Doctoral Thesis
Laia Briones Buixassa - 2016

Supervised by:
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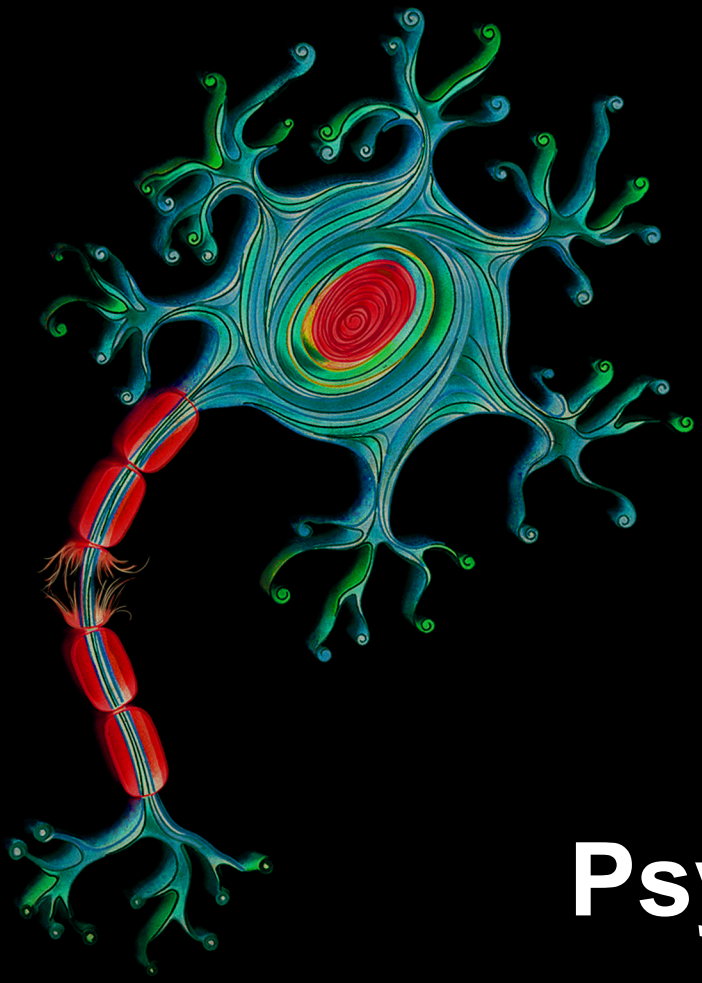
A thesis submitted for the degree of Doctor of Philosophy in:
Health, Welfare and Quality of Life

Universitat de Vic - Universitat Central de Catalunya



PsychoMSS Study:

Stress and Psychosocial Factors in Multiple Sclerosis

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DOCTORAL THESIS

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Centre d'Estudis Sanitaris i Socials

Facultat de Salut

Universitat de Vic - Universitat Central de Catalunya

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“The disease of the thousand faces.

As the thousand faces of the moon.

Even the shadows.”

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☺

Declaration by author

This thesis is comprised of original work. Jointly-authored works included, are clearly stated in each of the three phases of the thesis. Co-authors declare acceptance of being part of it.

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Publications during candidature

Journal publications

Phase One:

Briones-Buixassa, L., Milà, R., Aragonès, J.M., Bufill, E., Olaya, B., Arrufat, F. (2015) Stress and multiple sclerosis: a systematic review considering potential moderating and mediating factors and methods of assessing stress. *Health Psychology Open;* 2(2):1-16 DOI: 10.1177/2055102915612271

Phase Two:

Briones-Buixassa, L., Milà, R., Arrufat, F., Aragonès, J.M., Bufill, E., Luminet, O., Moss-Morris, R. (2016) A case-control study of psychosocial factors and their relationship to impairment and functionality in multiple sclerosis. *Journal of Health Psychology (Accepted for publication)*.

Phase Three:

Briones-Buixassa, L., Milà, R., Arrufat, F., Norton, S., Bufill, E., Aragonès, J.M., Moss-Morris, R. The stress effect and the role of coping in relapse occurrence, functionality and impairment in multiple sclerosis: a prospective study (under review).

Published abstracts

Briones-Buixassa, L., Mila, R., Aragones, J.M., Bufill, E., Arrufat, F. (2013) The influence of stress and psychosocial factors in multiple sclerosis: a review. *Psychother Psychosom*;82(suppl 1):1-134 DOI: 10.1159/000354142

Briones-Buixassa, L., Mila, R., Aragones, J.M., Bufill, E., Arrufat, F. (2015) The role of psychosocial moderator factors in the relationship between stress and multiple sclerosis: a case-control study. *Psychother Psychosom;*84(suppl 1):1-82 DOI: 10.1159/000438780

Conference presentations

Briones-Buixassa, L., Milà, R., Aragonès, J.M., Bufill, E., Arrufat, F. (2013) The influence of stress and psychosocial factors in multiple sclerosis: a review. Poster presentation: 22nd International Congress on Psychosomatic Medicine. Lisbon – Portugal. September 2013.

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Briones-Buixassa, L., Milà, R., Aragonès, J.M., Bufill, E., Arrufat, F. (2015) Stress and Multiple Sclerosis: a systematic review considering potential moderating factors and methods of assessing stress. Poster presentation: V Annual International Workshop on Higher Education. Vic – Spain. June 2015.

Briones-Buixassa, L., Milà, R., Aragonès, J.M., Bufill, E., Arrufat, F. (2015) The role of psychosocial moderator factors in the relationship between stress and Multiple Sclerosis: a case-control study. Poster presentation: 23rd International Congress on Psychosomatic Medicine. Glasgow – Scotland. August 2015.

Briones-Buixassa, L., Milà, R., Aragonès, J.M., Bufill, E., Arrufat. F. (2016) Psychosocial moderator and mediator factors of the stress response in multiple sclerosis and its relationship with disease progression: a case-control study. Oral communication. VI Annual International Workshop on Higher Education. Vic – Spain, June 2016.

List of contents

Presentation

The present thesis summarizes the main results of the project *"PsychoMSS Study: Stress and Psychosocial factors in Multiple Sclerosis"* developed in the region of Osona, in Catalonia (Spain). This region has an increasing incidence of Multiple Sclerosis (MS) and the prevalence ratio is one of the highest in Spain (Otero-Romero et al., 2013).

It was carried out within the Research Group of Mental Health and Social Innovation (SaMIS), in the Health and Social Care Research Centre (CESS) in Vic. This is an interdisciplinary and inter-institutional research group composed of professionals from the Consorci Hospitalari de Vic and the Universitat de Vic – Universitat Central de Catalunya. As a result of a research internship Prof. Rona Moss-Morris and Dr. Sam Norton from King's College London (United Kingdom) also participated in the study. Moreover, Dr. Beatriz Olaya from Parc de Recerca Sant Joan de Deu (Catalonia) and Dr. Olivier Luminet from Université Catholique de Louvain (Belgium) collaborated in the writing of papers one and two respectively.

The main goal of the present thesis was to study the effect of stress in Multiple Sclerosis taking into account different potential psychosocial moderators and mediators of this relationship. To date research conducted on this area has yielded disparate results and the measures and methods used to test this effect are so heterogeneous that they preclude drawing firm conclusions.

In order to contribute to the body of knowledge this study tries to address three important questions: first, which instruments and methods to assess stress and disease progression were used, and which factors were considered as moderators or mediators to date; second, which of the psychosocial factors proposed are different when comparing people with and without MS and what is their relationship with disease parameters; and third, what is the effect of stress on disease progression (and viceversa), and what is the role of the different psychosocial factors in this relationship.

In this thesis these questions are addressed through scientific papers submitted to international and peer-reviewed journals with the aim of ensuring the quality of the conducted research and the maximum dissemination and utility of the reported results.

The first phase is a systematic review called *Stress and multiple sclerosis: A systematic review considering potential moderating and mediating factors and methods of assessing stress,* published in the *Health Psychology Open* Journal in November

2015. The aim of this study was to summarize the results of the studies that addressed the effect of stress in Multiple Sclerosis focusing on the methods used to measure stress and potential moderators and mediators of this relationship.

The second phase is a cross-sectional, case-control study called *A case-control study of psychosocial factors and their relationship to impairment and functionality in multiple sclerosis.* It was accepted for publication in November 2016 in the *Journal of Health Psychology*. The aim of this study was to compare several psychosocial factors related to coping and appraisal between people with and without MS, and to observe their association with disease progression parameters of functionality and impairment.

The third phase is a prospective, longitudinal one year follow-up study called *The stress effect and the role of coping in relapse occurrence, functionality and impairment in Multiple Sclerosis: a prospective study.* It was submitted for publication in November 2016 and it is currently under review. A one year follow-up was conducted with people diagnosed with MS using several stress and disease progression assessments under a transactional approach. The aim of this study was to analyse the effect of stress on MS and to test the interaction role of coping on this relationship. Complementary analyses were conducted to analyse the interaction role of social support, anxiety, alexithymia and early-life stress.

These studies are presented in this thesis with the following format. First, a broad theoretical framework is provided along with the main aims. Then, a methods section summarizes the methodology used for the whole study (a detailed methodology is provided in each study). Afterwards in the results section, the three studies are presented as paper and manuscript formats providing a more detailed explanation and results of each phase. At the end, discussion of the results, summaries of the main findings, recommendations and implications, strengths and limitations, future direction for research and conclusions are provided.

Abstract

The stress effect on Multiple Sclerosis (MS) is a complex and understudied issue that has yielded disparate results. One reason for that may be the heterogeneity in how stress is measured and the presence of potential psychosocial moderators and meditators of this relationship.

Aims: to analyse the effect of stress on Multiple Sclerosis under a transactional approach and to elucidate the role of the psychosocial factors of coping, social support, anxiety, alexithymia and early life stress in the relationship between stress and MS.

Methods: the project *"PsychoMSS Study: Stress and Psychosocial Factors in Multiple Sclerosis"* was designed. It consisted in three phases: a) a qualitative systematic review focused on the main results, the stress assessment, and the moderators and mediators of the stress-MS relationship; b) a case-control study to compare the psychosocial factors mentioned above between people with MS (pwMS) and without MS, and to observe their association to disease parameters of functionality and impairment; and c) a longitudinal one year follow-up study in pwMS to see the effect of several measures of stress on the disease parameters of functionality, impairment and relapses, and the moderator effect of the psychosocial factors. Interviews, questionnaires, scales and self-reported diaries were carried out. Student T-tests, Chi-Squares, Correlations, Linear and Multiple Hierarchical Regressions Mixed models in long format data were used for the statistical analysis.

Results: the systematic review conducted in Phase One showed that most studies assessing the effect of stress on MS presented a negative association, giving the self-reported measures the most consistent results. The case-control study conducted in Phase Two showed that PwMS had a more passive coping pattern than controls, less perceived social support and higher levels of anxiety and alexithymia. Anxiety and avoidance coping were related to functionality and impairment. The follow-up study conducted in Phase Three showed that the effect of stress on MS was confirmed to be bidirectional but only with self-reported measures of perceived stress and functionality. Coping and anxiety showed a moderator effect between perceived stress and functionality.

Conclusions: stress and MS may follow a deteriorating vicious cycle that needs to be broken in the early stages of MS. Psychotherapeutic approaches should be focused on stress management, resources to adjust to MS, and potentially

modifiable psychosocial factors like anxiety, alexithymia or social support. Adding psychotherapies complementary to the clinical and pharmacological treatments may improve the adjustment to the disease, the functionality, and the quality of life in pwMS.

Abstract (Catalan version)

L'efecte de l'estrès en l'Esclerosi Múltiple (EM) és un tema complex i poc estudiat que ha donat lloc a resultats molt dispars. Això pot ser degut a l'heterogeneïtat en l'avaluació de l'estrès i a la presència de factors psicosocials potencialment moderadors i mediadors d'aquesta relació.

Objectius: analitzar l'efecte de l'estrès en l'EM sota un paradigma transaccional i, alhora, entendre quin és el rol dels factors psicosocials de l'afrontament, el suport social, l'ansietat, l'alexitimia i l'estrès primerenc en la relació entre l'estrès i l'EM.

Metodologia: es va desenvolupar el projecte ""*PsychoMSS Study: Stress and Psychosocial Factors in Multiple Sclerosis"* consistent en tres fases: a) una revisió sistemàtica qualitativa centrada en els resultats principals, l'avaluació de l'estrès, i els moderadors i mediadors de la relació entre l'estrès i l'EM; b) un estudi de cas control per tal de comparar els factors psicosocials abans esmentats entre les persones amb EM i sense EM, així com també, observar-ne la seva associació amb paràmetres de la malaltia com la funcionalitat i la discapacitat; i c) un estudi longitudinal d'un any de seguiment amb les persones amb EM per tal d'explorar l'efecte de diferents mesures de l'estrès en els paràmetres de funcionalitat, discapacitat i en la presència de brots, així com també l'efecte moderador dels factors psicosocials. Es van dur a terme entrevistes, qüestionaris, escales i auto-registres diaris. Els anàlisis estadístics van incloure: T de Student, Chi quadrat, Correlacions, Models de regressió lineal i models mixtes de regressió múltiple amb les dades en format longitudinal.

Resultats: la revisió sistemàtica duta a terme en la primera fase va mostrar que la majoria dels estudis revistats que avaluaven l'efecte de l'estrès en l'EM van presentar una associació negativa, i les mesures auto-informades van mostrar els resultats més consistents. L'estudi de cas-control dut a terme en la segona fase va mostrar que les persones amb EM van tenir un patró d'afrontament més passiu que el grup control, menys percepció de suport social i nivells més alts d'ansietat i alexitimia. L'ansietat i l'afrontament d'evitació es van relacionar amb la funcionalitat i la discapacitat. L'estudi de seguiment que es va dur a terme en la tercera fase va

mostrar que l'efecte de l'estrès en l'EM és bidireccional però només amb les mesures auto-informades d'estrès percebut i funcionalitat. L'afrontament i l'ansietat van mostrar un efecte moderador entre l'estrès percebut i la funcionalitat.

Conclusions: l'estrès i l'EM poden seguir un patró deteriorant cíclic que hauria de ser tractat en les primeres fases de la malaltia. Les intervencions psicoterapèutiques s'haurien de centrar en el maneig de l'estrès, recursos per millorar l'adaptació a l'EM, i en els factors psicosocials que son potencialment modificables com l'ansietat, l'alexitimia o el suport social. Afegir aquestes intervencions psicoterapèutiques de forma complementària al tractament clínic i farmacològic podría millorar l'adaptació a la malaltia, la funcionalitat i, en general, la qualitat de vida de les persones amb EM.

1. Introduction

Introduction

1.1 The Biopsychosocial Model and health psychology

In 1977 George Engel proposed the Biopsychosocial Model as an opposite approach to the predominant model to date, the Biomedical Model (Engel, 1989). This new approach postulated that health was the result of the interaction of biological, psychological and sociological aspects. The biological aspects referred to genetic and physiological mechanisms. The psychological processes referred to perceptions, emotions, beliefs and behaviours. The social aspects referred to the social structure, the cultural influence and the socioeconomic context. These three aspects of health were also included in the definition of health provided by the World Health Organization (1948), which postulated that *"Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity"*. From this point of view, psychological and social aspects are considered as important as biological mechanisms in the processes of health and disease.

Brannon and Feist (2001), in their book on health psychology highlighted the idea that as health and disease are increasingly linked to behaviour, psychology is becoming more involved in health-related issues. The health psychology discipline emerged in this context, trying to give a response and to put into practice the necessity for a wider approach to health and disease.

1.1.1 Health psychology and chronic diseases

The concept of health psychology was first defined by Matarazzo in 1980 *"Health psychology is an aggregate of the educational, scientific and professional contributions of the discipline of psychology to the promotion and maintenance of health, the prevention and treatment of illness, the identification of etiologic and diagnostic correlates of health, illness and related dysfunction and the improvement of*

the Health Care System and Health policy formation" (Abraham, Conner, Jones & O'Connor, 2008).

Several studies showed the impact and importance of health behaviours on individuals' health and, consequently, on public health systems. Sedentary behaviour, poor sleep, an unbalanced diet and drinking alcohol or smoking are habits that can promote some diseases in the long term, being able to predict mortality (Belloc & Breslow, 1972) and, accounting for almost 40 per cent of all deaths in the USA (Mokdad, Marks, Stroup & Gerderbing, 2004). In 2005, the World Health Organisation published a report on the importance of preventing chronic diseases as the new target for public health (WHO, 2005). In the UK National Health Service, Wanless (2002) conducted a review concluding that disease prevention strategies and high levels of public engagement in health care and maintenance were crucial to the economic viability and effectiveness of the National Health Service. For this reason it is important to promote preventive health behaviours, especially empowering people to cope with chronic diseases, the new epidemic of the 21st century. According to the World Health Organization approximately 58 million deaths were estimated to have occurred in 2005 and 35 million were caused by chronic diseases. Nearly 16 million chronic disease deaths occur each year in people under 70 years old, almost 80% in low and middle income countries and half are in women (WHO, 2005). But apart from death, chronic diseases increase the expenditure of societal costs. It was estimated that chronic diseases were responsible for 50% of the total disease burden in 2005 (Abegunde, Mathers, Adam, Ortegon & Strong, 2007) and, only in America, it was calculated that the most common chronic disease was costing the economy more than $1 trillion annually (DeVol et al., 2007).

Although it is well established that the main risk factors for chronic diseases are those related to an unhealthy diet, physical inactivity and tobacco consumption, the WHO (2005) highlighted the importance of different psychosocial factors that might be acting as risk factors or affecting the clinical course of some chronic diseases. Psychosocial factors can affect health along two pathways: the behavioural or indirect pathway and the psychophysiological or direct pathway. The indirect way influences disease through health-related behaviours like smoking, drug intake, poor diet and sleep, or sedentary behaviour, that ultimately deregulate our different systems and, over the long term, may cause diseases. For example, sedentary behaviour and the risk of cardiovascular disease (Ford & Caspersen, 2012), diet and the risk of diabetes (Waxman, 2005) or alcohol intake and cirrhosis (Becker et al., 1996), among other well described disease-behaviour relationships. The direct way affects disease through psychophysiological mechanisms like the activation of the sympathetic nervous system

or cortisol release. For example, chronic stress can deregulate the immune system increasing the risk of a common cold (Cohen, Tyrrell & Smith, 1991); or type A personality was linked to a higher blood pressure and heart rate, which increase the risk of a stroke (Smith & MacKenzie, 2006).

One of the main psychosocial factors postulated to affect health and disease through these two pathways was stress. It was related to unhealthy behaviours like a higher fat diet, less physical activity or smoking (Ng & Jeffrey, 2003); and at the same time, it was shown that exposure to chronic stress might cause deregulation in the internal individual homeostasis, especially through the effect on the immune system (Valdés & De Flores, 1990). For this reason, stress was postulated as a risk factor and a modifier of the clinical course in some autoimmune diseases like Multiple Sclerosis (MS; Artemiadis, Anagnostouli & Alexopoulos, 2011), Lupus (Peralta-Ramírez, 2004) or asthma (Nagata, Irie & Mishima, 1999), among others.

1.2 Multiple Sclerosis: a chronic disease

1.2.1 History, definition and types of MS

Multiple Sclerosis was first described by J.M. Charcot in 1868 as a separate disease with specific symptoms while he was working in La Salpêtrière in Paris. However, before its official discovery several cases of MS were described. In the 14th and 15th centuries different possible cases were reported, but it remains unclear whether they were in fact MS. The first considered proven case of MS was the case of Auguste d'Este, the cousin of Queen Victoria, who wrote one of the most famous accounts of MS. He wrote about a disabling disease with a relapsing-remitting course with the same symptoms of MS in the first half of the 19th century. Later, between 1938 and 1942 Jean Cruveilhier de Limoges and Robert Carswell drew in their anatomy notebooks pictures of an injured spinal cord with typical plaques or lesions of MS (Gónzalez-Morón & Villoslada, 2010).

