/60 or less. 5. Worse eye with maximal visual acuity (corrected) less than 20/200; grade 4 plus maximal acuity of better eye of 20/60 or less. 6. Grade 5 plus maximal acuity of better eye of 20/60 or less. *V. Unknown.* *X. Added to grades 0 to 6 for presence of temporal pallor.*
7) Cerebral (Cognitive) Functions; 0. Normal. 1. Mood alteration only (does not affect DSS score). 2. Mild decrease in mentation. 3. Moderate decrease in mentation. 4. Marked decrease in mentation (chronic brain syndrome-moderate). 5. Dementia or chronic brain syndrome-severe or incompetent. *V. Unknown.*
8) Other Functions; 0. None. 1. Any other neurologic findings attributed to MS (specify). *V. Unknown.*

Annex B: The expanded Disability Status Scale

Data from (99)

- 0 = normal neurological examination (all FS items are zero).
- 1.0 = no disability but minimal signs only in one section of the SF.
- 1.5 = no disability but minimal signs in more than one section of the SF.
- 2.0 = minimum disability in a section of the SF (at least one with a score of 2).
- 2.5 = minimum disability (two sections of the SF scoring 2).
- 3.0 = moderate disability in a FS (one FS scores 3 but the others between 0 and 1). The patient wanders without difficulty.
- 3.5 = wanders without limitations but has moderate disability on one FS (one has a grade 3) or has one or two FS that score a grade 2 or two FS score a grade 3 or 5 FS have a grade 2 although the remainder are between 0 and 1.
- 4.0 = wanders without limitations, is self-sufficient, and moves around 12 hours per day despite a relatively significant disability according to a grade 4 on a SF (the remainder between 0 and 1). Able to walk without help or rest for about 500 meters.
- 4.5 = wanders fully without assistance, goes from one place to another for a large part of the day, able to work a full day, but has certain limitations for full activity, or requires minimal assistance. The patient has a relatively significant disability, usually with a grade 4 SF section (the remainder between 0 and 1) or a high combination of the other sections. He is able to walk without help or rest for around 300 meters.
- 5.0 = walks without help or rest for around 200 meters; her inability is sufficient to affect daily life functions, e.g. work all day without special measures. The usual FS equivalents are one of grade 5 only, the others between 0 and 1, or combinations of lower grades usually higher than grade 4.
- 5.5 = walks without help or rest for about 100 meters; the disability is severe enough to completely impede the activities of daily living. The usual FS equivalent is a single grade 5, others 0 to 1, or a combination of lower grades above level 4.

- 6.0 = requires constant help, either unilaterally or intermittently (cane, crutch or brace) to walk around 100 meters, without or with rest. FS equivalents represent combinations with more than two Grade 3 FSs.
- 6.5 = constant bilateral help (canes, crutches or braces) to walk about 20 meters without rest. The usual FS is equivalent to combinations with more than two Grade 3+ FS.
- 7.0 = unable to walk more than a few steps, even with assistance, basically confined to a wheelchair and able to move from it to another location or can drive to the toilet for 12 hours a day. The usual FS equivalents are combinations of two or more than one Grade 4+ FS. Very rarely grade 5 pyramidal syndrome only.
- 7.5 = unable to walk more than a few steps. Limited to wheelchair. You may need help to get out of it. It cannot be propelled in a normal chair and may require a motorized vehicle. The usual FS equivalents are combinations with more than one grade 4+ FS.
- 8.0 = basically confined to bed or chair, although able to turn around in wheelchair, can stay out of bed for much of the day, and is able to perform most of the activities of daily living. Generally, uses arms effectively. The usual FS equivalent is a combination of several systems at grade 4.
- 8.5 = basically confined to bed most of the day, has some useful use of one or both arms, able to carry out some activities of his own. The usual FS is equivalent to various combinations generally of a grade 4+.
- 9.0 = invalid patient in bed, can communicate and eat. The usual FS equivalents are combinations of a grade 4+ for most items.
- 9.5 = totally disabled in bed, unable to communicate or eat or swallow. The FS equivalents are usually combinations of almost all functions at grade 4+.
- 10 = death from multiple sclerosis.