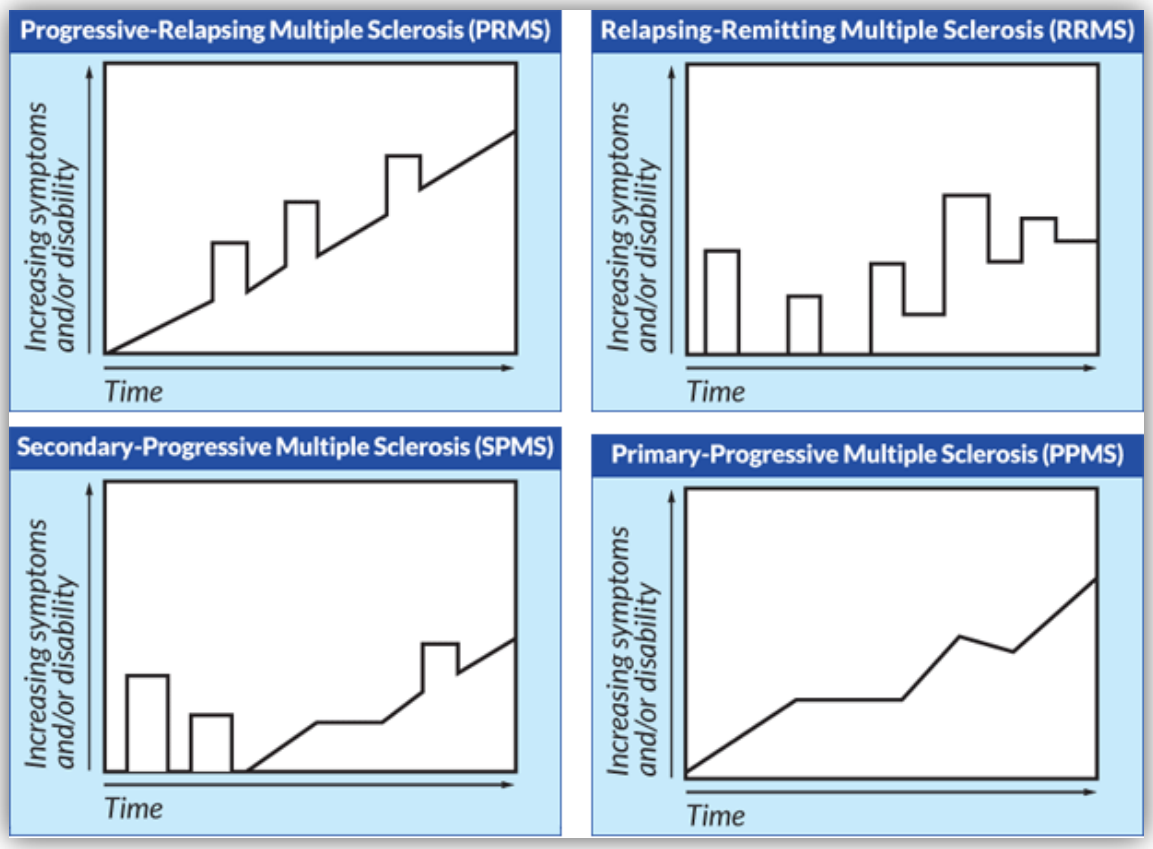
Nowadays, MS is one of the world's most common neurological disorders. In many countries, MS is the leading cause of non-traumatic disability in young adults (Browne et al., 2014), and it has major implications for the quality of life of people with MS (pwMS) and their caregivers (Aronson, 1997), and a great cost to themselves and their families and for the healthcare systems (Whetten-Goldstein, Sloan, Goldstein & Kulas, 1998; Kobelt, Berg, Lindgren, Fredrikson & Jönsson, 2006).

Clinically MS is considered an autoimmune disease that affects mainly the white matter in the central nervous system and involves different pathogenic mechanisms: autoimmunity, inflammation and degeneration. It is thought that the immune system attacks certain myelin sheaths causing lesions in the white matter that provoke a slowdown in the electric impulses. Demyelination might remit partially or totally but, over the years, there is neurodegeneration and loss of functions (Noseworthy, Lucchinetti, Rodriguez & Weinshenker, 2000).

There are different types of MS or clinical forms based on the progression of the disease and the presence of relapses during the clinical course (see figure 1). Eighty-

five percent of pwMS debut with a relapsing-remitting course, the most common clinical type of MS, which alternates periods of relapse with periods of remission with total or partial recovery. After several years most of them become secondary progressive, getting progressively worse and with a lower relapse rate. Finally, the primary progressive type is considered in those people that start with a progressively worsening clinical form, with or without relapses (Del Pino, Olascoaga & Arias, 2010).

Figure 1. Types of MS



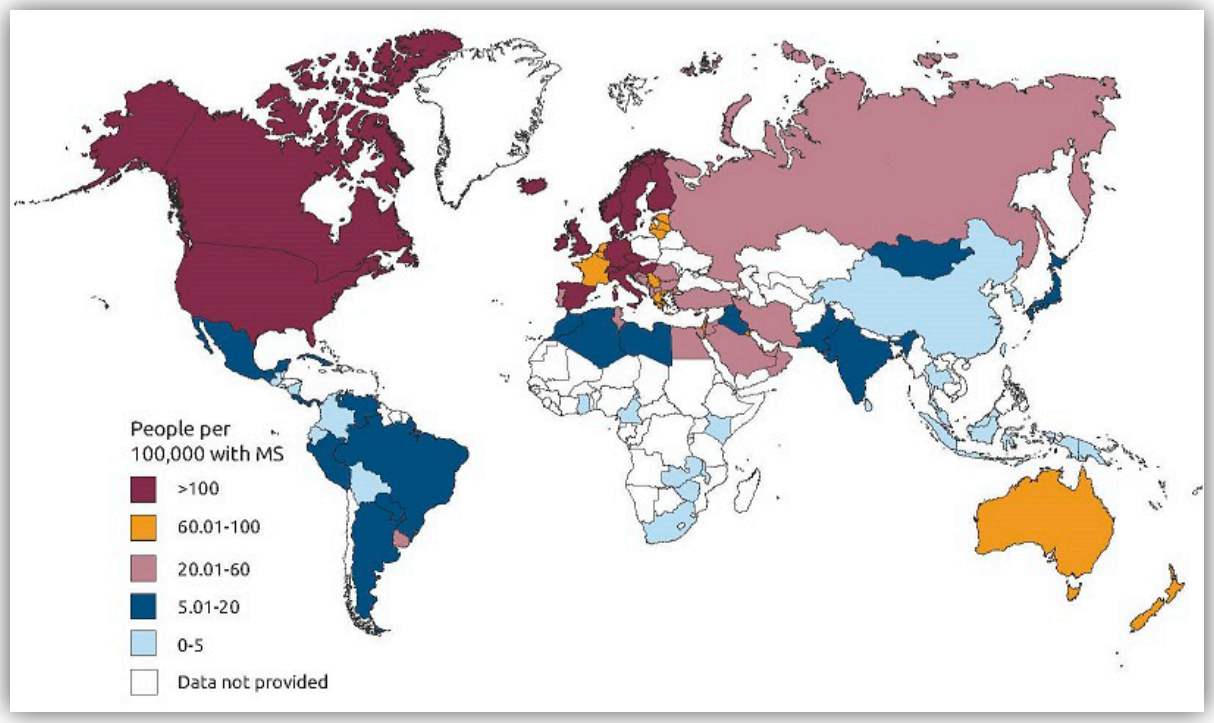
Source: ModerndayMS.com (2016)

1.2.2 Epidemiology

There were approximately 2.3 million people around the world diagnosed with MS in 2013. The estimated number increased from 2.1 million in 2008 and the global median prevalence increased from 30 in 2008 to 33 per 100,000 inhabitants in 2013. However, this increase can be due to better diagnosis and reporting (Browne et al.,

2014). The female-to-male ratio is 2:1; although in some countries higher ratios have been reported like East Asia (3:1) or the Americas (2.6:1).

Figure 2. Prevalence of MS by Country (2013)



Source: Multiple Sclerosis International Federation (2013)

Kurtzke classified regions around the world according to the prevalence of MS following these criteria: low prevalence <5 cases, intermediate prevalence between 5–30 cases or high prevalence >30 cases per 100,000 inhabitants (Kurtzke, 1995). According to this criteria Spain is considered a high-risk country for MS. Prevalence studies from 1968 to 2012 have shown an increasing incidence rate, with the latest data on prevalence showing between 79 to 125 cases per 100,000 inhabitants (Ares et al., 2007; Fernandez et al., 2012, Otero-Romero et al., 2013). In Osona, a specific region of Catalonia where the study was conducted, prevalence has increased to the point of becoming one of the highest reported in Spain, from 58 cases in 1991 to 91.2 cases per 100,000 inhabitants in 2008 (Otero-Romero et al., 2013).

1.2.3 Aetiology

The aetiology of Multiple Sclerosis is unknown, but it is believed to be a complex disease, involving multiple genes and environmental factors in its pathogenesis. The genetic link has been established mainly with HLA region and interleukin gens (IL) 2 and 7 through studies with families, twins, ethnic groups, and migrants (for a review see Dyment, Ebers & Sadovnick, 2004). A person with a first-degree relative who is affected by MS has a 3-5% risk, whereas the general population has a 0.1-0.2% risk. The children of both parents affected have around a 30% risk of suffering MS, as well as monozygotic twins, whereas dizygotic twins only have a 3-5% risk (Dyment et al., 2004).

However, genetic predisposition alone does not explain the aetiology of MS and environmental factors have been postulated. Some of them are the low sunlight exposure and vitamin D deficiency (Acherio & Munger, 2007b; Munger et al.,2004), several virus infections like Epstein-Barr, measles, varicella zoster or herpes virus 6 (Ascherio & Munger, 2007a), and exposure to organic solvents (Riise, Moen & Kyvik, 2002), as well as different behaviours and lifestyles like smoking (Riise, Nortvedt & Ascherio, 2003), oral contraceptives (Alonso et al., 2005), diet (Zhang, Willet, Hernán, Olek & Ascherio, 2000) or stress (for a review, see Artemiadis et al., 2011).

1.2.4 Diagnostic, symptoms and treatment

The criteria for the initial diagnosis of MS evolved from the criteria postulated by Schumacher et al. in 1965, which were updated by Poser et al. in 1983, and more recently by McDonald et al. in 2001, reviewed by Polman et al., in 2005 and in 2011.

Multiple Sclerosis generates a wide variety of symptoms, depending on the brain area affected. Common symptoms reported are fatigue, paresis, paraesthesia and vertigo. Other typical symptoms occur when inflammatory changes affect the autonomic nervous system. These are deregulation of the bladder and bowel, sexual dysfunction, abnormalities in cardiovascular reflexes, alterations in sweating and thermoregulation and pupillomotor disturbances among others (Merkelbach et al. 2006).

As we mentioned above, 85% of pwMS debut with the relapsing-remitting type of MS. A relapse can be defined as a worsening of existing symptoms or appearance of new ones lasting more than 24 hours after at least 30 days of improvement or stability not associated with fever (McDonald et al., 2001). In general, relapses are classified according to the functionality of the affected system in efferent relapses (motor symptoms, ataxia) or afferent relapses (sensory symptoms, visual disturbances) but, in general, different types of relapses can occur depending on the brain area affected by the disease activity, from cognitive or motor impairments to sensitive or visual disturbances, with different levels of affectation.

In MS the impairment level is measured through the Expanded Disability Status Scale (Kurtzke, 1983). This scale measures impairment through the evaluation of 8 different functional systems: pyramidal (motor function), cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral or mental, and “others”. Then, along with the ability to walk an overall score is obtained. It ranges from 0 to 10 in 0.5 unit increments that represent higher levels of impairment. A score of 7 and above means daily life support is required. A score of 10 means death due to MS.

There is not a definitive cure for MS. Currently medical treatments are focused on slowing down the progression of the disease and reducing relapses and symptomatology through the suppression of the immune system, thereby preventing inflammatory reactions. Some of the most prescribed drugs are fingolimod or interferon (Cohen et al., 2010).

1.3 Stress: definition, theories and impact on health

A common definition of stress is the one we find in the Oxford Dictionary, where stress is considered *"a state of mental or emotional strain or tension resulting from adverse or demanding circumstances"* (Stevenson, 2010). Etymologically the word stress comes from the Latin verb "*stringere"*, which means "*to tighten*". Until the 10th century the word stress was mainly used to refer to fight, difficulties or adversities (14th century) or referred to the load or weight applied to a structure (17th century; Cooper & Dewe, 2008). In 1932 Walter Cannon used the word stress for the first time in a health or medical context; he was the first to talk in experiments about the *"conditions that imply strain to the nervous system"* (Cannon, 1932). Subsequently, the physician and physiologist Hans Selye formalized and extended its use and was considered the "father" of the concept of stress. He defined it as *"the non-specific response of the body to any demand made upon it"* and developed the concept of General Adaptation Syndrome (GAS) in 1956 as a way to explain the stress response pattern (Selye, 1956). This definition and concept of stress are still used at the present time, but they are restricted to physiological stress. Afterwards, in the 1980's, the attention of research was focused on psychological and social aspects of stress giving rise to new theoretical approaches like the Transactional Theory of Lazarus and Folkman (1984) or the Conservation of Resources Theory of Hobfoll (1989).

Traditionally, there are three different approaches to the study of stress: the response-based or medico-physiological approach; the stimulus-based or engineering approach; and the psychological "interaction-appraisal" or transactional approach (Sandín, 1999).

The response-based approach mainly considers stress as a physiological reaction to noxious events like changes in blood pressure, sympathetic activation or cortisol release. In this approach stress is considered as a dependent variable inherent to the body. From this point of view, psychological mediating processes are not taken into account. The General Adaptation Syndrome Theory of Hans Seyle (1956) is based on this approach.

The stimulus-based approach views stress as an external phenomenon like a pain stimulation, the death of a relative or any stressful event considered as a demand on an individual from their environment which produces a strain reaction. From this approach stress is considered as an independent variable and stress response is the reaction to the stressor: the greater the strain, the larger the reaction. This approach does not account for individual psychological processes either. The Holmes & Rahe life events theory (1967) is based on this approach.

Finally, the interactional-appraisal or transactional approach is the most current conceptualization of stress. It considers stress as a process, an interaction (or transaction) between the individual and the environment. These theories have pointed out the importance of psychological mediating and moderating processes trying to explain the variation in responses to similar stressful events. The Transactional Theory of Stress of Lazarus and Folkman (1984) or the Conservation of Resources Theory of Hobfoll (1989) are based on this approach.

1.3.1 The General Adaptation Syndrome of Hans Seyle (1956)

Hans Seyle defined stress as a physiological reaction that was always the same regardless of whether the stressor was good (eustress) or bad (distress). He postulated the General Adaptation Syndrome in 1956 as an explanation to describe the response pattern to stress in three main stages:

a) Alarm: physiologic immediate reaction caused by the stressor appearance. In this stage stress hormones are released and, as a result, several physiological changes prepare the body for action (fight or flight response). If the stressful situation remains the body goes to the next stage.
b) Resistance: if stress is prolonged, organism activation and levels of stress hormones remain high. It seems that there is some kind of adaptation but, if the stressful situation still remains, resources are exhausted and the last stage appears.
c) Exhaustion: if stress remains the individual becomes more vulnerable to organic dysfunction of body systems like immune and nervous systems. In the long term this can lead to illness and even death.

This approach was criticised because it does not take into account the idiosyncratic response of each person to different stressful events or the similarities in biologic response in the face of “bad” stressors like the death of a relative or “good” stressors like a birthday surprise (Lacey, 1967).

1.3.2 The Life Events Theory of Holmes and Rahe (1967)

This theory considers stress as a stimulus, focusing on external stressful events and the environment. Stressful events are defined as unexpected or unplanned events that negatively affect people in a physical or psychological way (Sandín & Chorot, 1999). Usually people do not have time to prevent or prepare to face events and attribute their tension to these events for example, a divorce or being fired from the workplace. The stressful event can be labelled and measured, and its properties are considered to affect people in the same way. Holmes and Rahe developed a widely known taxonomy to classify stressful events, called the “Social Readjustment Rating Scale” (1967). It classifies different stressful events from highest to lowest and gives a score to each stressor: the higher the score, the higher the stress. However, this theory does not take into account the individual differences in appraisal, assuming that all people rank events in a similar way. For example, the death of a spouse can be considered a distressing event in a happy marriage or a relief if it occurs to a person who is suffering domestic violence. Moreover, this approach fails to address the different factors that can moderate the relationship between stressful events and diseases (Morrison & Bennet, 2006).

1.3.3 The Transactional Theory of Lazarus and Folkman (1984)

The Transactional Theory of Stress defines stress as a *“particular relationship between the person and the environment that is appraised by the person as taxing or exceeding his or her resources and endangering his or her well-being*” (Lazarus &

Folkman, 1984). It emphasizes the psychological process, considering the cognitive appraisal and the coping process as key aspects in the conceptualization of stress (see figure 3). Stress is not considered as a stimulus or a property of the environment, nor is it a response or a property of the individual; it is a transaction between the individual and the environment.

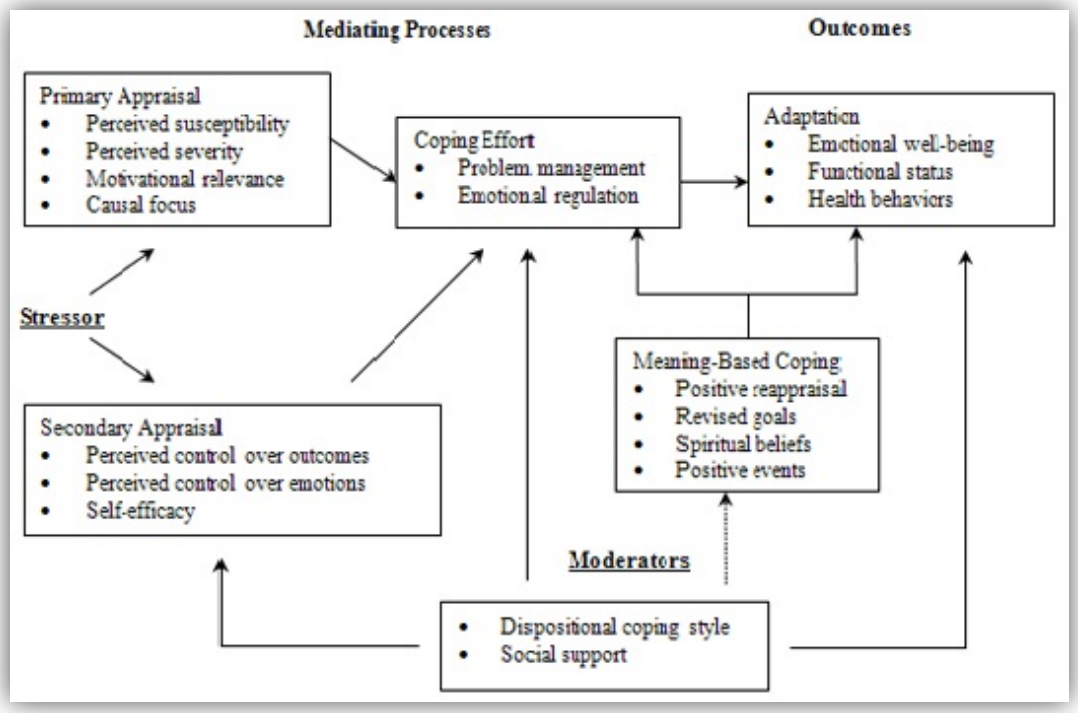
When facing a stressful event a person may appraise the situation as a loss, harm, threat or, in a positive and optimistic view, as a challenge. The appraisal will then determine the person's coping process, which subsequently will determine new appraisals. The physiological activation appears as a result of the cognitive appraisal, individual characteristics and personal resources to deal with stressors (Lazarus & Folkman, 1987).

Appraisal is defined as a cognitive mediator of the stress response. It is a process in which people assess the meaning of what is happening in relation to their own wellbeing. There are three types of appraisal; primary appraisal, secondary appraisal and reappraisal:

a) Primary Appraisal is the evaluation of the stressful situation, demands and consequences. It can be assessed as positive or a challenge or stressful as a harm, threat or loss (Lazarus, 2000). However, they are not mutually exclusive; a job promotion can be seen at the same time as a challenge, a loss and even a threat.
b) Secondary Appraisal is the evaluation of the resources and abilities to deal with the stressful situation. Primary and secondary appraisal will determine which coping strategies will be implemented.
c) Reappraisal refers to the new primary appraisal after changes or new information has become available.

Furthermore, Lazarus suggests that stress is a complex phenomenon which involves many variables and moderating or mediating factors associated with appraisal and coping. This point of view has implications for the way stress is measured (Lazarus, 1990). He suggests that stress has to be assessed with different measures capturing different aspects of the stress process, including environmental inputs (daily stressors or life events), measures of individual differences, coping and psychological and physiological responses. Moreover, as stress is considered a process it is critical to take repeated assessments over time. A recommended tool (Folkman, 2008) to measure stress from the transactional approach is the Perceived Stress Scale by Cohen, Kamarak & Mermelsetein (1983).

Figure 3. The Transactional Model of Stress and Coping



Source: www.med.upenn.edu 2016

1.3.4 The Conservation of Resources Theory of Hobfoll (1989)

The Conservation of Resources Theory considers that resources are the key variables in the resources-demands stress interaction and that people try to *"retain, protect and build resources"* (Hobfoll, 1989). From this point of view stress is defined as a reaction to loss, a threatened loss, or a failure to gain resources after an investment of resources. Hobfoll suggests that when people are facing a stressful situation they will try to minimize the potential loss of resources seeking to build new resources or to be protected against stressful situations that may occur in the future. Resource loss is considered to have a greater impact than resource gain.

Like the Transactional theory, this model considers stress as an interaction between demands and resources, but its emphasis is on resources whereas the Transactional theory emphasizes appraisals. Another distinction is that this model highlights the importance of proactive coping given that resources are built for prevention or protection against future stressful events and not as a response to a present cognitive appraisal (Hobfoll, 2001).

1.3.5 The biology of stress

Regardless of whether stress is considered a stimulus, a physiological process or an interaction between demands and resources, suffering stress has a biological effect on the body through the activation of two systems: the Sympathetic-Adrenal-Medullary system (SAM) and the Hypothalamic-Pituitary-Adrenal axis (HPA; Valdés & De Flores, 1990) (see figure 5). To explain how these two systems are activated we can use the analogy from Clow (2001): activating the SAM system is like lighting a match, is easy, has an instant effect, and the effect does not last long. The HPA is activated in extreme circumstances: like lighting a fire takes more effort and its effects last longer.

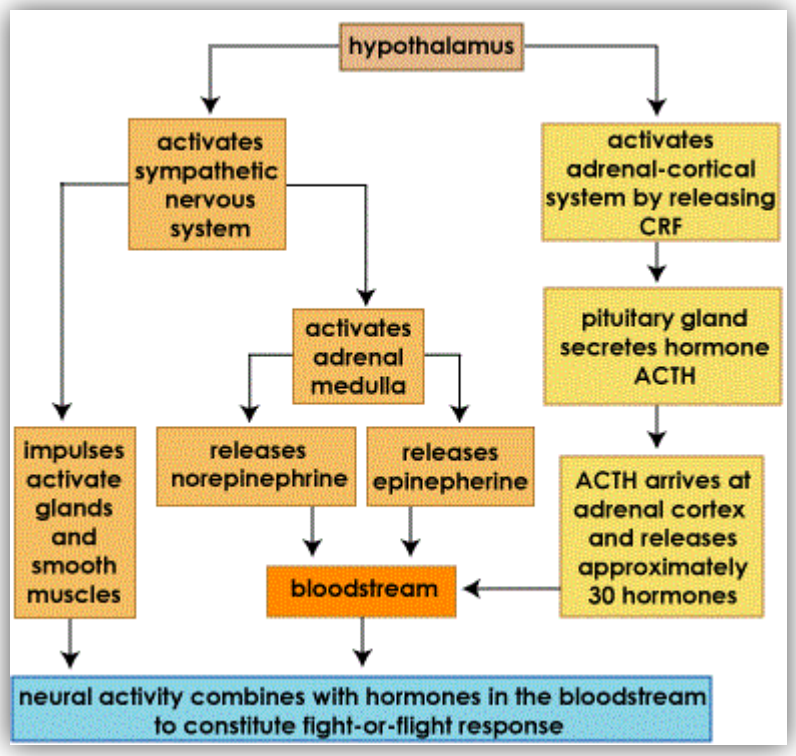
The SAM system is responsible for activating the fight or flight response and placing the body on alert. After a stressful, threatening or frightening situation the brain sends a message to the adrenal glands. There are two adrenal glands located on the top of each kidney and each has a central core called the adrenal medulla, which secretes the hormones of adrenaline and noradrenaline. Noradrenaline activates internal organs whereas adrenaline prepares the body to give a response (Valdés and De Flores, 1990). They increase heart rate and mobilize glucose into the bloodstream; the digestive system slows the activity because the muscles need more blood, breathing quickens and the eyes dilate to allow more light in. Different organs increase the metabolic rate and, if these organs do not have the opportunity to relax and restore themselves some dysfunctions can appear (Wimbush & Nelson, 2000).

The HPA axis is, in evolutionary terms, responsible for helping to ensure survival and giving an adaptive response to the environment. The hypothalamus releases corticotrophin releasing factor (CRF) to the bloodstream which reaches the pituitary gland. Then the pituitary gland releases adrenocorticotrophic hormone (ACTH) to the bloodstream and it reaches the adrenal cortex stimulating the production of mineralocorticoids and glucocorticoids (Valdés & De Flores, 1990). One of the most important glucocorticoids is cortisol (corticoesterone in rodents), usually known as the stress hormone and widely measured in physiological stress studies. Cortisol increases protein and fat mobilization and access to energy stores, and decreases inflammation.

To maintain internal homeostasis this stress response needs to return to normality after a short period of time. However, nowadays the stress system is usually repeatedly activated and this activation can become chronic and deregulate different

body systems like the nervous and the immune system (Lazarus, 2000). An explanation from Sapolsky (2004a) best illustrates this fact. He explained that stress-related disease emerges, predominantly, out of the fact that we so often activate a physiological system that has evolved for responding to acute physical emergencies but we turn it on for months on end, worrying about mortgages, relationships, and promotions.

Figure 5. The biology of stress: SAM system and HPA axis activation



Source: HowStuffWorks 2005

Finally, it is important to highlight a new theoretical approach to stress psychobiology. According to the studies of Taylor et al. (2000), stress would not only prepare the body for a fight or flight response, but also for socialization. This would be related to a hormonal mechanism, the production of oxytocin. Under stressful conditions females release oxytocin, a hormone related to attachment, social relationships and friendship. This theory postulates that the organism not only reacts to stress driving the body towards movement, but also towards the need to socialize.

1.3.6 Psychological stress and the immune system

The immune system protects the body from damage by invading microorganisms – bacteria, viruses, fungi, and parasites. These foreign materials are called antigens (Cohen & Herbert, 1996). For many years the immune system was thought to be autonomous. Now it is well known that the immune system responds to signals from other systems in the body, particularly the nervous system and the endocrine system (Segerstrom & Miller, 2004). The interrelation between the immune system and the nervous system is called psychoneuroimmunology and was first described by Robert Ader and Nicolas Cohen (Ader & Cohen, 1975; review in Ader & Cohen, 1993). Their study of behaviourally conditioned immunosuppression in rats unveiled the knowledge that the immune system could be conditioned. This finding led to a large amount of research mainly focused on the potential influence of psychological stress in different aspects of the immune system. An outstanding meta-analytic study of Segerstrom and Miller (2004) reported the relationship of psychological stress and the human immune system through the analysis of more than 300 empirical articles in 30 years of inquiry.

As we mentioned above, stress can have direct and indirect effects on the immune system, and in general, the health condition. The indirect effects appear through harmful lifestyles or noxious coping strategies like poor sleep or unhealthy diet, which may have immunosuppressive effects, and the direct effects through the activation of the stress axes that promote neuroendocrine, immunologic and emotional changes (Glaser & Kiecolt-Glaser, 2005). Both pathways may potentially alter the immune function, worsening several health related aspects. For example, it can precipitate the occurrence of a health disorder, altering a disease course or causing new sources of stress (Sandín, 1999).

But what is the mechanism by which stress alters the immune function? The first model postulates that stress is mainly immunosuppressive (Seyle, 1976). The diminished immune responses were assumed to promote infectious and neoplastic diseases in chronically stressed individuals (Andersen, Kiecolt-Glaser & Glaser, 1994). Later, Dhabar & McEwen (1997, 2001) postulated the biphasic model in which acute stress was considered to enhance whereas chronic stress was considered to supress the immune response. However, chronic stress was related to disease outcomes

associated with inadequate immunity (infectious and neoplastic disease) but was also associated to excessive immune activity (allergic and autoimmune diseases). To solve this paradox Marshal and Chambers (1998) proposed a model focused on how chronic stress might shift the balance of the immune response. This model hypothesizes that chronic stress elicits simultaneous enhancement and suppression of the immune response by altering patterns of cytokine secretion, and this would affect individuals differently depending on other genetic and environmental pathways. This deregulation could occur through the increased secretion of stress hormones such as cortisol. It is well known that chronic stress has the capacity for inducing long-term decline via overexposure to stress hormones (Kiecolt-Glaser, McGuire, Robles & Glaser, 2002a).

1.3.7 Stress, health and autoimmune diseases

Although stress has an effect on the immune system, in the short term, a healthy host should not be adversely affected because of the immune system changes do not persist for a sufficient duration to enhance disease susceptibility or because the flexibility and self-regulation of this system. However, several causes may alter the immune function promoting a higher susceptibility to negative immunological effects to stress like aging (Ferguson, Wikby, Maxson, Olsson & Johansson, 1995; Grubeck-Loebenstein & Wick, 2002), suffering from a disease or genetic, psychological or environmental factors (Kiecolt-Glaser, McGuire, Robles & Glaser, 2002).

In autoimmune diseases there is a loss of immune system self-regulation. The main function of the immune system is to defend the body against invaders, distinguishing between “self” and “non-self” agents. In autoimmune diseases the immune system confounds self-tissue with an invader and reacts against self-components causing pathologies like multiple sclerosis, lupus or rheumatoid arthritis, among others (Segerstrom & Miller, 2004). This imbalance in the immune system is believed to make people with an autoimmune disease more prone to being affected by the negative effect of stressors. Some diseases like multiple sclerosis, rheumatoid arthritis or coronary heart disease are characterized by inflammatory processes. In this sense stress might worsen the course of the disease involving excessive nonspecific inflammation (Ershler & Keller, 2000; Rozanski, Blumenthal & Kaplan, 1999).

However, it remains unclear or poorly understood whether stress can trigger an autoimmune disease in a genetic vulnerable individual or not. Multiple sclerosis, lupus

or rheumatoid arthritis are believed to be complex diseases, which means that genetic and environmental factors are involved in their pathogenesis. Relatively few studies have addressed the study of stress effects on the onset of autoimmune diseases (for a review see Cohen & Herbert, 1996), and the results are still inconclusive, probably due to the lack of large cohort designs that prevent researchers from establishing causal relationships.

The Stress-Diathesis Model postulated the idea that some people are genetically more vulnerable to stressors than others. It describes the interaction between genetic, biologic, physiologic, cognitive and personality-related factors with environmental stress which results in a disorder or condition (Ingram & Luxton, 2005). This model has been mainly used in the field of psychological disorders, postulating that an individual who is vulnerable or has a predisposition to a specific psychological disorder could develop it triggered by stressful life events. However, in terms of health outcomes, Kanner, Coyne, Schaefer and Lazarus (1981) argued that it was the “day-to-day” events that ultimately have a significant impact on health and that it is their accumulative effect that should be assessed.

1.4 Stress and Multiple Sclerosis

1.4.1 The effect of stress on MS

Interest in the effect of stress on MS was first considered by Charcot, who described that grief, vexation, and adverse changes in social circumstances were related to the onset of the disease (Charcot, 1877). Since this first report different studies have addressed this topic, but the results are far from being conclusive. Possible explanations include great differences in the study designs and methodologies used which makes comparison of the results difficult, and also the lack of consideration for possible mediators and moderators of the stress response (Artemiadis et al., 2011). Considering the methodology used, these studies can be classified according to the study design: retrospective, prospective, case-control or cohort; the topic of the study: the effect of stress on disease onset or disease progression; the stress concept: physiological, stimulus or transactional approach; and the disease measure: diagnostic and relapse criteria, health symptoms, impairment and disability, and biological measures. Considering the possible mediators and moderators of the stress response, different factors were proposed like personality, coping style, anxiety, social support or stressor features, among others. In order to present the different results in a suitable and easy to follow read, the different studies are presented following a chronological order taking into account these two main points. This will allow us to see how methods and concepts have changed over time and which mediators and moderators have been considered.

Since the early 1900 until the beginning of the 21st century few studies were published. The first studies addressing this topic were mainly retrospective and assessed the occurrence of emotional stress before the onset of MS, and exacerbation through semi-structured interviews about the patient's life story or case studies (Braceland & Giffin, 1949; Brickner & Simons, 1950; Pratt, 1951; Philippopoulos, Wittkower, & Cousineau, 1958; Mei-Tal, Meyerowitz & Engel, 1970). In these studies stress was categorized as different objectively stressful events like a funeral, surgery,

or significant events in the family, among others. Some studies showed that a large number of patients reported stressful events before the onset and exacerbation of the disease (Mei-Tal et al., 1970; Philippoulos et al., 1958), but compared to other neurologic controls it was not statistically significant (Pratt, 1951). Other studies did not find that the disease was affected by previous stressful events (Braceland & Giffin, 1950; Brickner & Simons, 1950).

Later, in the eighties and nineties, retrospective methods were also predominant but with different types of comparison groups and methods of stress assessment, showing again disparate results. On the one hand, some studies showed a positive relationship between stress and MS. Warren, Greenhill and Warren (1982) conducted a study with 100 patients of MS and 100 patients with rheumatology and neurological problems other than MS, as controls. They found that pwMS experienced significantly more unwanted emotional stress during the two years immediately prior to the age of onset. Similarly, Grant et al. (1989) found that the proportion of pwMS who experienced marked life adversity in the year prior to the onset of symptoms was significantly higher than for non-patients, being most evident in the 6 months prior to onset. On the other hand, other studies did not show significant differences. Palumbo, Fontanillas, Salmaggi, La Mantia and Milanese (1998) compared pwMS and people with non-genetically determined chronic polyneuropathies and non-significant differences were found in stressful life events within the 7 years prior to onset. Considering the occurrence of a relapse, Gasperini et al. (1995) also failed to find significant differences in stressful life circumstances occurring three months prior to the relapse, comparing pwMS in an exacerbation phase with pwMS in a remission phase. All these studies had the retrospective design in their methodology in common, which makes it easy to introduce some kind of bias: either forgetfulness bias, or conversely “effort after meaning”. Forgetfulness bias refers to the lack of proper memories about stressful events. “Effort after meaning” describes the phenomenon of people making sense of something retrospectively, which means that pwMS may find an explanation for the exacerbation in past stressful events.

In 1999, the therapeutics and technology assessment subcommittee of the American Academy of Neurology made a report on the relationship of MS to psychological stress. The main conclusion was that “*the relationship between antecedent stress and either MS onset or exacerbation was considered possible*”. Moreover, they pointed out that the main limitations of the studies to date was *“the lack at present of a clear biological model, the lack of an agreed-upon definition of stress, the possible bias of retrospective interviews, the apparent inconsistency of the relationship, and, perhaps most importantly, the lack of any conclusive prospective*

data" (Goodin et al., 1999). This report promoted a change in the methodology of research on stress and MS, and the highlighted limitations were the starting point in the design of the following studies. Prospective design became widely used, with the aim of reducing biases and establishing a temporary relationship between the stress event and the disease manifestation, either its onset or exacerbation.

Those studies evaluating the effect of stress on disease onset did not support a major role of stress in the development of MS (Nielsen et al. 2014a; Nielsen, Pedersen, Stenager, Koch-Henriksen & Frisch, 2014b; Riise et al. 2011). However, Riise et al. (2011) found an elevated but non-significant risk among women having been forced into sexual activity several times, both during childhood and adolescence. Nielsen et al. (2014ab) did not find any relationship between stressful events like a divorce, becoming widowed, parental death, the death of a sibling or the loss of a child and the risk of MS onset. However, they did find a 13% increased risk of developing MS in those people exposed to parental divorce (Nielsen et al., 2014b).

On the other hand, all those studies evaluating the effect of stress on disease progression, whether assessing changes in health status and symptoms, the relapse occurrence, or the changes on impairment and disability, showed some kind of association (Schwartz et al., 1999; Ackerman et al., 2002; Buljevac et al., 2003; Brown et al., 2006a; Brown et al., 2006b; Mitsonis et al., 2008; Potagas et al., 2008; Oveisgharan, Hosseini, Arbabi & Nafissi, 2014). Some of these studies tested the bidirectional hypothesis, which means testing the effect of stress on MS and the effect of MS on stress, showing a positive relationship in both directions (Ackerman et al., 2002; Brown et al., 2006a; Schwartz et al., 1999). Other studies tested the effect of stress through self-reported diaries of stressful experiences, finding a temporal relationship between the stressful event and the subsequent occurrence of a relapse (Buljevac et al., 2003; Mitsonis et al., 2008; Potagas et al., 2008). A complete meta-analysis (Mohr, Hart, Julian, Cox & Pelletier, 2004) that evaluated 14 studies examining the effects of stressful life events on MS exacerbation, found a significantly increased risk of exacerbation associated with stressful events with an effect size of d=.53.

Other studies tried to find a biological link testing the effect of stress on disease progression through the occurrence of new lesions on the brain. Mohr et al. (2000) examined the relationship between stressful life events and psychological distress, and the subsequent development of gadolinium-enhancing (Gd+) brain lesions monitored by Magnetic Resonance Imaging (MRI). They found that conflict and disruption in routine (negative and moderate) stress was followed by increased odds of developing new brain lesions 8 weeks after. However, this relationship was not sufficiently robust to predict clinical exacerbations reliably in individual patients. Recently, a study of

Burns, Nawacki, Kwasny, Pelletier and Mohr (2014) showed that major negative stressful events predicted increased risk of Gd+ and T2 lesions, while positive stressful events predicted a decreased risk.

Finally, it is important to highlight that all these studies assessed the stress that emerged from daily life situations. Few studies assessed the effect of stress under extreme situations like a war. In this line, Yamout, Itani, Hourany, Sibaii and Yaghi (2010) found that the total number of relapses during the war period was significantly higher than during non-war periods and that patients exposed to war had more Gd+ lesions in the brain compared to the non-exposed control group. Nevertheless, the study of Nisipeanu and Korczyn (1993) showed that the number of relapses during the war and the following 2 months was significantly lower than expected, based on the frequency during the preceding 2 years. This suggested that not all stress conditions increase the risk of exacerbations in MS and that the temporal framework is an important point to be considered.

In relation to this, Mohr and Pelletier (2006) presented an interesting review suggesting three different hypotheses for potential mechanisms of the temporal relationship between stressful life events and MS disease activity: the *Stress Resolution hypothesis,* the *Glucocorticoid Resistance hypothesis* and the *Mast Cell hypothesis.*

The *Stress Resolution hypothesis* postulates that it is the resolution of the stress rather than the onset of stress that facilitates the development of active inflammation. In a stressful situation cortisol level rises and there is some control over inflammation. After the stress resolution the reduction in cortisol would decrease the control over inflammatory processes, and could increase the risk of an exacerbation.

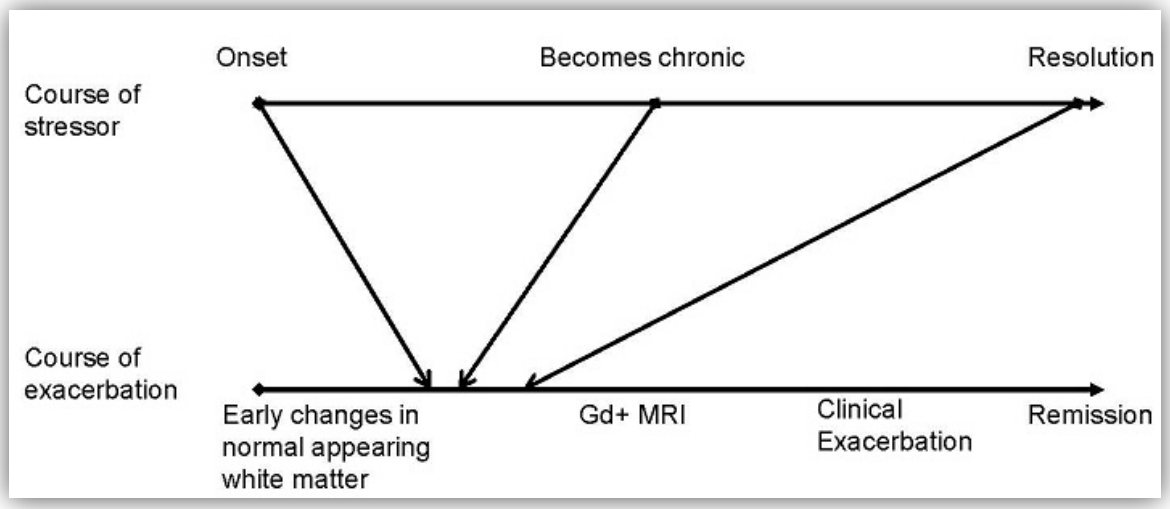
The *Glucocorticoid Resistance hypothesis* suggests that chronic stress can reduce the number and/or function of glucocorticoid receptors on immune cells. As a result, the immune cells would become less responsive to regulatory control by cortisol being more vulnerable to inflammation processes. In relation to this, the study of Reder, Makowiec and Lowy (1994) showed through post-mortem studies that pwMS had adrenal size as being 36% larger than in other patients. This may allow for excessive glucocorticoid secretion in response to stress and affect immune regulation making them insensitive to glucocorticoid feedback regulation.