Annex C: Information sheet

FULL D'INFORMACIÓ AL PACIENT

BENEFITS OF YOGA FOR REDUCE FATIGUE IN MULTIPLE SCLEROSIS

INVESTIGADORS PRINCIPALS: Dr Lluís Ramió i Torrentà i estudiant Sandra Ramis Pozuelo

TÍTOL DE L'ESTUDI: *"Benefits of yoga for reduce fatigue in multiple sclerosis"*

CENTRES: participen en l'estudi l'Hospital Santa Caterina (Girona).

INTRODUCCIÓ: ens dirigim a vosté per donar-li información d'un estudi en el qual està convidat a participar. Dins d'aquest full intentarem fer-li arribar tota la información necessària per a decidir si vol o no participar. Agraïriem llegís atentament tota la informació i no dubti en consultar en cas de dubte.

PARTICIPACIÓ VOLUNTÀRIA: la seva participació en aquest estudi és de caràcter totalment voluntari. Si decideix no participar-hi, les seves dades i mostres no es tindran en compte en cap moment i no li suposarà absolutament cap perjudici en un futur.

DESCRIPCIÓ DE L'ESTUDI: la finalitat de l'estudi proposat és millorar la fatiga crònica en pacients amb eslcerosi múltiple, per això, s'ha proposat com a tractament la pràctica de Yoga. Avui dia, s'en coneix poc sobre el paper del tractament no farmacològic sobre la fatiga i l'objectiu d'aquest estudi és definir la seva utilitat o no. Volem encoratjar la seva participació i unir-se a l'estudi, el qual serà format per dos grups: un primer grup en el qual es durà a terme una classe de yoga a la setmana i un segon que realitzarà la seva activitat de la vida quotidiana.

Per poder realitzar l'estudi, necessitarem que els participants omplin una sèrie d'escales els dies de visita.També, seria necessari accedir a la seva història clínica per la obtenció d'algunes dades rellevants en l'estudi.

CONFIDENCIALITAT: les dades dels participants seran confidencials, segons el "Reglamento (UE) 2016/679 del Parlamento Europeo y del Consejo, de 27 de abril de 2016, relativo a la protección de las personas físicas en lo que respecta al tratamiento de datos personales y a la libre circulación de estos datos", i la "Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales".

La informació serà emmagatzemada en una base de dades anonimitzada. En cas d'acceptar la participació en l'estudi, en qualsevol moment vostè pot sol·licitar l'esborrament de les seves dades als investigadors.

Annex D: Informantion consent

CONSENTIMENT INFORMAT

Jo, _____ , amb document d'indentificació personal (DNI/NIE)_____ declaro que:

- He rebut una còpia del full d'informació pel pacient.
- He rebut i entès tota la información que apareix en el document d'informació pel pacient.
- He pogut plantejar qualsevol dubte que m'ha sorgit, i me l'han resolt adequadament.
- Estic conforme amb la quantitat d'informació que se m'ha proporcionat.
- Entenc que la meva participación és voluntària i no remunerada.
- Entenc els potencials riscs i beneficis derivats de participar en aquest estudi.
- Comprenc que les meves dades i proves serán confidencials

A més, comprenc que tot i haver firmat el consentiment informat, puc revocar-ho en qualsevol momento i que això no suposarà un prejudici en el meu tractament ni assistència sanitària.

En conseqüència;

- Dono lliurement la meva conformitat a participar en l'estudi "*Benefits of yoga for reduce fatigue in multiple sclerosis*" i estic d'acord en què la informció obtinguda en aquest assaig clínic pugui ser utilitzada en investigacions futures.
- Accept que els investigadors del projecte puguin posar-se en contacte amb mi en un futur si es considera oportú.
- Accept l'obtenció de dades de la història clínica.