The *Mast Cell hypothesis* proposes that the onset of stress might have a permissive effect on MS exacerbation by facilitating the breakdown of the Blood Brain Barrier (BBB) through mast cell activation. Through a complex process stress can increase immune CRH and induce mast cell degranulation, thereby increasing BBB

permeability (Esposito et al., 2001; 2002). This hypothesis would explain the immediate effect experienced by patients after a stressful situation.

These three hypotheses present different temporal relationships *(see figure 5)*. The Mast Cell hypothesis emphasises the effect at the onset of the stressor, the Glucocorticoid Resistance hypothesis focuses on the point when a stressor becomes chronic, and the Stress Resolution hypothesis focuses on the resolution of the stressor. These proposals may be compatible and complementary to each other, not necessary mutually exclusive or exhaustive as they explained all the symptomatology reported by pwMS over time.

Figure 5. Temporal Model of Stress and Exacerbation (Mohr & Pelletier, 2006)



Source: Mohr & Pelletier (2006)

1.4.2 Psychosocial moderators and mediators of the stress response

In general, the relationship between stress and MS seems to be significant and clinically meaningful. However, it is also inconsistent. Some people are more vulnerable than others to the effects of stress and, at the same time, the same person can be affected by a stressful situation at some point but not at others. This suggests the presence of moderators and mediators of the stress response (Mohr & Pelletier, 2006). In general terms, a moderator is a qualitative or quantitative variable that affects

the direction and/or strength of the relation between an independent or predictor variable and a dependent or criterion variable. On the other hand, a given variable may be said to function as a mediator to the extent that it accounts for the relation between the predictor and the criterion variable (Baron & Kenny, 1986). Potential moderators of the stress-MS relationship include types of stress, MS disease characteristics, environmental factors, and patient biological, social and psychological characteristics (Mohr, Goodkin, Nelson, Cox & Weiner, 2002).

Among the studies that addressed the stress-MS relationship the possible mediators and moderators considered were: the premorbid personality (Pratt, 1951; Liu et al., 2009); stressor characteristics like duration, source, severity, frequency, valence or typology (Mei-Tal et al., 1970; Grant et al., 1989; Warren, Warren & Cockerill, 1991; Gasperini et al., 1995; Schwartz et al., 1999; Mohr et al., 2000; Ackerman et al., 2002; Buljevac et al., 2003; Brown et al. 2006a; Mitsonis et al., 2008; Potagas et al, 2008; Mitsonis et al., 2010; Oveigharan et al., 2014); coping style (Warren et al., 1982; Warren et al., 1991; Mohr et al., 2002; Brown et al., 2006b), early-life stress (Warren et al., 1982; Riise et al., 2011; Nielsen et al., 2014), psychophysiological measures like cardiovascular reactivity, resting heart rate and blood pressure (Ackerman et al., 2003), social support (Brown, et al., 2006b; Liu et al., 2009), anxiety (Brown et al., 2006b; Potagas et al., 2008), escitalopram intake (Mitsonis et al., 2010) and other psychosocial factors like mental health symptoms (Liu et al., 2009), and depression, health locus of control, and optimism (Brown et al., 2006b).

The great majority of the studies addressed this topic considering stress as a stimulus or external event and assessing the stressor features as the main moderator factor. Few of them analysed psychological and social factors. From the point of view of the transactional approach (Lazarus & Folkman, 1984), psychosocial factors are critical to understand the individual's appraisal process of the stressors, the coping strategy used to deal with it, and the specific stress response given by the individuals. How people respond to demands from their environment can be seen as a function of their personality, constitution, perceptions, and the context in which the stressor occurs (Meichenbaum, 1977; Cronkite & Moos, 1984).

After reviewing most of these studies it was seen that the factors more closely linked to some disease, and specifically to MS, were those related to coping, personality features and past experiences. In general, personality and coping may interact to affect an individual's risk of negative health outcomes. Personality and coping styles were associated with the onset and clinical course of chronic and progressive health problems (Scheier & Bridges, 1995), and predicted mortality and diseases in initially healthy adults (Maruta, Colligan, Malinchoc & Offord, 2000;

Peterson, Seligman & Vaillant, 1988). Coping strategies are different for every person and are the key to the stress response given (Lazarus & Folkman, 1984). How people deal with a stressful situation determines what their emotions, thoughts and consequences are, and their behaviour in future situations.

Personality features or dispositional factors affect the cognitive appraisal, and in turn, the stress response given. Some examples are the locus of control, trait anxiety, extraversion/introversion, alexithymia, and so on. In the present thesis, anxiety and alexithymia were selected due to the fact that they are two of the most related psychosocial factors linked to diseases and, specifically to MS (Chahraoui, Duchene, Rollot, Bonin & Moreau, 2014; Kiecolt-Glaser et al., 2002a; Minden & Schiffer, 1991; Potagas et al., 2008; Tolmunen, Lehto, Heliste, Kurl & Kauhanen, 2010).

Finally, stress management in adulthood is also influenced by the stressful events that people live in early-life ages. Early-life stress can affect individuals both psychologically or emotionally and, also biologically through modifying underlying neuroendocrine processes in the brain that might remain into adulthood increasing vulnerability to future stressful events (Heim et al., 2000; Lupien, McEwen, Gunnar & Heim, 2009; Pace et al., 2006; Yang et al., 2013).

1.4.2.1 Coping

Most studies conducted on coping in MS have been developed under the Lazarus and Folkman's transactional model. From this point of view, coping strategies are defined as the cognitive and behavioural efforts developed to deal with external and internal demands that are considered to exceed the individual's resources (Lazarus & Folkman, 1987). To measure these coping responses Folkman and Lazarus (1988) developed the Ways of Coping questionnaire (WOC), categorising the coping responses into three main dimensions: problem-focused coping, emotion-focused coping and seeking social support. However, the WOC questionnaire received much criticism. In several studies a low reliability and deficiencies in validity were found, discouraging its use (Olmedo & Ibáñez, 2003; Soriano & Zorroza, 1999). A part from that, this coping point of view is focused on the individual, failing to consider all the social aspects involved in coping response.

In the 90s the social dimension of coping started to be considered as a main axis upon which coping strategies were based (Coyne & Smith, 1991). Hobfoll and Cols highlighted the idea that coping always takes place in social scenarios for three

main reasons: most stressors are interpersonal or have some interpersonal component; the individual effort to counteract stressors have social consequences; and because coping often requires an interaction with others (Hobfoll, 2002). In relation to this approach, Hobfoll developed the Strategic Approach to Coping Scale questionnaire (SACS) based on the Conservation of Resources Theory of Hobfoll (1989) and includes 9 categories of coping: assertiveness, aggressiveness, antisocial action, indirect action, avoidance, social alliance, social support, cautious action and instinctive action. The Spanish version of this scale (Pedrero, Santed & Perez, 2011) resulted in 7 coping strategies: 1) Assertive action (conflict identification and attempt to solve the problem), 2) Social joining (have "significant others" as collaborators), 3) Seeking social support (seek external resources), 4) Cautious action (leisurely assessment of threat, resources, needs, and aid), 5) Instinctive action (immediate, irreflexive and spontaneous action), 6) Avoidance (avoiding conflictive elements, minimizing emotional impact), 7) Aggressive/Antisocial action (prioritizing one's own needs and immediate resolution). Moreover, these strategies were categorized into three main axes: Pro-social vs Anti-social, Active vs Passive, and Direct vs Indirect (Dunahoo, Hobfoll, Monnier, Hulsizer & Johnson, 1998). Both the WOC questionnaire and Hobfoll's SACS questionnaire measure coping under a transactional approach, but the WOC questionnaire focused more on the appraisal process and the Hobfoll's SACS on the coping process. Moreover, when assessing coping there are mainly two approaches to do so: the trait approach, which assesses coping style across a range of situations; and the state approach, which assesses strategies used to cope with specific events (Pakenham, 1999). Both questionnaires measure coping following a trait approach but, under a transactional approach where coping is considered as a process, repeated measures over time linked to specific stressors are needed.

In general, active coping seems to be a protective factor for stress (Afshar et al., 2015), whereas the coping related to denial, avoidance, self-blame, and irrational confrontation increased vulnerability to stress (Buceta & Bueno, 2001). In people with chronic illness, the coping strategies focused on solving the problem or confronted coping are usually linked to better wellbeing (Folkman, Lazarus, Gruen & DeLongis, 1986; Viñas, Caparrós & Massegú, 1999). On the other hand, strategies focused on emotions or avoidance were linked to a worse wellbeing (Scheier & Carver, 1993; Unger et al., 1998) and were prospectively associated with both more chronic and more acute life stressors 4 years later (Holahan, Moos, Holahan, Brennan & Schutte, 2005). Moreover, it was seen that people who used repression and denial coping, characterized by denial or minimization of distress and negative emotions, reacted to

stressful events with higher autonomic arousal than persons with high anxiety or distress (Weinberger, Schwartz & Davidson,1979).

Considering the effect on the immune system, it was observed that optimism and coping moderated immunological response to stress (Bosch et al., 2001; Nes & Segerstrom, 2006; Segerstrom, 2005; Stowell, Kiecolt-Glaser & Glaser, 2001). On the other hand, coping styles such as repression, rejection sensitivity, attribution style, and sociability were associated with altered immune cell counts in peripheral blood and deregulated cellular immune function (Segerstrom & Miller, 2004).

In pwMS, confronted or problem-focused coping showed a positive relationship with the disease (Pakenham, Stewart & Rogers, 1997), a better adjustment to MS and less disability (Pakenham, 1999), and less depressive symptoms (Mohr, Goodkin, Gatto & Van Der Wende, 1997). On the other hand, a more passive or emotion-focused coping seems to be less adaptive and often goes together with increased levels of stress (Holahan et al., 2005; Mc Cabe, McKern & McDonald, 2004). Moreover, emotion-focused, passive, and avoidance coping were related to poorer adjustment to MS and lower levels of quality of life (McCabe et al., 2004; Mohr et al., 1997; Pakenham, 1999; Pakenham et al.,1997). Similarly, the study developed by Mohr et al. (2002), which measured the relationship between coping and the development of new brain lesions in MS, showed that greater use of distraction was associated with a decreased relationship between stress and new Gd+ lesions. Instrumental coping was marginally associated with a decreased relationship between stress and Gd+ lesions, whereas emotional preoccupation was marginally associated with an increased relationship. Compared with healthy controls, pwMS are less likely to use coping styles related to problem solving and seeking social support (McCabe et al., 2004) and, among them, those in an exacerbation phase significantly favoured more emotion-focused coping (Warren et al., 1991) and passive avoidant or aggressive coping (Kroencke & Denney, 1999). However, most of these results are done in pwMS in a relapsing-remitting phase and the conclusions may not be generalizable to all the MS types. In a progressive type of the disease some forms of emotion-focused coping were related to a better adaption to MS (Brooks & Matson, 1982).

1.4.2.2 Social Support

The transactional approach of Hobfoll considers the social perspective as a central component of coping. In line with this, social support has been proposed to be a

key aspect of the coping process, being one of the main factors affecting (buffering or amplifying) the stress response to stressful situations (Cohen & Willis, 1985).

The link between personal relationships and the function of the immune system is one of the most robust findings in psychoneuroimmunology (Uchino, Cacioppo & Kiecolt-Glaser, 1996). It seems that social support can attenuate stress-or-threat-related responding through reducing neural activity in regions that respond to basic survival threats and through activating safety-related neural regions (Eisenberger, 2013). On the other hand, people socially isolated are more stressed due to the lack of social support, which may lead to a chronic activation of the stress system (Sapolsky, 2004b). Social isolation is a major risk factor for mortality and morbidity, comparable to other well-established risk factors like smoking, obesity and lack of physical activity (House, Landis & Umberson, 1988). However, when social support becomes a dependent state it will be more likely to result in helplessness in the face of stressful situations, increasing anxiety (Buceta et al., 2001).

In several diseases social support also seems to play an important role in the disease progression and the immune function. In breast cancer patients, high quality emotional support, perceived social support, and actively seeking social support were related to better immune cell activity (Levy et al., 1990). Similarly, in a sample of HIV-positive men, a more rapid decline in immune cells was associated with low perceived emotional support (Theorell et al., 1995).

In pwMS, perceived social support was positively associated to a perceived physical and mental health status (Krokavcova et al., 2008), to a better quality of life (Costa, Sá & Calheiros, 2012) and, along with other psychosocial factors like depressive symptoms and economic adequacy, social support partially mediated the effect of functional limitations on disability (Phillips & Stuifbergen, 2010). In addition, considering the type of stressors which have an impact on the risk of exacerbations, several studies showed that most of them are considered social in nature (Mohr et al., 2000; Sibley, 1997).

1.4.2.3 Anxiety

According to DSM-V (A.P.A., 2014, p.189) anxiety is defined as "*an anticipatory response to a future threat related to muscle strain, hyperarousal related to a future danger and cautious or avoidance behaviour"*. It is important to highlight that anxiety is anticipatory in nature. This is related to the biologic-adaptive function that anxiety plays

in the organism (Ohman, 2008). From this point of view, anxiety is defined as an emotional reaction involved in the adaptation process in the face of aversive or dangerous anticipated events. This reaction has two action mechanisms: cognitive and behavioural. The first one activates a state which gives priority to the signals related to potential dangers. The second one mobilizes resources to face the danger or to run away before it causes some unavoidable damage (Castillo & González, 2010).

Anxiety can be categorised into two different constructs: trait anxiety and state anxiety. This distinction was first made by Spielberger in 1966 in the Trait-State Theory of Anxiety. Trait anxiety is defined as a relatively stable way to respond with anxiety: a disposition to perceive situational stimuli as dangerous or threatening and the tendency to react to them with anxiety states. On the other hand, state anxiety is a transitory emotional state which includes feelings of fear, nervousness and autonomic arousal that are triggered by the anticipation of a potential danger (Spielberger, 1966). A well-established and widely used questionnaire to measure both constructs is the State-Trait Anxiety Inventory developed by Spielberger (1983).

Trait anxiety is considered a vulnerability factor when considering different situations as stressful. In general, people increase arousal in the face of an acute stressful situation. However, when stress becomes chronic, people with high trait anxiety remain in this arousal state whereas those with low trait anxiety develop strategies to reduce activation (Mogg, Bradley & Hallowell, 1994). High trait anxiety puts individuals at risk for more dramatic threats and appraisals of loss, whereas low trait anxiety buffers the experience of stress (Jerusalem, 1990). Moreover, people with high trait anxiety tend to pay more attention to the information consistent with the source of anxiety (Mogg, Bradley & Hallowell, 1994). For example, those patients worried about social preoccupation were more prone to pay attention to words of social threat. Nevertheless, this effect occurred only with negative information (Ruiz-Caballero & Bermúdez, 1997).

In turn, clinically diagnosed anxiety disorders have been associated with immune changes and have an effect on different diseases (for a review, see Kiecolt-Glaser et al., 2002a). For example, in cardiovascular heart diseases anxiety contributes to poorer prognosis after acute coronary events, including death and recurrent ischemic events (Kiecolt-Glaser et al. 2002a). In pwMS those who have higher levels of anxiety range from 19% to 34%, a greater prevalence than in the general population (Minden & Schiffer, 1991; Stenager, Knudsen & Jensen, 1994). A possible explanation may be the uncertainty and perceived potential threat of the disease (Mullins et al., 2001), although other biological explanations related to serotonin (5-HT) neurotransmission may be provided (Chaouloff, 2000). Besides, in pwMS high levels of

anxiety were associated with 2.9 times the rate of relapse (Potagas et al., 2008) and, in turn, pwMS treated with escitalopram, an antidepressant drug that reduces anxiety, showed 2.9 times less risk for relapse than the control group (Mitsonis et al., 2010).

1.4.2.4 Alexithymia

Alexithymia was first introduced by Sifneos in 1973 to describe a group of symptoms observed in psychosomatic disease patients. It can be defined as a difficulty in identifying, experiencing, expressing and describing emotional responses and one's own feelings to others; a restricted imaginative process, a tendency to act in order to avoid resolving conflicts and a detailed description of facts, events, and physical symptoms (Taylor, 1984; 2000). Literally, alexithymia means a lack of words to express emotions. One of the most widely used instruments to measure alexithymia is the Toronto Alexithymia Scale. It was developed by Taylor, Ryan and Bagby (1985) in a 26-item version and reformulated some years later in a 20-item version (TAS-20; Bagby, Parker & Taylor, 1994). It measures three main aspects: difficulties identifying feelings; difficulties describing feelings; and externally oriented thinking. The TAS-20 showed good psychometric properties, transcultural reliability and structural validity (Paez et al., 1999; Velasco & Paez, 1996).

Since the beginning alexithymia has been linked to psychosomatic diseases. In Kojima (2012) some mechanisms linking alexithymia and illness were reviewed. First, the impaired emotion-processing and regulating capacities might induce disruption of homeostasis through alterations of autonomic, endocrine, and immune activities. Second, inadequate coping strategies used to deal with stressful situations that include unhealthy behaviours such as poor nutrition, alcohol and drug use. Third, difficulties in recognizing their own physical and emotional symptoms may be linked to a delay or excessive use of medical support resulting in a worse prognosis. Finally, difficulties describing feelings and understanding other people's emotions may make it difficult to maintain a good social support network, which is good to protect from pathological influences of stressful events. Other studies have postulated and partially confirmed the decoupling hypothesis (Martin & Pihl, 1986; Soria, Garcia & Sanchez, 2001), which postulated that alexithymia may lead to the inaccurate self-perception of stress states in stressful situations, impeding an appropriate self-regulation.

In spite of these arguments, the evidence to consider alexithymia as a prognostic risk factor for health problems is insufficient. In some pathologies like

colorectal cancer (Ripetti, Ausania, Bruni, Campoli & Coppola, 2008), or pelvic pouch surgery (Weinryb, Gustavsson, Liljeqvist, Poppen & Rössel, 1997) high levels of alexithymia were linked to a better quality of life and low levels of distress, respectively. However, in other studies, alexithymia was associated to increased cardiovascular mortality in middle-aged men (Tolmunen et al., 2010), to pain interference and catastrophizing in chronic pain (Makino et al., 2013) and, in general, to a greater risk of death in middle-aged men (Kauhanen, Kaplan, Cohen, Julkunen & Salonen, 1996). Moreover, higher levels of alexithymia were observed in asthma patients (Moes-Wójtowicz, Wójtowicz, Postek & Domagala-Kulawik, 2012) and diabetis mellitus type 2 patients (Topsever et al., 2006), among many other diseases.

In pwMS higher levels of alexithymia were also reported compared to the general population (Chahraoui, Duchene, Rollot, Bonin & Moreau, 2014; Prochnow et al., 2011). Moreover, in pwMS alexithymic patients reported higher levels of fatigue and depression than non-alexithymic patients (Bodini et al., 2008) and alexithymia contributed to the severity of fatigue and depression. In the study conducted by Chahraoui et al. (2014) it was observed that alexithymia correlated with anxiety and depression, but also with relapses. However, the relationship between alexithymia and MS symptoms and progression still remains poorly explored.

1.4.2.5 Early-life stress

Early-life stress or childhood trauma defined as abuse, maltreatment, neglect or loss is a stressor that affects the physical and mental well-being of humans from infancy throughout the lifespan (Lupien et al., 2009). One of the most widely used instruments to measure early-life stress is the Childhood Trauma Questionnaire-short form (CTQ-SF; Bernstein & Fink, 1998; Bernstein et al., 2003). It assesses five types of maltreatment: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect. CTQ-SF has shown adequate psychometric properties, a good fit of the five-factor structure across clinical and non-referred samples, satisfactory specificity, good sensitivity and good convergent and discriminant validity (Bernstein & Fink, 1998; Bernstein et al., 2003; Scher, Stein, Asmundson, McCreary & Forde, 2001). Moreover, the Spanish version has shown internal consistency, reliability and validity (Hernández et al., 2012).

In general, child maltreatment and other stressful childhood experiences are considered risk factors for multiple risk behaviours like smoking, overeating or use of

drugs and alcohol (Anda et al., 1999; Burke, Hellman, Scott, Weems & Carrion, 2011). In addition, it was seen that adverse childhood experiences predicted ischemic heart disease (Dong et al., 2004), lung cancer (Brown et al., 2010) or, in general, it was related to several physical disorders (Goodwin & Stein, 2004). Lupien et al., (2009) suggested that early adverse experience such as childhood abuse, neglect and loss might be a predisposing factor that interferes with successful adaptation to stress. Evidence from neuroscience suggests that early-life stress in a specific time of vulnerability modifies the organism's response to stress throughout the individual's life. The effect of early-life stress in the long term occurs through brain circuits and the integration of endocrine, autonomic and immune systems (Anda et al., 2006; Meaney, 2001), but also through epigenetic mechanisms (Yang et al., 2013). Related to the immune system and the glucocorticoid release, it was seen in rodents that some kinds of early-life stress like maternal deprivation caused high levels of glucocorticoids during stressful situations and a worst recovery once stress was completed (Plotsky et al., 2005). In humans, DeBellis and Thomas (2003) showed that children who had suffered abuse had higher levels of glucocorticoids and less activity in the frontal cortex. Finally, childhood stress was linked also to an increased likelihood of hospitalization with a diagnosed autoimmune disease decades into adulthood (Dube et al., 2009).

There are just a few studies assessing early-life stress in pwMS. In a large cross-sectional study Spitzer et al. (2012) found that pwMS scored significantly higher than adults from the general population in all CTQ-SF subscales apart from physical abuse and neglect. Moreover, although trauma was not associated with the degree of current MS-related disability, pwMS with histories of physical and/or sexual abuse had significantly higher relapse rates than patients without early-life stress (Spitzer et al., 2012). In two other large cohort studies that evaluated the risk of developing MS in people who had suffered childhood trauma a weak association was shown. Riise et al. (2011) showed no significantly increased risk of MS among those who reported severe physical abuse during childhood or adolescence, but a weak tendency among those repeatedly forced into sexual activity in childhood or adolescence was found. On the other hand, Nielsen et al. (2014b) found that persons exposed to any stressful life event in childhood were at an 11% elevated risk of MS, compared to non-exposed persons. It was found that those persons exposed to parental divorce were especially at risk, at 13% (Nielsen et al., 2014b).

1.4.3 Interventional studies of stress management in MS

Stress management therapies have shown to be effective improving the disease's clinical course, the adjustment to MS and the quality of life in pwMS (Reynard, Sullivan, Rae-Grant, 2014). The most common therapies are based on Cognitive Behavioural Therapies (CBT), like the Inoculation Stress Therapy (IST), but recently new therapies like mindfulness or Acceptance and Commitment Therapy (ACT) are emerging with promising results.

From the point of view of the transactional model of Lazarus and Folkman (1984), in the IST the individual is considered an active agent who assesses his/her own resources, stressor appraisals and the coping strategy used to deal with the stressful situation (Meichenbaum & Deffenbacher, 1988). IST has two main levels: cognitive (thoughts, previous experiences, feelings) and behavioural (environment and biological levels). This therapy teaches relaxation techniques, stress management and emotion processing, and teaches the abilities to deal with the present and future stressful situations (Meichenbaum & Deffenbacher, 1988). A recent systematic-review of Reynard et al. (2014) revised the efficacy of 8 stress-management intervention studies in pwMS, mainly based on CBT trials. Most studies showed positive changes in outcomes assessed, but the methodological quality among the published studies made it difficult to draw firm conclusions.

Other psychosocial therapies that showed positive effects on pwMS were therapies based on mindfulness. Muñoz et al. (2016) conducted a review where several studies were evaluated in order to review available evidence of mindfulness therapies in pwMS. This review was focused on symptoms of anxiety and depression and the perceived stress of the diagnosed patients. It concluded that mindfulness interventions focused on the reduction and management of stress may improve quality of life, depression and fatigue in pwMS (Muñoz et al., 2016).

However, additional large, prospective and multicentre studies are needed to clarify the role of stress-management interventions in the clinical course of MS.

1.5 Thesis aims

The literature review presented in this thesis has been focused on two main areas supporting the overarching aims of this thesis:

- To investigate the effect of stress on the clinical course and some disease parameters of Multiple Sclerosis.

- To elucidate the role of the psychosocial factors of coping, social support, anxiety, alexithymia and early-life stress in the relationship between stress and Multiple Sclerosis and their relationship with some disease parameters.

In order to address the main aims of this thesis the complete study called *"PsychoMSS Study: Stress and Psychosocial Factors in Multiple Sclerosis"* was developed. It comprises three different phases: Phase One is a systematic review of the studies on the effect of stress on MS, focused on the assessment of stress and the moderators and mediators of this relationship. Phase Two is a case-control study comparing pwMS and people without MS in terms of the psychosocial factors mentioned above and their relationship with some disease parameters. Phase Three is a longitudinal one year follow-up of pwMS that evaluates several measures of stress, coping and disease progression.

In line with the three different phases of the studies the specific aims of this thesis are the following:

- Phase One systematically reviews the results of the studies that address the effect of stress on MS. Specifically, it assesses which measures used to evaluate stress provide the most consistent results, and what the most evaluated psychosocial moderators and mediators of the stress-MS relationship are, and the main results provided.

- Phase Two aims to compare the psychosocial factors of coping, social support, anxiety, alexithymia and early-life stress in people with and without MS. Moreover, it assesses the relationship of these psychosocial factors with the disease parameters of impairment and functionality.

- Phase Three investigates through a one year follow-up the relationship of stress (perceived stress and number of stressful events) with the disease parameters of functionality, impairment and relapses. It also evaluates the moderator role of coping, social support, anxiety, alexithymia and early-life stress on this relationship.

2. Methods

Methods

In this section we provide a summary of the general methods used for the whole study. Due to the fact that the results of the different phases are given in manuscript and paper formats a complete and detailed methods section is provided in each phase of the study.

2.1 Study design and procedure

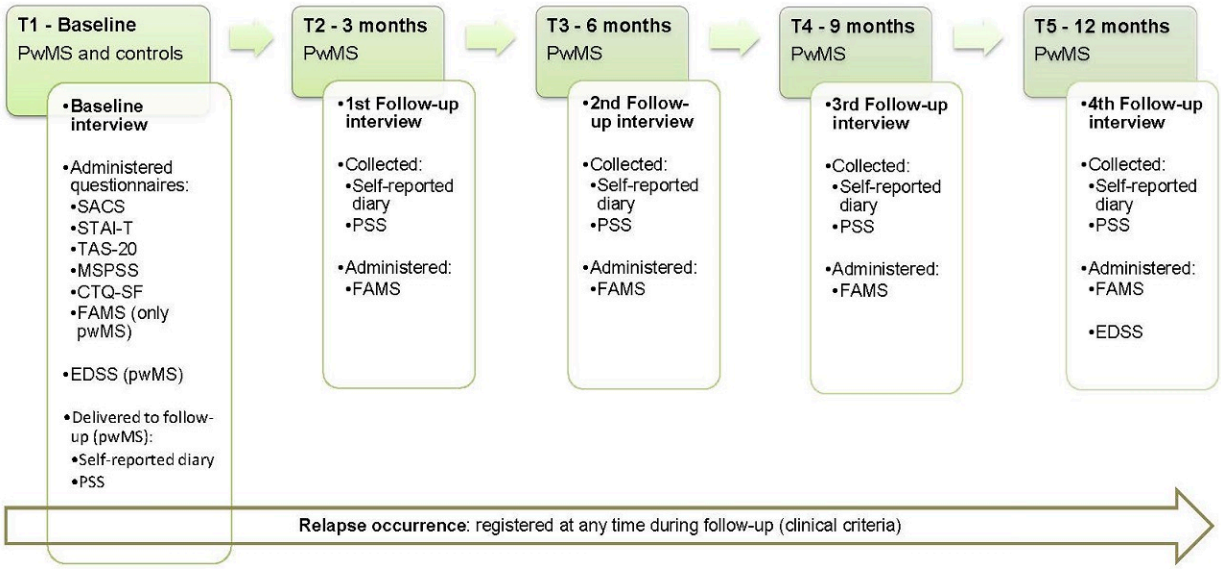
The project *"PsychoMSS Study: Stress and Psychosocial Factors in Multiple Sclerosis"* was developed in Osona, a region with increasing incidence of MS (Otero-Romero et al., 2013) from October 2012 to September 2016. It was conducted with patients of the Consorci Hospitalari de Vic and healthy volunteers from the Consorci Hospitalari de Vic and the Universitat de Vic-Universitat Central de Catalunya.

This project was made up of three main phases: a systematic review, a case-control study and a longitudinal follow-up study.

- Phase One. The systematic review. This was conducted in order to summarize knowledge about stress and MS from 1900 to 2014, focusing on the stress assessments and the moderator and/or mediator factors of this relationship.
- Phase Two. The case-control study. This was an observational study carried out to observe which psychosocial factors related to stress and MS showed differences between pwMS and healthy controls, to see which of them could be potential moderators and mediators of this relationship. The psychosocial factors observed were coping, social support, anxiety, alexithymia and early-life stress. The link of these psychosocial factors to disease progression parameters of functionality and impairment was also observed in pwMS.
- Phase Three. The longitudinal follow-up study. This was an observational longitudinal one year follow-up study conducted in pwMS. The bidirectional hypothesis was tested, observing the effect of several measures of stress on impairment, functionality and relapses and viceversa.

The design and procedure of Phases Two and Three is shown in Figure 6.

Figure 6. Study Design and Procedure (Phases Two & Three): Time Points and Assessments.



The research fieldwork in Phases Two and Three was developed as follows. A trained psychologist conducted the interviews using the same protocol for all the participants. All the interviews were conducted in the Health Department of the Consorci Hospitalari de Vic from May 2014 to September 2015.

The first interview lasted 1 hour in healthy controls and 1 hour and a half in pwMS. A semi-structured interview was conducted to collect socio-demographic, lifestyle and clinical data, and afterwards a battery of standardised self-reported questionnaires was administered. In pwMS the first interview served as baseline assessments of functionality (FAMS) and impairment (EDSS). At the end, the instructions and material to properly complete the self-reported diaries and Perceived Stress Scale (PSS) questionnaires were provided. Other clinical data were collected through medical records.

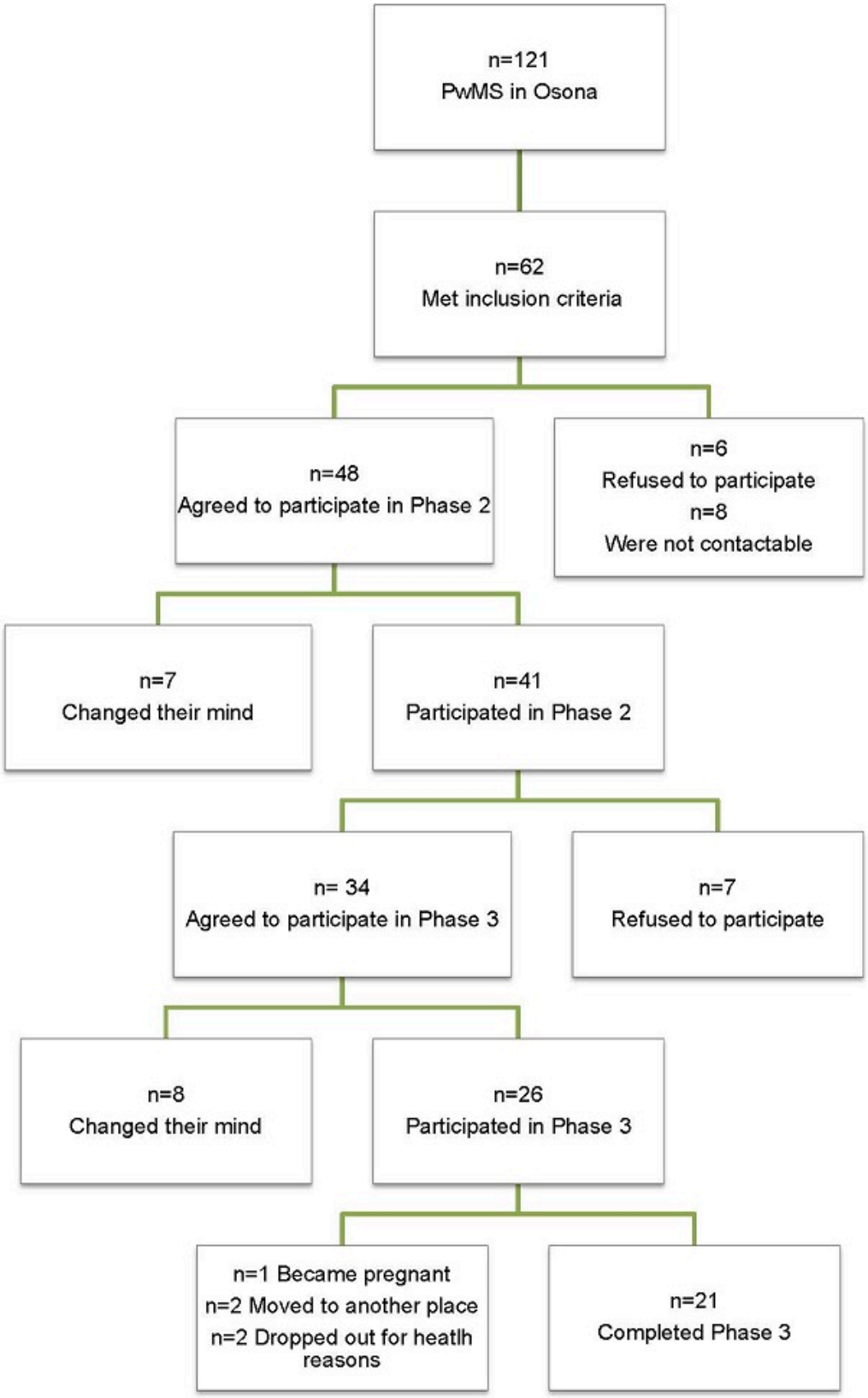
The follow-up interviews (only with pwMS) were trimonthly at 3, 6, 9 and 12 months. These interviews lasted 30 minutes. Self-reported diaries and PSS assessments were collected and the functionality questionnaire (FAMS) was administered. In the last interview the impairment score (EDSS) was also measured.

2.2 Participants

The participants of the study were recruited from the Neurology Department of the Consorci Hospitalari de Vic. All adult patients had clinically definite relapsing-remitting MS, based on McDonald criteria (Polman et al., 2005). From 121 pwMS in Osona, 62 met the inclusion criteria. Out of those, 8 were not contactable, 6 refused to participate, and 48 agreed to participate but 7 changed their minds. A total of 41 pwMS participated in Phase Two. Out of those, 34 agreed to participate in Phase Three (follow-up) but 8 changed their minds after the second interview. During the follow-up, 1 patient became pregnant, 2 moved to another place to live, and 2 left the study for health reasons but their data was used in the period covered (see Figure 7). The comparison group was obtained through local advertisement at the Consorci Hospitalari de Vic and the Universitat de Vic – Universitat Central de Catalunya. A total of 41 healthy volunteers were paired by age and gender with the MS participants.

To determine the exclusion criteria potential modifiers of disease progression and cognitive function were examined. Due to ethical reasons pwMS were allowed to continue with their current medication but this was registered. The exclusion criteria were: a) under 18 years old; b) pregnant; c) abuse of alcohol or drugs; d) Expanded Disability Status Scale (EDSS) ≥ 7; and e) diagnosis of other neurologic or psychopathological disease. The exclusion criteria for the comparison group were the same adding f) diagnosis of MS and other chronic illnesses.

Figure 7. Participants Flow Diagram



2.3 Variables and materials

General information about age, gender, marital status, educational level, lifestyle (toxic consumption, physical activity and occupational activity), and family history of diseases (MS, cancer, autoimmune, psychopathologic and neurologic diseases) were obtained for all the participants. Specific information on MS - year of diagnosis, MS type, EDSS score, MS treatment, and other diagnosed diseases - were obtained through medical records.

In Phase Two, different psychosocial factors were assessed for all the participants (pwMS and healthy controls) through several questionnaires. In pwMS, disease parameters were obtained through a questionnaire and a neurologist's evaluation. All the variables and measures are shown in Table 1.

In Phase Three, different measures of stress and coping were assessed during the one year follow-up through self-reported diaries and questionnaires. The disease progression was assessed through a questionnaire of functionality and through neurologist rated parameters like impairment (EDSS) or relapses. All the variables and measures are shown in Table 2.

Table 1. Summary of the Variables, Instruments and Validated Version Used in Phase Two

Variables	Instruments and measures	Validated Spanish version
Psychosocial factors		
Coping	Strategic Approach to Coping Scale (SACS) of Hobfoll	Pedrero, Santed & Perez, 2011
Social Support	Multidimensional Scale of Perceived Social Support (MSPSS)	Landeta & Calvete, 2002
Trait Anxiety	State-Trait Anxiety Inventory (STAI)	Spielberger, Cubero, Gorsuch & Lushene, 1982
Alexithymia	Toronto Alexithymia Scale (TAS-20)	Martinez-Sanchez, 1996
Early-Life Stress	Childhood Trauma Questionnaire-Short Form (CTQ-SF)	Hernandez et al., 2012
Disease parameters		
Impairment (neurologist rated)	- EDSS-tot: EDSS total score - EDSS-relative: dividing EDSS by years of disease	Kurtzke et al., 1983
Functionality	Functional Assessment of Multiple Sclerosis (FAMS)	Conway et al.1998

Table 2. Summary of the Variables, Instruments, Measures and Criteria, and frequency of the data collection used in Phase Three

Variables	Instruments/Measures/Criteria	Frequency
Stress and coping		
Stressful situations	Self-reported diary Answering the question in their own words: "Did you have a stressful situation this week? Which one?"	Weekly, 52 weeks, 1 year
Stress perceived	Perceived Stress Scale (PSS)	Every 4 weeks, 13 times, 1 year
Discomfort level	Self-reported diary Answering the question in their own words: "What level of discomfort are you suffering because of the stressful situation? Rate from 0 to 10"	Weekly, 52 weeks, 1 year
Coping style	Strategic Approach to Coping Scale (SACS) of Hobfoll	Once, at the baseline interview
Coping strategies	Self-reported diary Answering the question in their own words: "Which strategy did you use to deal with the stressful situation?"	Weekly, 52 weeks, 1 year
Disease progression		
Impairment	Expanded Disability Status Scale (EDSS) Neurologist rated	At baseline and at the end of the study
Functionality	Functional Assessment of Multiple Sclerosis (FAMS)	At baseline and at 3, 6, 9 and 12 months
Relapses	Clinical criteria: worsening of existing symptoms or appearance of new ones lasting more than 24 hours after at least 30 days of improvement or stability not associated with fever. Neurologist rated.	At any time during the 1 year follow-up

2.4 Statistical Analysis

The data analyses were conducted using SPSS (version 23.0; SPSS Inc., Chicago, Illinois). To present descriptive data, means and standard deviations were used for continuous variables and absolute frequencies and percentages for categorical variables. To test the data normality the Shapiro-Wilk test was used. Significance level was set at 5% ($p \leq .05$).

In Phase Two, to compare the different variables between groups (pwMS and healthy controls) Independent T-tests were used for continuous variables and Chi square for categorical variables. To calculate effect size Cohen's d was used for t-test comparisons (Small<0.2, Medium 0.2-0.5, Large>0.8) and Phi coefficient and Cramer's V for Chi square comparisons (Small<0.1, Medium 0.1-0.3, Large>0.3). Afterwards bivariate correlations were calculated between the psychosocial factors and the disease parameters only in pwMS. Those that showed a significant correlation were included and two hierarchical regression analyses were conducted to determine which of the psychosocial potential mediators and moderators predicted disease parameters after controlling for relevant socio-demographic variables.

In Phase Three, different analyses were conducted. First, independent t-tests were used to compare different variables among people who suffered relapses and people who did not. In those who suffered relapses a period of 4 weeks before and after the relapse was compared using paired t-tests. Second, bivariate correlations were calculated between the stress measures (perceived stress and number of stressful events) and the disease progression assessments (impairment and functionality). Data were transformed in long format and multiple hierarchical regression mixed models were conducted to test the bidirectional hypothesis after controlling for relevant socio-demographic variables. Coping style, categorised as active or passive, was entered into the models to see both the main and interaction effect on the stress-MS relationship. Complementary hierarchical mixed regression models were conducted to test the moderator effect of social support, anxiety, alexithymia and early-life stress in the stress-MS relationship.