☐ Sí ☐ No

Signatura del pacient	Signatura de l'investigador

REVOCACIÓ DEL CONSENTIMENT INFORMAT

Jo, _____, amb document de identificació personal (DNI/NIE) _____ _____, revoco el consentiment prèviament firmat per a la participació en l'assaig clínic: "*Benefits of yoga for reduce fatigue in multiple sclerosis".*

Signatura del pacient	Signatura de l'investigador

Lloc i data: _____, _____ de _____ de l'any _____

Annex E: MODIFIED FATIGUE IMPACT SCALE (MFIS)

Following is a list of statements that describe how fatigue may affect a person. Fatigue is a feeling of physical tiredness and lack of energy that many people experience from time to time. In medical conditions like MS, feelings of fatigue can occur more often and have a greater impact than usual. Please read each statement carefully, and then circle the one number that best indicates how often fatigue has affected you in this way during the past 4 weeks. (If you need help in marking your responses, tell the interviewer the number of the best response.) Please answer every question. If you are not sure which answer to select, please choose the one answer that comes closest to describing you. The interviewer can explain any words or phrases that you do not understand.

MFIS-1: Data from (87)

Because of my fatigue during the past 4 weeks ....

	Never	Rarely	Sometimes	Often	Almost always
1. I have been less alert.	0	1	2	3	4
2. I have had difficulty paying attention for long periods of time.	0	1	2	3	4
3. I have been unable to think clearly.	0	1	2	3	4
4. I have been clumsy and uncoordinated.	0	1	2	3	4
5. I have been forgetful.	0	1	2	3	4
6. I have had to pace myself in my physical activities.	0	1	2	3	4
7. I have been less motivated to do anything that requires physical effort.	0	1	2	3	4

8. I have been less motivated to participate in social activities.	0	1	2	3	4
9. I have been limited in my ability to do things away from home.	0	1	2	3	4
10. I have had trouble maintaining physical effort for long periods.	0	1	2	3	4
11. I have had difficulty making decisions.	0	1	2	3	4
12. I have been less motivated to do anything that requires thinking.	0	1	2	3	4
13. my muscles have felt weak.	0	1	2	3	4
14. I have been physically uncomfortable.	0	1	2	3	4
15. I have had trouble finishing tasks that require thinking.	0	1	2	3	4
16. I have had difficulty organizing my thoughts when doing things at home or at work.	0	1	2	3	4
17. I have been less able to complete tasks that require physical effort.	0	1	2	3	4

18. my thinking has been slowed down.	0	1	2	3	4
19. I have had trouble concentrating.	0	1	2	3	4
20. I have limited my physical activities.	0	1	2	3	4
21. I have needed to rest more often or for longer periods.	0	1	2	3	4

Annex F: HEALTH STATUS QUESTIONNAIRE (SF-36)

Data from (87)

This survey asks for your views about your health and daily activities. If you are marking your own answers, please circle the appropriate responses (0, 1, 2, ...). If you need help in marking your responses, tell the interviewer the number of the best response (or what to fill in). Please answer every question. If you are not sure which answer to select, please choose the one answer that comes closest to describing you. The interviewer can explain any words or phrases that you do not understand.

1. **In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor
1	2	3	4	5

2. **For each statement please circle the one number that indicates how true or false that statement is for you.**

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
a) I seem to get sick a little easier than other people.	1	2	3	4	5
b) I am as healthy as anybody I know.	1	2	3	4	5
c) I expect my health to get worse.	1	2	3	4	5
d) My health is excellent.	1	2	3	4	5

3. **Compared to one year ago, how would you rate your health in general now?**

Much Better	Somewhat Better	Same	Somewhat Worse	Much Worse
1	2	3	4	5

4. **Now, think about the activities you might do on a typical day. Does your health limit you in these activities? If so, how much?** Please circle 1, 2 or 3 for each item to indicate how much your health limits you.