2.5 Ethical considerations

The study was approved by the local ethics committee of the Consorci Hospitalari de Vic, FORES Foundation on July 23, 2013 (register number 2013841-PR71).

The design of the study was conducted in accordance with the Declaration of Helsinki, which comprises the ethical principles for medical research involving human subjects proposed by the World Medical Association (2009).

All of the participants gave written informed consent (see annex 1).

3. Phase One

Systematic literature review of methods of assessing stress and potential moderators and mediators of the stress-MS relationship

Pha
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One

3.1 Paper

Stress and multiple sclerosis: a systematic review considering potential moderating and mediating factors and methods of assessing stress

Critical Review

HEALTH PSYCHOLOGY OPEN

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Stress and multiple sclerosis: A systematic review considering potential moderating and mediating factors and methods of assessing stress

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Abstract

Research about the effects of stress on multiple sclerosis has yielded contradictory results. This study aims to systematically review the evidence focusing on two possible causes: the role of stress assessment and potential moderating and mediating factors. The Web of Knowledge (MEDLINE and Web of Science), Scopus, and PsycINFO databases were searched for relevant articles published from 1900 through December 2014 using the terms "stress*" AND "multiple sclerosis." Twenty-three articles were included. Studies focused on the effect of stress on multiple sclerosis onset ($n = 9$) were mostly retrospective, and semi-structured interviews and scales yielded the most consistent associations. Studies focused on multiple sclerosis progression ($n = 14$) were mostly prospective, and self-reported diaries yielded the most consistent results. The most important modifying factors were stressor duration, severity, and frequency; cardiovascular reactivity and heart rate; and social support and escitalopram intake. Future studies should consider the use of prospective design with self-reported evaluations and the study of moderators and mediators related to amount of stress and autonomic nervous system reactivity to determine the effects of stress on multiple sclerosis.

Keywords

moderating and mediating factors, multiple sclerosis, stress, stress evaluation

Introduction

Multiple sclerosis (MS) is a chronic, progressive, autoimmune disease that affects the central nervous system (Lutton et al., 2004). About 2.5 million people worldwide have MS, it is one of the most common neurological disorders and cause of disability of young adults (WHO, 2006). Although the etiology is unknown, MS is a complex disease that probably involves multiple genes and environmental factors. The most widely studied environmental factors include vitamin D deficiency (Munger et al., 2004), Epstein–Barr virus (Ascherio and Munger, 2010), and stress (Artemiadis et al., 2011).

Stress is the factor that has generated the most controversial results. Some studies report an association between stress and MS (Buljevac et al., 2003; Mohr et al., 2000; Warren et al., 1982) but others failed to find this association or only found a quasi-significant relationship (Gasperini et al., 1995; Riise et al., 2011). These disparate results can be explained by heterogeneity in study design (Artemiadis et al., 2011) as well as by the indirect way stress affects MS

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through other variables (Mohr et al., 2002). Factors proposed as potential moderators and mediators between stress and MS include stressor properties, environmental factors, and patients' biological, social, and psychological characteristics (Mohr et al., 2002).

Some studies have reviewed articles published on the relationship between stress and MS. In 1999, the American Academy of Neurology found class II evidence both for and against an association between stress and the onset or exacerbation of MS, concluding that a relationship between MS and psychological stress was possible but data were insufficient for reasonable medical certainty (Goodin et al., 1999). In 2004, Mohr et al. analyzed 14 studies and found a consistent association between stressful life events and subsequent exacerbation in MS. Finally, in a recent systematic review, Artemiadis et al. (2011) found that 15 of 17 studies reported a significant stress–MS relationship; however, they pointed out that the heterogeneity in the measurement of stress precluded secure conclusions. Other authors highlight the need to identify factors that might modify the stress–MS association (Ackerman et al., 2002; Brown et al., 2006b). All these reviews focused on the quality and main results of the studies, but none examined the results in function of the way stress was measured or of potential moderators and mediators.

This study aims to review the evidence on the association between stress and MS, focusing on the methods used to evaluate whether stress affects MS and the role of potential moderator and mediator factors on this association. This knowledge can be useful for the design of future studies and for developing better interventions in MS patients.

Methods

Literature search

We searched the Web of Knowledge (MEDLINE and Web of Science), Scopus, and PsycINFO databases for relevant articles published from 1900 through December 2014. We searched for the terms *stress** AND *multiple sclerosis*. To obtain additional eligible articles, we also examined the reference lists of the articles located.

Selection criteria

We selected articles that met the following inclusion criteria: (1) published in international peer-reviewed academic journals (book chapters, abstracts of conference proceedings, and dissertations were excluded), (2) published in English or Spanish, (3) measuring psychosocial stress in everyday situations (induced stress studies were excluded), (4) evaluating MS onset, relapse rate during a period of time, or MS-related health status, and (5) observational and non-stress interventional studies in human subjects (stress-interventional and animal studies were excluded).

Two reviewers (L.B.B. and R.M.V.) independently selected articles and examined titles and abstracts to exclude those out-of-scopes. When the first two reviewers disagreed, three reviewers (L.B.B., R.M., and F.X.A.N.) reached a consensus about disagreements. Then, full papers were reviewed and selected for this study. All the processes were done following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements (Moher et al., 2009).

The qualitative appraisal was based on Newcastle–Ottawa quality assessment scale recommended by the Cochrane Non-Randomized Studies Methods Working Group (Wells et al., 1999), following the adaptation for stress and MS made by Artemiadis et al. (2011).

Data extraction

We arranged papers into chronological order and extracted details on (1) source (authors, year, and country); (2) whether the study measured onset, relapse, or both; (3) design; (4) sample; (5) diagnostic criteria for MS, relapse, and health status; (6) study period; (7) qualitative assessment; (8) the instruments used to measure stress; (9) modifying factors considered; and (10) results regarding the relationship between stress and MS and influences of modifying factors.

Following Mohr et al. (2002), we classified modifying factors according to the following criteria: the nature of the stressor; the environmental context; and the patient's biological, social, and psychological characteristics. We classified articles according to whether they evaluated disease onset or progression; however, we decided not to analyze disease type and process because the disease process cannot be controlled and almost all the papers reviewed dealt with remittent-recurrent or secondary-progressive clinical types.

Risk of bias

Our approach carries a risk of different biases. First, the selection process is susceptible to publication bias. Second, there is a risk of excluding papers using different terms to refer to the same concepts, for example, disseminated sclerosis instead of MS or anxiety instead of stress. Third, we may have missed other potential modifying factors because we only analyze factors included in studies that first focused on the relationship between MS and stress.

Results

Study selection

The initial database search provided 5030 records and we identified 11 records from other sources. After we removed duplicate studies and irrelevant titles, 336 unique and potentially relevant abstracts remained (Figure 1). After excluding out-of-scope records, we checked the full texts

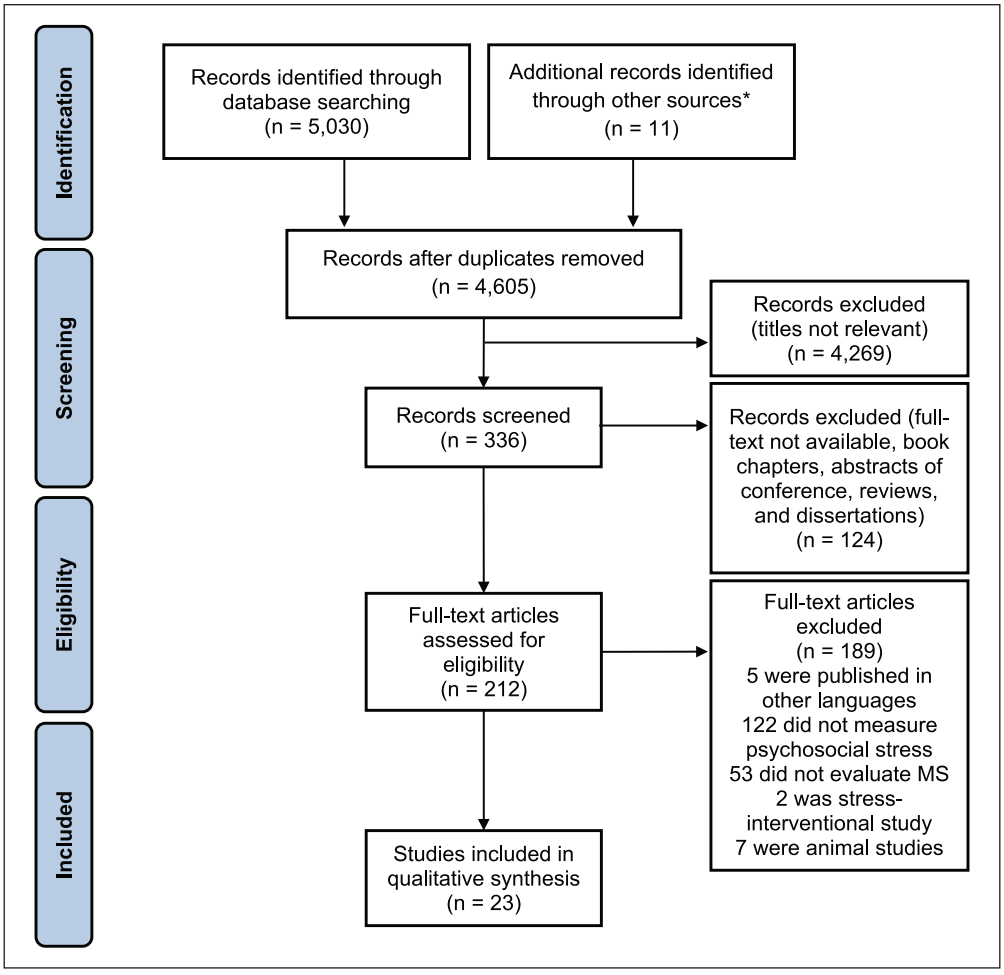

Figure 1. Search and exclusion process.
*References of other papers.

of 212 records. We excluded 189 articles because they did not meet the inclusion criteria: 5 (2.6%) were not published in English or Spanish; 122 (64.6%) did not measure psychosocial stress in everyday situations; 53 (28%) did not evaluate MS onset, relapse rate, or health status; 2 (1.1%) were stress-interventional studies; and 7 (3.7%) were animal studies. Thus, 23 studies were included.

Characteristics of the studies

Table 1 reports the main characteristics of the selected papers. When we grouped papers according to whether they evaluated the effects of stress on onset or progression, we found 9 papers evaluating the effects of stress on onset (Grant et al., 1989; Liu et al., 2009; Mei-Tal et al., 1970; Nielsen et al., 2014a, 2014b; Palumbo et al., 1998; Pratt, 1951; Riise et al., 2011; Warren et al., 1982) and 14 evaluating the effects on disease progression, of which 13 focused on relapses (Ackerman et al., 2002, 2003; Brown et al., 2006a, 2006b; Buljevac et al., 2003; Gasperini et al., 1995; Mitsonis et al., 2008, 2010; Mohr et al., 2000, 2002; Oveisgharan et al., 2014; Potagas et al., 2008; Warren et al., 1991) and 1 on health status (Schwartz et al., 1999).

A wide variety of countries were represented, but nine (39%) were done in or in collaboration with the institutions in the United States.

Despite the broad range of years searched, all the papers selected were published after 1950. One paper was published in the 1950s, 1 in the 1970s, 2 in the 1980s, 4 in the 1990s, 10 in the 2000s, and 5 from 2010 to 2014.

The samples in the studies ranged from 23 to 170 participants with MS, with the exceptions of the three large cohort studies (Nielsen et al., 2014a, 2014b; Riise et al., 2011), which followed between 230,000 and 30 million people initially healthy participants. The control/comparison groups consisted of other individuals with MS in three studies (Gasperini et al., 1995; Mitsonis et al., 2010; Warren et al., 1991), of healthy individuals in three studies (Grant et al., 1989; Liu et al., 2009; Schwartz et al., 1999), and of individuals with other diseases in three studies: organic diseases of the central nervous system (Pratt, 1951), rheumatologic/neurologic

Table 1. Main characteristics of papers selected (sorted by onset/relapse in chronological order).

Author, year, and country	Onset/ relapse	Study design	Sample	Diagnostic criteria	Relapse criteria	Study period of time	Quality assessment
Papers measuring disease onset							
Pratt (1951), United Kingdom	Onset and relapse	Case–control (retrospective)	*n* = 100 MS *n* = 100 controls (organic CNS diseases) (*n* = 50/50 females/males)	Not mentioned	Not mentioned	Onset: unspecific time to onset Relapse: since onset to interview	Selection: 3 Comparability: 1 Exposure: 1
Mei-Tal et al. (1970), Israel/ United States	Onset and relapse	Cross-sectional/ cohort (retrospective)	*n* = 32 MS (*n* = 22 females/*n* = 10 males)	Not mentioned	Not mentioned	Onset: unspecific time to onset Relapse: since onset to interview	Selection: 1 Comparability: 0 Outcome: 1
Warren et al. (1982), Canada	Onset	Case–control (retrospective)	*n* = 100 MS *n* = 100 controls (rheumatology/neurology) (females 2.3:1 males)	Schumacher	Not mentioned	Two years before onset	Selection: 3 Comparability: 1 Exposure: 2
Grant et al. (1989), United States/ United Kingdom	Onset	Case–control (retrospective)	*n* = 39 MS *n* = 40 controls (healthy) (*n* = 29/30 females/*n* = 10 males)	Poser	Not mentioned	One year before onset	Selection: 3 Comparability: 1 Exposure: 1
Palumbo et al. (1998), Italy	Onset	Case–control (retrospective)	*n* = 65 MS *n* = 27 controls (non-genetic chronic PNP) (*n* = 40/12 females/*n* = 25/15 males)	Not mentioned	Not mentioned	One year before onset	Selection: 1 Comparability: 0 Exposure: 2
Liu et al. (2009), China/United States	Onset	Case–control (retrospective)	*n* = 41 MS *n* = 41 controls (healthy) (*n* = 26 females/*n* = 15 males)	Poser	Not mentioned	Three years before onset	Selection: 3 Comparability: 1 Exposure: 1
Riise et al. (2011), Norway/United States	Onset	Cohort (prospective)	*n*C1 = 121,700 *n*C2 = 116,671 (healthy female nurses)	Poser	Not mentioned	Follow-up 30 years	Selection: 3 Comparability: 1 Outcome: 3
Nielsen et al. (2014a), Denmark	Onset	Cohort (prospective)	*n*C3/*n*C4 = 30 million people (healthy people)	McDonald	Not mentioned	Follow-up 28 years	Selection: 4 Comparability: 1 Outcome: 3

Table 1. (Continued)

Author, year, and country	Onset/ relapse	Study design	Sample	Diagnostic criteria	Relapse criteria	Study period of time	Quality assessment
Nielsen et al. (2014b), Denmark	Onset	Cohort (prospective)	*n*C5 = 2.9 million people (healthy people)	McDonald	Not mentioned	Follow-up 18 years	Selection: 4 Comparability: 1 Outcome: 3
Papers measuring disease progression							
Warren et al. (1991), Canada	Relapse	Case–control (retrospective)	*n* = 95 MS in exacerbation *n* = 95 MS in remission (2.3 females:1 males)	Poser	Clinical criteria[2]	Three months prior relapse (exacerbation group) or interview (remission group)	Selection: 4 Comparability: 1 Exposure: 2
Gasperini et al. (1995), Italy	Relapse	Case–control (prospective)	*n* = 89 MS in exacerbation *n* = 89 MS in remission (*n* = 62 females/*n* = 27 males)	Poser	Clinical criteria[3]	Follow-up 1 year 3 months before exacerbation	Selection: 4 Comparability: 1 Exposure: 2
Schwartz et al.(1999), United States	Health status	Cohort (prospective)	*n* = 101 MS *n* = 96 controls (healthy) (*n* = 75 females/*n* = 26/21 males)	Poser	Not mentioned	Follow-up 6 years	Selection: 3 Comparability: 1 Outcome: 2
Mohr et al. (2000), United States	Relapse	Cohort (prospective longitudinal)	*n* = 36 MS (*n* = 22 females/*n* = 14 males)	Poser	Clinical criteria[4] New MRI Gd+ lesions	Follow-up for 28–100 weeks	Selection: 3 Comparability: 1 Outcome: 3
Ackerman et al. (2002), United States	Relapse	Cohort (prospective longitudinal)	*n* = 23 MS (females)	Poser	Clinical criteria[6]	Follow-up 1 year	Selection: 4 Comparability: 0 Outcome: 3
Mohr et al. (2002), United States	Relapse	Cohort (prospective longitudinal)	*n* = 36 MS (*n* = 22 females/*n* = 14 males)	Poser	New MRI Gd+ lesions	Follow-up for 28–100 weeks	Selection: 3 Comparability: 2 Outcome: 2
Ackerman et al. (2003), United States	Relapse	Cohort (prospective longitudinal)	*n* = 50 MS (females)	Poser	Clinical criteria[6]	Follow-up 1 year	Selection: 4 Comparability: 1 Outcome: 3
Buljevac et al. (2003), The Netherlands	Relapse	Cohort (prospective longitudinal)	*n* = 73 MS (*n* = 56 females/16 males)	Not mentioned	Clinical criteria[5]	Follow-up 1.4 years (average 74 weeks, range 8–120 weeks)	Selection: 3 Comparability: 1 Outcome: 3

(Continued)

Table 1. (Continued)

Author, year, and country	Onset/ relapse	Study design	Sample	Diagnostic criteria	Relapse criteria	Study period of time	Quality assessment
Brown et al. (2006a), Australia	Relapse	Cohort (prospective longitudinal)	*n* = 101 MS (*n* = 81 females/*n* = 20 males)	Poser	Clinical criteria[6]	Follow-up 2 years	Selection: 4 Comparability: 2 Outcome: 2
Brown et al. (2006b), Australia	Relapse	Cohort (prospective longitudinal)	*n* = 101 MS (*n* = 81 females/*n* = 20 males)	Poser	Clinical criteria[6]	Follow-up 2 years	Selection: 4 Comparability: 2 Outcome: 2
Mitsonis et al. (2008), Greece	Relapse	Cohort (prospective longitudinal)	*n* = 26 MS (females)	McDonald	Clinical criteria[5]	Follow-up mean 56.3 weeks	Selection: 4 Comparability: 0 Outcome: 3
Potagas et al. (2008), Greece/ France	Relapse	Cohort (prospective longitudinal)	*n* = 37 MS (females)	McDonald	Clinical criteria[5]	Follow-up 1 year	Selection: 3 Comparability: 2 Outcome: 3
Mitsonis et al. (2010), Greece	Relapse	Cohort (prospective)	*n* = 24 MS (SSRI) *n* = 24 MS (no SSRI) (females)	McDonald	Clinical criteria[5]	Follow-up 1 year	Selection: 1 Comparability: 1 Outcome: 3
Oveisgharan et al. (2014), Iran	Relapse	Cohort (prospective)	*n* = 57 MS patients (*n* = 46 females/*n* = 11 males)	McDonald	Clinical criteria[1] unspecified	Follow-up 1 year	Selection: 1 Comparability: 0 Outcome: 3

MS: multiple sclerosis; CNS: central nervous system; PNP: polyneuropathy; *n*C1: *n* cohort 1; *n*C2: *n* cohort 2; *n*C3: *n* cohort of persons who became parents between 1968 and 2010; *n*C4: *n* cohort of persons who married between 1968 and 2010; *n*C5: *n* cohort of people born from 1968 to 2011; MRI: magnetic resonance imaging; Gd+: gadolinium; SSRI: selective serotonin reuptake inhibitor (escitalopram); EDSS: Expanded Disability Status Scale.

Clinical criteria for relapses: 1. Unspecified. 2. Sudden appearance of a symptom typical of MS, which may have been new to participants or experienced during a previous relapse. Remission was defined as no symptoms in the previous 6 months. 3. New neurological symptom associated with a change of at least 1.0 point in EDSS which lasted more than 24 hours. 4. Increase of 1.0 point on the EDSS from the previous examination. 5. A worsening of existing symptoms or appearance of new symptoms, lasting more than 24 hours and after at least 30 days of improvement or stability not associated with fever. 6. Occurrence, recurrence, or worsening of symptom(s) of neurological dysfunction, associated with confirmatory change on neurological examination, lasted more than 48 hours, not associated with fever and occurred after at least 30 days of improvement or stability.

diseases (Warren et al., 1982), and polyneuropathy (Palumbo et al., 1998).

Study design. Six of the nine studies examining the relationship between stress and the onset of MS were retrospective: one (Mei-Tal et al., 1970) was cross-sectional and five (Grant et al., 1989; Liu et al., 2009; Palumbo et al., 1998; Pratt, 1951; Warren et al., 1982) case–control; these studies focused on a period from 1 to 3 years before onset or on an unspecific period of time before onset (Mei-Tal et al., 1970; Pratt, 1951). Three prospective studies that examined the relationship between stress and the onset of MS were longitudinal, following a cohort of initially healthy people from 18 to 30 years (Nielsen et al., 2014a, 2014b; Riise et al., 2011).

The 14 studies examining the relationship between stress and progression of MS were all prospective; 12 of these were cohort studies (Ackerman et al., 2002, 2003; Brown et al., 2006a, 2006b; Buljevac et al., 2003; Mitsonis et al., 2008, 2010; Mohr et al., 2000, 2002; Oveisgharan et al., 2014; Potagas et al., 2008; Schwartz et al., 1999) and 2 were case–control studies (Gasperini et al., 1995; Warren et al., 1991). The duration of these studies ranged from 28 weeks to 8 years, but in most it was about 1 year.

Criteria for diagnosing MS and relapse. The criteria for the initial diagnosis of MS have evolved from those in Schumacher et al., (1965) publication, which were updated by Poser et al. (1983), and more recently by McDonald et al. (2001), last reviewed by Polman et al. (2011).

The criteria for diagnosing relapse varied widely. Whereas some articles used biological criteria (new lesions on gadolinium-enhanced magnetic resonance imaging (MRI)) to determine disease progression (Mohr et al., 2000, 2002), most studies used clinical criteria to define relapse, either changes in Expanded Disability Status Scale score (Gasperini et al., 1995; Mohr et al., 2000) or worsening or new symptoms (Ackerman et al., 2002, 2003; Brown et al., 2006a, 2006b; Buljevac et al., 2003; Mitsonis et al., 2008, 2010; Oveisgharan et al., 2014; Potagas et al., 2008; Warren et al., 1991), with some variation in the definition of these concepts. Nevertheless, the most commonly used clinical criteria describe relapse as a worsening of the existing symptoms or appearance of new ones lasting more than 24 hours (labeled clinical criteria 5 in Table 1) or more than 48 hours (labeled clinical criteria 6 in Table 1) after at least 30 days of improvement or stability not associated with fever.

Regarding relapse criteria, we observed that studies that used biological criteria (new gadolinium-enhanced lesions) or changes in Expanded Disability Status Scale found a positive but not significant association (odds ratio (OR) = 2.3, 95% confidence interval (CI) = 0.9–5.6) between stress and MS (Gasperini et al., 1995) or an association not sufficiently robust (OR = 1.64, 95% CI = 1.22–2.20) to predict clinical exacerbations (Mohr et al., 2000).

Methods used to evaluate stress and results: onset studies

Two studies (Mei-Tal et al., 1970; Pratt, 1951) used non-validated interviews; both found more emotional stress before onset (unspecific period of time), although in Pratt (1951) the difference was not significant ($\chi^2 = 1.8$, $p > .05$).

Two other studies (Grant et al., 1989; Warren et al., 1982) used semi-structured interviews designed on the basis of previous information about stress; both showed a temporal relationship between greater emotional stress and MS. In the study by Grant et al. (1989), compared to matched controls without MS, more MS patients had experienced marked adversity in the year prior to onset of symptoms, (77% vs. 35% of controls; $\chi^2 = 14.08$, $p < .001$). Similarly, Warren et al. (1982) found that MS patients had more unwanted stress than controls in the 2 years before onset (79% vs. 54%; $\chi^2 = 12.93$, $p < .001$).

Two studies (Palumbo et al., 1998; Riise et al., 2011) used ad hoc questionnaires to determine the amount of stress. Palumbo et al. (1998) observed a nonsignificant trend toward more stressful events in MS patients than in patients with polyneuropathy (24.6% vs. 14.8%) in the year before onset. Riise et al. (2011) observed no effect of stress on MS development in 30 years' follow-up of a large cohort of initially healthy subjects.

One study used a rating scale of stressful events. Liu et al. (2009) found significant differences ($p < .01$) between MS and controls in different symptoms related to stress such as mental health symptoms, negative life events, family problems, and social support.

Finally, two studies (Nielsen et al., 2014a, 2014b) used data about specific stressful events from the National Multiple Sclerosis Registry and observed little evidence for a causal association between major stressful events and MS risk. Only parental divorce in childhood increased modestly the risk of MS (Nielsen et al., 2014b).

Methods used to evaluate stress and results: progression studies

Progression studies can be classified into two categories: those that evaluated the stress patients experienced in a period of time before a relapse retrospectively after the relapse occurred (Gasperini et al., 1995; Warren et al., 1991) and those that evaluated stress systematically before the relapse occurred (Ackerman et al., 2002, 2003; Brown et al., 2006a, 2006b; Buljevac et al., 2003; Mitsonis et al., 2008, 2010; Mohr et al., 2000, 2002; Oveisgharan et al., 2014; Potagas et al., 2008; Schwartz et al., 1999).

In the first category, Warren et al. (1991) used a questionnaire and different scales and observed a significant positive relationship between stress and MS exacerbation: patients scoring 5 or above in Goldberg and Hillier's General Health

Questionnaire-28 (Goldberg and Hillier, 1979) had a relative risk (RR) of exacerbation of 3.1 (95% CI). In contrast, Gasperini et al. (1995) used a structured interview to determine whether patients had undergone a single stressful event and found no differences between MS patients who had relapsed and those who had not, although cumulated stressful events were associated with a nonsignificantly higher risk of MS relapse (OR = 2.3, 95% CI = 0.9–5.6).

In the second category, eight studies used different combinations of questionnaires, scales, and interviews. Mohr et al. (2000, 2002) used different scales to evaluate stressful events and hassles monthly, considering the 8 weeks after every stressful event a period at risk for relapse; these studies found that *Conflict and disruption in routine* increased the odds of developing new gadolinium-enhanced lesions (OR = 1.64, 95% CI = 1.22–2.20, $p < .001$), but was not robust enough to reliably predict clinical exacerbations. Oveisgharan et al. (2014) used a trimonthly questionnaire and observed no differences in stressful events between patients with or without subsequent relapses. Ackerman et al. (2002, 2003) used a weekly questionnaire and a semi-structured interview at the beginning and end of the study. Both studies showed that stress was a potential trigger of MS exacerbations and vice versa; considering the 6 weeks after an stressful event as a period at risk for relapse, 85 percent of relapses were associated with an stressful event and 49 percent of stressful events were associated with relapses. Brown et al. (2006a, 2006b) found similar results using the same semi-structured interview at the beginning and every 3 months, also confirming the bidirectional hypothesis.

Schwartz et al. (1999) using a self-reported stressful event scale every 6 months also found a bidirectional relationship between stress and MS exacerbation, in which MS progressed after stress and stress increased after MS exacerbations in a vicious cycle. More than one stressful event increased the risk of disease progression (OR = 1.13, $p < .001$) and disease progression increased the risk of self-reported stress (OR = 2.13, $p < .001$).

Finally, four studies (Buljevac et al., 2003; Mitsonis et al., 2008, 2010; Potagas et al., 2008) used self-reported diaries. All these studies showed increased risk for exacerbation during the 4 weeks after a stressful event. Buljevac et al. (2003) found that one or more stressful events were associated with a 2-fold risk of relapse (RR = 2.2, 95% CI = 1.2–4.0, $p < .05$), concluding that the increased risk of relapse was not "dose-dependent." In contrast, Mitsonis et al. (2008) and Potagas et al. (2008) found that cumulative stressful events (three or more) increased the risk of MS relapse (from OR = 5.36 to OR = 16.78, 95% CI).

Moderating and mediating factors: evaluation and results

All but 2 of the 23 studies took into account potential modifying factors of the relationship between stress and MS (Table 2). We classified these factors into three main categories: stressor properties, individual characteristics, and environmental factors.

Stressors properties. Thirteen studies analyzed stressor properties such as type, duration, severity, valence, source, and frequency. Among the different stressor properties, type and source (for example, work stress) were the least significant (Ackerman et al., 2002; Grant et al., 1989; Mei-Tal et al., 1970; Mitsonis et al., 2008). However, Mohr et al. (2000) observed that only the type of stressor referred to as "Conflict and disruption in routine" was associated with new gadolinium-enhanced lesions. The duration of exposure to a stressor was more important. Stressors associated with relapses were mainly sustained and protracted or long-term stressors (versus acute stressors), lasting more than 48 hours (Ackerman et al., 2002; Brown et al., 2006a; Grant et al., 1989; Mei-Tal et al., 1970). With regard to severity of the stressor, most studies found a stronger association with MS relapses for intermediate-to-severe intensity stressors (Ackerman et al., 2002; Grant et al., 1989; Warren et al., 1991). Finally, frequency was important; in general, studies found that cumulated stress or the presence of various stressful events increased the risk of relapse compared with a single stressful event (Brown et al., 2006a; Gasperini et al., 1995; Mitsonis et al., 2008; Oveisgharan et al., 2014; Potagas et al., 2008; Schwartz et al., 1999).

Patients' characteristics. Eight studies evaluated the impact of different patient characteristics on the stress–MS relationship. Seven considered psychosocial factors such as premorbid personality (Pratt, 1951), coping style (Brown et al., 2006b; Mohr et al., 2002; Warren et al., 1982, 1991), and mental health symptoms (anxiety, depression, optimism) (Brown et al., 2006b; Liu et al., 2009; Potagas et al., 2008). Only one study (Ackerman et al., 2003) evaluated biological factors (cardiovascular reactivity, resting heart rate, and blood pressure).

Personality did not seem to affect disease progression (Pratt, 1951), but other psychosocial factors differed significantly between MS patients and controls (Liu et al., 2009), including a trend toward worse mental health in MS patients. In a recent study by Potagas et al. (2008), a Hamilton Rating Scale for Anxiety (Hamilton, 1959) score $\geqslant 18$ was associated with a hazard rate of 2.9 (95% CI = 1.3–6.4, $p < .05$) for MS relapse.

There seems to be modest evidence that coping style affects MS; Mohr et al. (2002) found greater use of distraction had a protective effect against MS (OR = 0.69, 95% CI = 0.49–0.98, $p < .05$), but instrumental coping was only marginally associated with a decrease in the strength of the stress–MS relationship (OR = 0.77, 95% CI = 0.57–1.04, $p > .05$). Other coping styles showed no effects on the relationship. Warren et al. (1982) neither found differences in coping styles between MS patients and controls but, in a more recent study of Warren et al. (1991) comparing MS

Table 2. Stress measuring instruments, moderator factors and results.

Author/year	Instruments used to measure stress	Moderating mediating factors	Instruments to measure moderating/mediating factors	Results (1, stress–MS relationship; 2, moderating/mediating factors)
Papers measuring disease onset				
Pratt (1951)	Non-validated interview (life story)	Premorbid personality	Allotting each patient in the personality schemes of Jung (extraversion–introversion) and Sheldon (viscerotonia, somatotonia, cerebrotonia)	(1) Emotional stress antedates onset or relapse but no significant differences between MS and controls ($\chi^2 = 1.8$, $p > .05$). (2) No specific premorbid personality type was defined in patients of MS.
Mei-Tal et al. (1970)	Non-validated interview (life story)	Stressor typology and duration	Classifying SLEs into: a) Sudden and transient b) Sudden and sustained c) Gradual and protracted	(1) 28 of 32 patients reported data indicating the illness was preceded by an SLE. (2) Stressor duration is mainly sustained and protracted; stressor typology is indifferent.
Warren et al. (1982)	Interview based on a modified version of Holmes and Rahe Social Readjustment Rating Scale	Early life stress, coping style	Questions in the interview: a) Emotional climate at home during childhood/ adolescence b) Assess how to react to life problems prior to onset age	(1) There is a relationship between emotional stress and MS onset. More unwanted stress in MS patients (79%) than in controls (54%) ($\chi^2 = 12.93$, $p < .001$). (2) Early life stress and coping style: no differences between MS patients and control group.
Grant et al. (1989)	Semi-structured interview LEDS	Stressor severity, typology, and duration	Classifying SLEs into: a) Severely threatening events (punctual event + long-term > 48 hours + very or moderately severe threat + self-focus) b) Marked difficulties (difficulty ⩾ 4 weeks + very, moderately, or severe threat)	(1) Temporal relationship between marked adversity and MS symptoms (77% MS patients vs. 35% non-patients, $\chi^2 = 14.08$, $p < .001$). (2) More marked life adversity (severely threatening events and marked difficulties) in MS patients 1 year before onset but most evident from 6 months to onset.
Palumbo et al. (1998)	Non-validated questionnaire modeled on DSM-IV	No		No significant differences but more SLE in MS patients (24.6%) than in PNP patients (14.8%) the year before onset.
Liu et al. (2009)	Questionnaire, once: LES	Personality, social support, and mental health symptoms	Questionnaires, once: Eysenck Personality Questionnaire Social Support Reevaluate Scale Symptom Check List 90	(1) and (2) significant differences ($p < .01$) were found between MS and control group in mental health symptoms, negative life events, family problems, and social support. Negative correlation of social support with negative emotions suggesting lack of ability in MS patients to use social support.
Riise et al. (2011)	Questionnaire including questions on stress at home and work	Early life stress	Questionnaire including 22 questions on physical and sexual abuse in childhood and adolescence Questions on physical abuse adapted from the Revised Conflict Tactics Scale	(1) No increased risk of MS associated with severe stress at home or work (HR 0.85 (95% CI) 0.32–2.26). (2) Elevated but not significant risk among women having been forced into sexual activity several times during childhood (OR 1.51 (95% CI) 0.90–2.55) and adolescence (OR 1.25 (95% CI) 0.70–2.23).

(Continued)

Table 2. (Continued)

Author/year	Instruments used to measure stress	Moderating mediating factors	Instruments to measure moderating/mediating factors	Results (1, stress–MS relationship; 2, moderating/mediating factors)
Nielsen et al. (2014a)	Stressful life events: lose a child get divorced or widowed	No		No increased risk of MS in bereaved parents compared to those who did not lose a child. No increased risk in divorced or widowed persons compared with married persons.
Nielsen et al. (2014b)	Stressful life events: parental divorce parental death death of sibling	Early life stress	SLEs (until age 18 years): parental divorce parental death death of sibling	(1) and (2) Persons exposed to any SLE in childhood were at 11% elevated risk for MS (RR 1.11 (95% CI) 1.03–1.20), compared to non-exposed persons. Parental death and death of sibling were not associated. Persons exposed to parental divorce were at 13% increased risk (RR 1.13 (95% CI) 1.04–1.23).
Papers measuring disease progression				
Warren et al. (1991)	Questionnaires: Goldberg and Hillier's GHQ-28 Hassles' Scale Uplifts' Scales	Coping style, stressor severity, and frequency	Questionnaires: Ways of Coping Checklist Stressor intensity measured by Hassles Scale Stressor frequency is the number of SLEs in a 3-month period	(1) Relative risk of an exacerbation associated with a score of 5 or above in GHQ was 3.1 (95% CI), suggesting an emotional stress–exacerbation relationship. (2) Daily hassles: more severity in patients in exacerbation, no differences in frequency, suggesting that perceived impact is more important than number. No significant differences in coping strategies, but patients in exacerbation who favored emotion-focused coping were consistently higher ($\chi^2 = 8.4$, $p < .01$).
Gasperini et al. (1995)	Structured interview about SLEs	Stressor frequency	Number of SLEs in a period of 3 months	(1) No differences between groups for a single SLE. (2) Cumulated SLEs were associated with higher risk of relapse but not significant (OR 2.3 (95% CI) 0.9–5.6).
Schwartz et al.(1999)	Self-reported stressful events every 6 months following: Holmes and Rahe checklist	Stressor frequency	Number of SLEs (evaluated every 6 months)	(1) and (2) Increased risk of disease progression by level of stress (more than one SLE) (OR 1.13, $p < .001$). Increased risk of reported stress by rate of disease progression (OR 2.13, $p < .001$). Vicious cycle "stress progression."
Mohr et al. (2000)	Questionnaires (monthly): Modified SRRS Hassles Scale Profile of Mood States	Stressor frequency and typology	Number of SLEs (evaluated every 4 weeks) Classification of typology: a) Major negative events b) Conflict and disruption in routine c) Positive life events	(1) and (2) *Conflict and disruption in routine* increased odds (OR 1.64 (95% CI) 1.22–2.20, $p = .00083$) of developing new MRI Gd+ lesions (8 weeks later). Not sufficiently robust to predict clinical exacerbations reliability.

Table 2. (Continued)

Author/year	Instruments used to measure stress	Moderating mediating factors	Instruments to measure moderating/mediating factors	Results (1, stress–MS relationship; 2, moderating/mediating factors)
Ackerman et al. (2002)	Questionnaire, weekly: Psychiatric Epidemiologic Research Interview Semi-structured interview at the beginning/end of the study: LEDS	Stressor severity, duration, frequency, and source	Classifying SLEs by severity: a) Likert scale: *more severe* (1) to *less severe* (4) Duration: a) Short-term <15 days b) Long-term ⩾ 15 days Source (different categories) Frequency (number of SLEs)	(1) Stress is a potential trigger of exacerbations in patients with MS. 85% of relapses were associated with an SLE and 49% of SLEs were associated with relapses in a 6-week time frame. (2) An increase in frequency of life events was associated with greater likelihood of MS exacerbations (HR 13.18 (95% CI) 1.67–104.39, $p < .05$).
Mohr et al. (2002)	Questionnaire (monthly): Modified Social Readjustment Rating Scale	Coping style	Coping with Health Injuries and Problems questionnaire	(1) and (2) Modest support for that coping can moderate stress–MS relationship. Greater use of distraction (OR 0.69 (95% CI) 0.49–0.98, $p = .037$) and instrumental coping (OR 0.77 (95% CI) 0.57–1.04, $p = .81$) was marginally associated with decreased stress–MS relationship. Other coping forms did not.
Ackerman et al. (2003)	Questionnaire, weekly: Psychiatric Epidemiologic Research Interview Semi-structured interview at the end of the study: LEDS	Cardiovascular reactivity, resting heart rate, and blood pressure	Measures on: cardiovascular reactivity to an acute experimental stressor (Stroop task) resting heart rate blood pressure	(1) Stress is a potential trigger of relapse. They are more likely at-risk periods (6 weeks after SLE). Deteriorating cycle. (2) Participants with higher cardiovascular reactivity to acute stress and higher baseline heart rate had a greater number of exacerbations ($r(47) = 0.320$, $p < .05$) and weeks ill ($r(47) = 0.350$, $p < .05$).
Buljevac et al. (2003)	Self-reported weekly diaries of emotionally stressful events	Stressor frequency	Number of SLEs (evaluated weekly)	(1) At least one SLE is associated with double risk for relapse (RR 2.2 (95% CI) 1.2–4.0, $p = .014$) in a risk period (4 weeks). No differences in exacerbation risk after 1 or more SLE. Not dose dependent.
Brown et al. (2006a)	Semi-structured interview, at the beginning and every 3 months: LEDS	Stressor valence, typology, frequency, duration, and severity	Classifying SLEs in typology: a) Emotional threat b) Goal frustration Duration: a) Acute events <6 months b) Chronic difficulties >6 months Valence (positive, negative) Severity: a) 4-point Likert scale: 0 (*mild or non-threatening*) to 4 (*severe*) Number of SLEs	(1) Bidirectional stress-illness hypothesis was confirmed. (2) Acute events predicted greater relapse risk (<6 months) than chronic difficulties (>6 months). The number of SLE is the most important property in relation to MS relapse risk.