	Yes, Limited, A lot	Yes, Limited, A little	No, Not Limited, At All
a) Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b) Moderate activities, such as moving a table, pushing a vacuum cleaner or bowling, or playing golf	1	2	3
c) Lifting or carrying groceries	1	2	3
d) Climbing several flights of stairs	1	2	3
e) Climbing one flight of stairs	1	2	3
f) Bending, kneeling, or stooping	1	2	3
g) Walking more than a mile	1	2	3
h) Walking several blocks	1	2	3
i) Walking one block	1	2	3
j) Bathing and dressing yourself	1	2	3

5. **During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?** Please circle "1" (Yes) or "2" (No) for each item.

	YES	NO
a) Cut down on the amount of time you spent on work or other activities	1	2
b) Accomplished less than you would like	1	2

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health? Please circle "1" (Yes) or "2" (No) for each item.

	YES	NO
c) Were limited in the kind of work or other activities	1	2
d) Had difficulty performing the work or other activities 1 (for example, it took extra effort)	1	2

6. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe
1	2	3	4	5	6

7. During the past 4 weeks, how much did pain interfere with your normal work (including work both outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
1	2	3	4	5

8. During the past 4 weeks, have you had the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)? Please circle "1" (Yes) or "2" (No) for each item.

	YES	NO
a) Cut down on the amount of time you spent on work or other activities	1	2
b) Accomplished less than you would like	1	2
c) Did do work or other activities less carefully than usual	1	2

9. During the past 4 weeks, to what extent have your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	A little bit	Moderately	Quite a bit	Extremely
1	2	3	4	5

10. The next set of questions is about how you feel and how things have been with you during the past 4 weeks. For each question, please circle the one number for the answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks ...

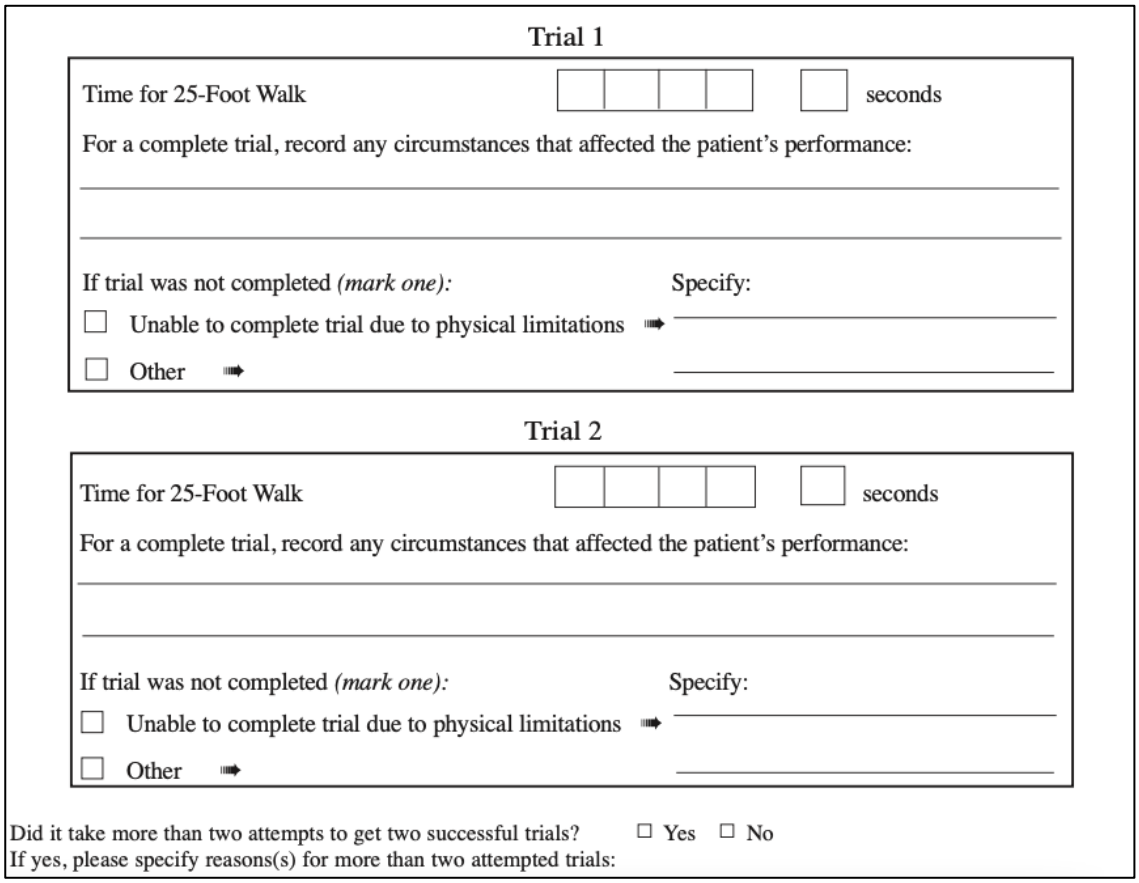
	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a) did you feel full of pep?	1	2	3	4	5
b) have you been a very nervous person?	1	2	3	4	5
c) have you felt so down in the dumps nothing could cheeryouup?	1	2	3	4	5
d) have you felt calm and peaceful?	1	2	3	4	5
e) did you have a lot of energy?	1	2	3	4	5
f) have you felt down hearted and blue?	1	2	3	4	5
g) did you feel worn out?	1	2	3	4	5
h) have you been a happy person?	1	2	3	4	5
i) did you feel tired?	1	2	3	4	5

11. Finally, during the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
1	2	3	4	5

Annex G: The 25-foot timed walk

Data from (88)



Trial 1

Time for 25-Foot Walk ☐☐☐☐ ☐ seconds

For a complete trial, record any circumstances that affected the patient's performance:

If trial was not completed *(mark one):* Specify:

☐ Unable to complete trial due to physical limitations ➡

☐ Other ➡

Trial 2

Time for 25-Foot Walk ☐☐☐☐ ☐ seconds

For a complete trial, record any circumstances that affected the patient's performance:

If trial was not completed *(mark one):* Specify:

☐ Unable to complete trial due to physical limitations ➡

☐ Other ➡

Did it take more than two attempts to get two successful trials? ☐ Yes ☐ No

If yes, please specify reasons(s) for more than two attempted trials:

Annex H: Brief Balance Evaluation Systems Test

Data from (100)

Section 1. Biomechanical Constraints			
Item 1: Hip/Trunk Lateral Strength "Rest fingertips in my hands while you lift your leg to the side and hold, keep trunk vertical. You will hold for 10 s." Count 10 s, watch for straight knee; if they use moderate force on your hands, score as "without keeping trunk vertical."	(3) Normal (10 s with trunk vertical) bilateral (2) Mild (10 s without trunk vertical) bilateral (1) Moderate (1 hip abducts with trunk vertical) (0) Severe (neither hip, 10 s and vertical or not vertical)--cannot abduct either hip 10 s, with or without trunk vertical		
Section II. Stability Limits			
Item 2: Functional Reach Forward "Stand normally; lift both arms straight in front of you; reach as far forward as you can with arms parallel to the ruler without lifting your heels." 2 attempts Observe that patient does not lift heels, rotate trunk, or protract scapula. Watch for vertical initial alignment. Record best reach.	(3) >32 cm (12.5 in) (2) 16.5–32 cm (6.5–12.5 in) (1) <16.5 cm (6.5 in) (0) No measurable lean (or must be caught)	Trial 1 (cm or in) Trial 2 (cm or in)	_____ _____
Section III. Transitions–Anticipatory Postural Adjustment			
Items 3 and 4: Stand on One Leg–Left and Right "Look ahead; hands must stay on hips; bend one leg behind you; stand on 1 leg as long as you can for up to 30 s. Do not let your lifted leg touch the other leg." Allow 2 attempts, record best attempt; record time up to 30 s (stop time if hands off hips or leg on floor or leg touches supporting leg).	(3) Normal (stable >20 s) (2) Trunk motion OR 10–20 s (1) Stand 2–10 s (0) Unable	Left Seconds Right Seconds	 _____ _____ _____
Section IV. Reactive Postural Response			
Items 5 and 6: Compensatory Stepping–Lateral, Left and Right "Stand with feet nearly together; lean into my hands; I will remove my hands; do whatever necessary to keep balance, trying to take 1 step." Note: Stand next to and behind participant. Place hand on greater trochanter and brace yourself to hold the person's weight shifted to supported leg.	(3) Recovers with 1 side/crossover step (2) Several steps to recover independently (1) Steps but needs assist to prevent fall (0) No step OR falls	Left Right	 _____
Section V. Sensory Orientation			
Item 7: Stance With Eyes Closed, on Foam Surface "Stand on foam with your eyes closed, your hands on your hips, and your feet close but not touching. Start by looking straight ahead, and I will start timing when you close your eyes. Stay as stable as possible and try to keep your eyes closed for the entire time. The goal is 30 s." Two trials, if necessary. Patient must step off foam between trials.	(3) 30 s stable (2) 30 s unstable (1) <30 s (0) Unable	Trial 1 (s) Trial 2 (s)	_____ _____
Section VI. Stability in Gait			
Item 8: Timed "Up & Go" Test "When I say 'go,' stand up and walk quickly but safely to the tape, turn, and walk back and sit in chair." Start with back against chair, stop timing when buttocks hit the chair; chair should have arms to push from, if necessary. Imbalance might include trips or lateral/backward stumbles or crossovers.	(3) Fast, <11 s, good balance (2) Slow, >11 s, good balance (1) Fast, <11 s, imbalance (0) Slow, >11 s, imbalance	Time (s)	_____
	TOTAL:		

Annex I: Tampa Scale for Kinesiophobia

Data from (23)

1 = strongly disagree 2 = disagree 3 = agree 4 = strongly agree

1. I am afraid of injuring myself if I exercise	1	2	3	4
2. If I tried to get over it, my pain would increase	1	2	3	4
3. My body tells me I have something dangerously wrong	1	2	3	4
4. Pain always means that I have hurt my body	1	2	3	4
5. I am afraid of accidentally hurting myself	1	2	3	4
6. Just being careful not to make unnecessary movements is the surest thing I can do to prevent my pain from getting worse	1	2	3	4
7. I wouldn't have as much pain if there wasn't something potentially dangerous in my body	1	2	3	4
8. Pain tells me when to stop exercising so as not to injure myself	1	2	3	4
9. It really is not certain that a person with a condition like mine is physically active	1	2	3	4
10. I can't do all the things normal people do because it's so easy for me to injure myself	1	2	3	4
11. No one should have to exercise when they are in pain	1	2	3	4

Annex J: Pittsburgh Sleep Quality Index

Data from (101)

Component 1: Subjective sleep quality

Examine question #6, and assign scores as follows:

Response	Component 1 score
"Very good"	0
"Fairly good"	1
"Fairly bad"	2
"Very bad"	3

Component 1 score:

Component 2: Sleep latency

1. Examine question #2, and assign scores as follows:

Respo\nse	Score
≤15 minutes	0
16-30 minutes	1
31-60 minutes	2
> 60 minutes	3

Question #2 score: _____

2. Examine question #5a, and assign scores as follows:

Response	Score
Not during the past month	0
Less than once a week	1
Once or twice a week	2
Three or more times a week	3

Question #5a score: _____

3. Add #2 score and #5a score

Sum of #2 and #5a: _____

4. Assign component 2 score as follows:

Sum of #2 and #5a	Component 2 score
0	0
1-2	1
3-4	2
5-6	3

Component 2 score:

PSQI Page 3

Component 3: Sleep duration

Examine question #4, and assign scores as follows:

Response	Component 3 score
> 7 hours	0
6-7 hours	1
5-6 hours	2
< 5 hours	3

Component 3 score:_____

Component 4: Habitual sleep efficiency

1. Write the number of hours slept (question #4) here:_____
2. Calculate the number of hours spent in bed:

   Getting up time (question #3):_____

   Bedtime (question #1):_____

   _____

   *Number of hours spent in bed:*_____

3. Calculate habitual sleep efficiency as follows:

   (Number of hours slept/Number of hours spent in bed) X 100 = Habitual sleep efficiency (%)

   (_____/_____) X 100 = %

4. Assign component 4 score as follows:

Habitual sleep efficiency %	Component 4 score
> 85%	0
75-84%	1
65-74%	2
< 65%	3

Component 4 score:_____

Component 5: Step disturbances

1. Examine questions #5b-5j, and assign scores for each question as follows:

Response	Score
Not during the past month	0
Less than once a week	1
Once or twice a week	2
Three or more times a week	3

5b score: _____

5c score: _____

5d score: _____

5e score: _____

5f score: _____

5g score: _____

5h score: _____

5i score: _____

5j score: _____

2. Add the scores for questions #5b-5j:

   Sum of #5b-5j: _____

3. Assign component 5 score as follows:

Sum of #5b-5j	Component 5 score
0	0
1-9	1
10-18-4	2
19-27	3

Component 5 score:

Component 6: Use of sleeping medication

Examine question #7 and assign scores as follows:

Response	Component 6 score
Not during the past month	0
Less than once a week	1
Once or twice a week	2
Three or more times a week	3

Component 6 score:

Annex K: Beck Depression Inventory

This depression inventory can be self-scored. The scoring scale is at the end of the questionnaire. Data from (102).

1.	0	I do not feel sad
	1	I feel sad
	2	I am sad all the time and I can't snap out of it
	3	I am so sad and unhappy that I can't stand it
2.	0	I am not particularly discouraged about the future
	1	I feel discouraged about the future
	2	I feel I have nothing to look forward to
	3	I feel the future is hopeless and that things cannot improve
3.	0	I do not feel like a failure
	1	I feel I have failed more than the average person
	2	As I look back on my life, all I can see is a lot of failures
	3	I feel I am a complete failure as a person
4.	0	I get as much satisfaction out of things as I used to
	1	I don't enjoy things the way I used to
	2	I don't get real satisfaction out of anything anymore
	3	I am dissatisfied or bored with everything
5.	0	I don't feel particularly guilty
	1	I feel guilty a good part of the time
	2	I feel quite guilty most of the time
	3	I feel guilty all of the time
6.	0	I don't feel I am being punished
	1	I feel I may be punished
	2	I expect to be punished
	3	I feel I am being punished
7.	0	I don't feel disappointed in myself
	1	I am disappointed in myself

	2	I am disgusted with myself
	3	I hate myself
8.	0	I don't feel I am any worse than anybody else
	1	I am critical of myself for my weaknesses or mistakes
	2	I blame myself all the time for my faults
	3	I blame myself for everything bad that happens
9.	0	I don't have any thoughts of killing myself
	1	I have thoughts of killing myself, but I would not carry them out
	2	I would like to kill myself
	3	I would kill myself if I had the chance
10.	0	I don't cry any more than usual
	1	I cry more now than I used to
	2	I cry all the time now
	3	I used to be able to cry, but now I can't cry even though I want to
11.	0	I am no more irritated by things than I ever was
	1	I am slightly more irritated now than usual
	2	I am quite annoyed or irritated a good deal of the time
	3	I feel irritated all the time
12.	0	I have not lost interest in other people
	1	I am less interested in other people than I used to be
	2	I have lost most of my interest in other people
	3	I have lost all of my interest in other people
13.	0	I make decisions about as well as I ever could
	1	I put off making decisions more than I used to
	2	I have greater difficulty in making decisions more than I used to
	3	I can't make decisions at all anymore
14.	0	I don't feel that I look any worse than I used to
	1	I am worried that I am looking old or unattractive

	2	I feel there are permanent changes in my appearance that make me look unattractive
	3	I believe that I look ugly
15.	0	I can work about as well as before
	1	It takes an extra effort to get started at doing something
	2	I have to push myself very hard to do anything
	3	I can't do any work at all
16.	0	I can sleep as well as usual
	1	I don't sleep as well as I used to
	2	I wake up 1-2 hours earlier than usual and find it hard to get back to sleep
	3	I wake up several hours earlier than I used to and cannot get back to sleep.
17.	0	I don't get more tired than usual
	1	I get tired more easily than I used to
	2	I get tired from doing almost anything
	3	I am too tired to do anything
18.	0	My appetite is no worse than usual
	1	My appetite is not as good as it used to be
	2	My appetite is much worse now
	3	I have no appetite at all anymore
19.	0	I haven't lost much weight, if any, lately
	1	I have lost more than five pounds
	2	I have lost more than ten pounds
	3	I have lost more than fifteen pounds
20.	0	I am no more worried about my health than usual
	1	I am worried about physical problems like aches, pains, upset stomach, or constipation

	2	I am very worried about physical problems and it's hard to think of much else
	3	I am so worried about my physical problems that I cannot think of anything else
21.	0	I have not noticed any recent change in my interest in sex
	1	I am less interested in sex than I used to be
	2	I have almost no interest in sex
	3	I have lost interest in sex completely

INTERPRETING THE BECK DEPRESSION INVENTORY

Now that you have completed the questionnaire, add up the score for each of the twenty-one questions by counting the number to the right of each question you marked. The highest possible total for the whole test would be sixty-three. This would mean you circled number three on all twenty-one questions. Since the lowest possible score for each question is zero, the lowest possible score for the test would be zero. This would mean you circles zero on each question. You can evaluate your depression according to the Table below.

_____ Total Score_____ Levels of Depression

_____1-10 These ups and downs are considered normal

11-16 _____Mild mood disturbance

17-20 _____Borderline clinical depression

21-30 _____Moderate depression

31-40 _____Severe depression

Over 40 _____Extreme depression

Annex L: Sexual Satisfaction Scale

Data from (87)

INSTRUCTIONS

The next series of questions concerns your intimate relationships and your satisfaction with your sex life. Many of these questions are very personal, but this is an important topic to cover. If you are marking your own answers, please circle the appropriate response (0, 1, 2, ...). If you need help in marking your responses, tell the interviewer the number of the best response. Please answer every question. If you are not sure which answer to select, please choose the one answer that comes closest to describing you. The interviewer can explain any words or phrases that you do not understand.

1. Do you have a relationship with one primary partner?

No (GO TO THE NEXT QUESTIONNAIRE)	0
YES	1

2. During the past 4 weeks, how satisfied have you been with the amount of affection expressed physically in your relationship?

Extremely satisfied	Moderately satisfied	Slightly satisfied	Slightly dissatisfied	Moderately dissatisfied	Extremely dissatisfied
1	2	3	4	5	6

3. During the past 4 weeks, how satisfied have you been with the variety of sexual activities you engage in with your partner?

Extremely satisfied	Moderately satisfied	Slightly satisfied	Slightly dissatisfied	Moderately dissatisfied	Extremely dissatisfied
1	2	3	4	5	6

4. During the past 4 weeks, how satisfied have you been with your sexual relationship in general?

Extremely satisfied	Moderately satisfied	Slightly satisfied	Slightly dissatisfied	Moderately dissatisfied	Extremely dissatisfied
1	2	3	4	5	6

5. How satisfied do you think your partner has been with your sexual relationship in general, during the past 4 weeks?

Extremely satisfied	Moderately satisfied	Slightly satisfied	Slightly dissatisfied	Moderately dissatisfied	Extremely dissatisfied
1	2	3	4	5	6