(Continued)

Table 2. (Continued)

Author/year	Instruments used to measure stress	Moderating mediating factors	Instruments to measure moderating/mediating factors	Results (1, stress–MS relationship; 2, moderating/mediating factors)
Brown et al. (2006b)	Semi-structured interview, at the beginning and every 3 months: LEDS	Coping style, anxiety, depression, optimism, Health LOC, and Social Support	Questionnaires: Beck Depression Inventory STAI—T Ways of Coping Life Orientation Test MHLC Sarason Social Support	1 and 2) Exacerbation is predicted by acute stressor frequency counts and coping responses using social support but not by chronic stressors or other psychosocial factors. Seeking social support decreases the relationship stress–relapse.
Mitsonis et al. (2008)	Self-reported weekly diaries of emotionally stressful events	Stressor duration, type, frequency, and severity	Severity measure: Recent Life Change Questionnaire Type of stress (six categories) Duration (subjective measure): Short-term Long-term (10–14 days) Number of SLEs	(1) Women with cumulative SLEs (3 or more) may be at greater risk for relapse during period at risk (4 weeks). For 3 SLEs (HR 5.36 (95% CI) 1.74–6.46, $p = .003$). For 4 SLEs (HR 16.78 (95% CI) 4.64–60.56, $p < .001$). (2) Duration is the only stressor property that seems to increase risk for relapse (HR 3 (95% CI) 1.01–9.13, $p < .05$), but not stress type or severity.
Potagas et al. (2008)	Self-reported weekly diaries of emotionally stressful events	Anxiety stressor frequency	Questionnaire, every 4 weeks: Hamilton Rating Scale for Anxiety Number of SLEs (evaluated weekly)	(1) Three or more SLE increases in 6.7 times the risk of relapse in MS women (HR 6.7 (95% CI) 2.8–16.0, $p < .001$). (2) High level of anxiety (score >18 in HAM-A) is associated with 2.9 times the rate of relapse (HR 2.9 (95% CI) 1.3–6.4, $p = .008$) and with the number and severity of the SLE.
Mitsonis et al. (2010)	Self-reported weekly diaries of emotionally stressful events	SSRI intake (escitalopram), stressor duration, and frequency	Intake of escitalopram: 10 mg/day Classifying duration: a) Short-term b) Long-term (>14 days) Number of SLEs	(1) and (2) Risk for relapse was 2.9 times higher in c-group (HR 2.9 (95% CI) 1.7–5.9, $p < .001$), influenced only by long-term SLEs. In e-group only ⩾3 long-term SLEs were related to higher relapse risk.
Oveisgharan et al. (2014)	Questionnaire, trimonthly: Paykel's checklist	Stressor severity and frequency	Severity measure: Subjective appraisal scoring SLE from 0 to 20 Frequency measure: Number of SLE	(1) No differences in SLEs between patients with or without subsequent relapses. (2) Number of stressors was the only factor which reached near significance in predicting relapses ($p = .054$).

MS: multiple sclerosis; SLE: stressful life event, which produces emotional tension, different from everyday life; LEDS: Life Events and Difficulties Schedule; DSM-IV: *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.); PNP: polyneuropathy; LES: Life Event Scale; HR: hazard ratio; CI: confidence interval; OR: odds ratio; RR: relative risk; GHQ: General Health Questionnaire; SRRS: Social Readjustment Rating Scale; MRI: magnetic resonance imaging; Gd+: gadolinium; LOC: Locus of Control; STAI-T: State Trait Anxiety Inventory - Trait; MHLC: Multidimensional Health Locus of Control Scale; SSRI: selective serotonin reuptake inhibitor (escitalopram).

patients in exacerbation with MS patients in remission, it was found that patients in exacerbation did use more emotional-focused strategies than those in remission, $\chi^2 = 8.4$, $p < .05$.

Finally, Ackerman et al. (2003) found that higher cardiovascular reactivity to an acute stressor and higher baseline heart rate were significantly correlated with greater relapse rate ($r(47) = .320$, $p < .05$) and longer illness after relapse ($r(47) = .350$, $p < .05$).

Environmental factors. Six studies examined environmental factors such as early life stress (Nielsen et al., 2014b; Riise

et al., 2011; Warren et al., 1982), social support (Brown et al., 2006b; Palumbo et al., 1998), or escitalopram intake (Mitsonis et al., 2010).

Regarding the early life stress, Riise et al. (2011) found a nonsignificant trend toward developing MS in women who had been forced into sexual activity several times during childhood (OR = 1.51, 95% CI = 0.90–2.55) or adolescence (OR = 1.25, 95% CI = 0.70–2.23). However, Nielsen et al. (2014b) found that persons exposed to parental divorce in childhood were at 13 percent increased risk of developing MS (RR = 1.13, 95% CI = 1.04–1.023).

Finally, social support and intake of escitalopram seem to decrease the stress–relapse relationship. Liu et al. (2009) found a negative correlation between social support and negative emotions, suggesting that MS patients lacked the ability to use social support. Mitsonis et al. (2010) studied the effects of escitalopram on stress-related relapses in a randomized controlled trial, finding that patients in the control group (no intake) had a risk of relapse 2.9 times higher than those in the experimental group (receiving escitalopram) (hazard ratio (HR) = 2.9, 95% CI = 1.7–5.9, $p < .001$), but predicted only by long-term stressors (lasting more than 14 days).

Discussion

To elucidate the relationship between stress and MS and moderating and mediating factors that might influence this relationship, we analyzed the results of 23 studies in function of the methods they used to evaluate stress. We classified studies into two main categories: those that analyzed the effect of stress on the onset of MS and those that analyzed the effect of stress on the progression of MS. Studies focused on onset used a retrospective design with interviews being the main instrument to assess stress. In these studies, semi-structured interviews and scales were the instruments that showed more significant associations with the onset of MS. Studies focused on progression were mostly prospective and evaluated stress systematically prior to exacerbations using a combination of interviews, questionnaires, scales, and self-reported diaries. Almost all these studies showed a significant positive relationship between stress and progression, and self-reported diaries yielded the most consistent results. The potential moderating and mediating factors with the most consistent effect on the stress–MS relationship were the duration, severity, and frequency of the stressor; anxiety, cardiovascular reactivity, and heart rate; and social support and escitalopram intake.

As previous reviews (Artemiadis et al., 2011; Mohr et al., 2004) pointed out, one of the main problems in evaluating the evidence for the relationship between stress and MS is the wide variety of methods used to measure stress. Moreover, different studies not only used different combinations of several stress-measuring instruments but also different study designs, temporal frameworks between stress and disease (onset or progression), and different criteria to evaluate disease onset and progression.

The studies that evaluated disease onset with a prospective design or ad hoc questionnaires failed to show a significant relationship between stress and disease onset. Only studies using interviews with a retrospective design or questionnaires and scales in a case–control design showed a significant relationship, although this approach cannot establish a causal link. To firmly confirm or rule out whether stress is a risk factor for MS onset, prospective studies that frequently assess stressors are required.

Most studies evaluating disease progression assessed stress prospectively before the changes in disease progression became evident. Almost all these studies showed a positive relationship, regardless of the instruments used or the temporal framework considered as the period "at risk" (from 4 to 8 weeks). However, the studies that used self-reported diaries or weekly assessment (Ackerman et al., 2002, 2003; Buljevac et al., 2003; Mitsonis et al., 2008, 2010; Potagas et al., 2008) had more consistent results. Another important element for obtaining consistent results is the criteria used to measure relapse. As mentioned by Mohr and Pelletier (2006), after a stressful life event, the changes in MS manifest in the following order: first, MRI brain lesions, second, clinical symptoms or relapses, and third, the changes in the Expanded Disability Status Scale. Therefore, studies using the Expanded Disability Status Scale to evaluate MS progression after stress would probably show less progression because the scores often do not change until long after patients notice worsening symptoms or several relapses have occurred. Thus, biological or clinical criteria, or a combination of the two, are likely to provide more accurate results in early stages. In addition, since stress can affect disease without causing relapse, but only worsening symptoms, it seems necessary to add periodic functionality assessment to evaluate different categories of health status.

The relationship between stress and disease is modulated by several factors. The characteristics of the stressors have been the most widely studied. Although one study (not included in the systematic review) found that psychosocial and occupational stress were linked to a disease worsening (Strenge, 2001), overall the typology and source of stress do not apparently moderate the stress–MS relationship. In contrast, stressor duration, severity, and frequency have consistently been identified as modifying factors.

Chronic stress, defined as exposure to a stressor for more than 48 hours, had a greater effect on MS than acute stress (Ackerman et al., 2002; Brown et al., 2006a, 2006b; Grant et al., 1989; Mei-Tal et al., 1970). However, the studies reviewed often categorized duration differently. For example, for Ackerman et al. (2002), long-term stressors were those lasting at least 15 days, but for Brown et al. (2006a, 2006b), long-term stressors were those lasting

more than 6 months. The effect of chronic stress on MS could be explained by alterations in the stress-response systems of the hypothalamic–pituitary–adrenal axis and autonomic nervous system (for a review, see Gold et al., 2005).

Stressor severity is also important. Intermediate and severe stressors have shown the most consistent associations with disease progression. However, these results seem applicable only to everyday or common stress; in extremely stressing situations, such as war, relapse rate can decrease (Nisipeanu and Korczyn, 1993). The frequency of exposure to stress is also positively associated with disease progression: an increase in the number of stressful events is associated with an increase in the likelihood of relapse. The reason why stressor duration, severity, and frequency consistently modify the effects of stress on MS but source and typology do not is that the former directly determine the amount of stress, whereas the latter depend on personal assessment.

Many studies have also explored the potential modifying role of patients' individual characteristics on the effects of stress on MS. The most important factors identified are anxiety, cardiovascular reactivity, and heart rate, all of which are related to autonomic reactivity. The autonomic nervous system is one of the stress-response systems and could be involved in MS pathogenesis and progression (Gold et al., 2005). Future studies should take biological measures of stress into account, so they can analyze biological correlates of stressful situations. Biofeedback technology has been widely used to reduce stress and anxiety and might help teach people which emotional states cause greater activation of biological stress-response systems. In a recent review, Biondi and Valentini (2014) concluded that biofeedback therapies are able to produce somatic peripheral changes (neuroendocrine and neurovegetative systems).

Another patient factor that has been analyzed is coping style; however, the results for this factor have been contradictory. Whereas Mohr et al. (2002) found modest support for a moderating effect of coping style, Warren et al. (1982, 1991) found no significant differences between MS patients and control group but a tendency to use a more emotion-focused coping style in MS patients experiencing exacerbations compared to patients in remission. Brown et al. (2006b) found that only coping responses using social support had a modifying effect on stress. Other studies (not included in the systematic review) showed limited support for the stress-buffering effects of coping (Pakenham, 1999) and a tendency for people with MS, especially men, to be less likely than the general population to adopt coping styles related to problem-solving and seeking social support (McCabe et al., 2004). More research is needed to elucidate the effects of coping on stress.

Finally, the environmental factors escitalopram intake and social support decrease the effect of stress on MS (Brown et al., 2006b; Mitsonis et al., 2010). Escitalopram reduces the stress-dependent relapse rate in MS patients (Mitsonis et al., 2010). Escitalopram regulates serotonin reuptake and blunts autonomic reactivity, resulting in lower emotional reactivity to stressful situations (Fabre and Hamon, 2003). The efficacy of escitalopram in reducing the relapse rate in Mitsonis et al. (2010) clinical trial opens new directions for the study of MS. It could be interesting to study whether disease progression is linked to genetic factors related to serotonin transporters due to that serotoninergic neurotransmission in MS patients is altered in limbic and paralimbic regions as well as in the frontal cortex (Hesse et al., 2014).

Social support can attenuate responses to stress or threatening situations by reducing neural activity in regions that respond to basic survival threats while increasing activity in regions that process safety signals (Eisenberger, 2013). Other studies in MS patients have found that social support may moderate the impact of negative life events and have a positive effect on quality of life (Costa et al., 2012) and that it is a predictor of perceived health status (Krokavcova et al., 2008).

Although our systematic review showed little evidence for early life stress as a moderating factor, a recent case–control study (Spitzer et al., 2012) found that MS patients had more traumatic experiences in childhood and adolescence than healthy people. Moreover, patients with early life stress showed a higher relapse rate than those without. Early life stress can cause neuroendocrine alterations that remain into adulthood, increasing susceptibility to certain diseases (Panzer, 2008) and increasing the prevalence of severe psychological disorders (Alvarez et al., 2011) that predispose to inadequate coping in stressful situations. More prospective studies are needed to better understand the effect of early life stress in MS.

Our study has both strengths and limitations. To our knowledge, this is the first review of studies analyzing the relationship between stress and MS that takes into account how stress was evaluated and moderators of the stress–MS relationship. Although the first article included in our review dates from 1950, we searched three important databases compiling publications from 1900 to the present in an attempt to summarize all the evidence accumulated since Charcot first described MS in 1877. Moreover, we took into account English and Spanish languages, more comprehensive search than other papers. However, relatively few studies met the inclusion criteria. We did not include stress-intervention or animal studies, although these studies could surely contribute important data about the stress–MS relationship. Almost all the studies took at least one moderating factor into consideration; however, the wide variety of factors considered meant that few studies considered the same factors, precluding strong conclusions about the impact of most moderating and mediating factors. Almost all the studies reviewed were done in women, so despite the higher prevalence of MS in women, the results extracted may not be generalizable to the entire population.

Conclusion

The effect of stress on the onset of MS remains unclear. More prospective studies evaluating stress systematically are needed to better understand this effect. In stress progression studies, instruments and designs based on self-evaluation and subjective measures have shown more consistent results than objective ones or instruments based on standard stressors. This means that patients' subjective appraisal of the stress could be an important predictor of MS relapse and onset. Also, the criteria used to evaluate disease progression are important in the evaluation of results. The greatest amplifying or buffering effects on stress come from factors directly related to the amount of stress and autonomic nervous system reactivity. Future studies should clarify the biological mechanisms involved: combining self-reported measures with biofeedback technology and genetic evaluation can improve our knowledge about the relationships between stress and MS. We also strongly recommend including moderating factors in studies on the effects of stress on MS; this approach can provide information that might be useful for treating patients, since some factors such as anxiety and coping styles are potentially modifiable.

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4. Phase Two

Identification of potential psychosocial moderators or mediators of the stress-MS relationship and their association to the disease

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4.1 Manuscript

A case-control study of psychosocial factors and their relationship to impairment and functionality in multiple sclerosis

Title

A case-control study of psychosocial factors and their relationship to impairment and functionality in multiple sclerosis

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Abstract

The stress effect on Multiple Sclerosis remains unclear. Moderating psychosocial factors may be involved. This study compares some of them in people with MS and healthy controls, and their association with disease parameters. Coping style, social support, anxiety, alexithymia and early-life stress were measured, along with impairment and functionality. PwMS scored significantly higher on anxiety, alexithymia, and avoidance and instinctive coping but lower in social support. No differences were found in early-life stress. Impairment was related to avoidance, and functionality to avoidance and anxiety. Psychotherapeutic approaches focused on these psychosocial factors may improve functionality, impairment, and quality of life in pwMS.

Keywords: Multiple Sclerosis, Psychosocial factors, Stress, Functionality, Impairment.

1. Introduction

Multiple Sclerosis (MS) is a neurodegenerative autoimmune disease that affects 2.3 million people around the world. It is more prevalent in women than men 2:1 and is one of the main causes of non-traumatic disability in young adults (Browne et al., 2013). The aetiology involves multiple genes and environmental factors (Lutton, Winston & Rodman, 2004). One of the proposed environmental risk factors for MS onset and exacerbation is stress. Through psychoneuroendocrinologic pathways stress may affect autoimmune diseases (Segerstrom & Miller, 2004). Studies evaluating stress effects on MS have yielded contradictory results. Some studies found an increased risk for MS onset (Grant et al., 1989; Warren, Greenhill & Warren, 1982) or for a relapse (Buljevac et al., 2003; Mitsonis et al., 2008) after stressful events, whereas other studies did not show any relationship (Riise et al., 2011). One reason may be that stress doesn't affect people in a straightforward way and other psychosocial moderating factors need to be considered. According to Lazarus and Folkman's transactional model (1984, 1987) stress is defined as a relationship between the individual and the environment in which an individual responds through behavioural, emotional, and physiological mechanisms. Stress process involves many variables and moderating factors associated with appraisal and coping processes. These factors include environmental and psychological factors, individual differences and coping (Lazarus, 1990). This study aims to study some of these psychosocial factors in pwMS and healthy controls.

Previous research comparing people with and without MS on coping styles suggests that pwMS tend to use less problem-focused coping (trying to solve the problem) and to seek less social support than people without MS (McCabe, McKern & McDonald, 2004). Specially, those patients in an exacerbation phase showed a tendency to favour emotion-focused coping compared to those patients in a remission phase.

Of all the coping styles, seeking social support has been postulated to cause a buffering effect on stress. In pwMS social support decreases the relationship between stress and relapse (Brown et al., 2006) and enhances positive perceptions of physical and mental health (Costa, Sá & Calheiros, 2011; Krokavcova et al., 2008). PwMS tend to use less social support (McCabe et al., 2004), but there are no studies showing a comparison between pwMS and healthy controls on perceived social support.

There are also psychological dispositional factors that affect appraisal and coping including anxiety and alexithymia. High trait anxiety put individuals at risk for

more dramatic threats and loss appraisals, whereas low trait anxiety buffers the experience of stress (Jerusalem, 1990). In pwMS high levels of anxiety have been associated with 2.9 times the rate of relapse (Potagas et al., 2008). Alexithymia is defined as a difficulty in experiencing and expressing emotional responses. There is some evidence that pwMS report higher levels of alexithymia than the general population (Prochnow et al., 2011). Kojima (2012) suggests that alexithymia is related to illness through biological causes and inadequate coping processes, but the link with disease parameters remains unclear.

Finally, coping and appraisal are also affected by early-life traumatic experiences. Early-life stress can have behavioural and physical consequences that may remain into adulthood (Spertus, Yehuda, Wong, Halligan & Seremetis, 2003) promoting inadequate stress appraisal and coping later in life. In a large case-control study Spitzer et al. (2012) observed that pwMS showed significantly higher childhood stress than people without MS, and among patients, those with histories of physical or sexual abuse had higher relapse rates than patients without early-life stress.

There are few studies focused on the psychosocial factors that may moderate the stress-MS relationship. In a recent systematic review (Briones-Buixassa, et al., 2015) we highlight the importance of taking these into account, as some of the psychosocial factors mentioned above are potentially modifiable. According to literature review we hypothesise that pwMS will show more emotion-focused and avoidant coping patterns, lower social support and perception, and higher levels of anxiety, alexithymia and early-life stress than healthy controls. Moreover, we expect that these coping patterns and higher levels of anxiety, alexithymia and early-life stress will be negatively associated with disease parameters including impairment and functionality. For this reason this study aims to (a) compare the proposed psychosocial factors in pwMS and healthy controls and, (b) to analyse their association with disease parameters in the MS group.

2. Methods

2.1 Participants

Forty-one MS patients and 41 healthy participants, matched by age and gender, participated in the study from May 2014 to June 2015. MS patients were recruited from the Consorci Hospitalari de Vic. This study formed part of a larger study where some potential modifiers of disease progression were exclusion criteria. These were: a) under 18 years old, b) pregnant, c) abuse of alcohol or drugs, d) Expanded Disability

Status Scale (EDSS) ≥ 7, e) diagnosis of other neurologic or psychopathological diseases. The healthy control group was obtained through local advertisement. Exclusion criteria were the same adding f) diagnosis of MS and other chronic illnesses. All adult patients had clinically definite relapsing-remitting MS, according to McDonald criteria (Polman et al., 2005).

2.2. Study design and procedure

This is a case-control study nested within the project called *"PsychoMSS Study: Stress and Psychosocial Factors in Multiple Sclerosis"* developed in Osona (Catalonia, Spain). The study design consisted of an interview of one hour duration; conducted by a trained psychologist. Using the same protocol for all the participants, a brief semi-structured interview was conducted and a battery of standardised self-reported questionnaires was administered. Other clinical data were collected through medical records. The study was approved by the local ethics committee, FORES Foundation (23 July 2013, num. 2013841-PR71), and conducted according to the Declaration of Helsinki. All of the participants gave written informed consent.

2.3 Measures

Information about age, gender, marital status, educational level, lifestyle, and family history of diseases were obtained. For the pwMS also year of diagnosis, MS type, EDSS score, treatment, and other diagnosed diseases were obtained from medical record.

Psychosocial factors

Coping processes were assessed using the *Strategic Approach to Coping Scale (SACS)* of Hobfoll, a 52-ítem scale, Spanish version (Pérez, Germán & García, 2012), assessing 7 coping strategies: 1) Assertive action (conflict identification and attempt to solve the problem), 2) Social joining (have "significant others" as collaborators), 3) Seeking social support (seek external resources), 4) Cautious action (leisurely assessment of threat, resources, needs, and aid), 5) Instinctive action (immediate, spontaneous action), 6) Avoidance (avoiding conflictive elements, minimizing emotional impact), 7) Aggressive/Antisocial action (priorizing own needs and immediate resolution). Higher scores mean higher use of the particular coping strategy.

Perceived social support was assessed by *Multidimensional Scale of Perceived Social Support (MSPSS),* a 12-ítem scale, Spanish version (Landeta & Calvete, 2002) assessing 3 sources of social support; family, friends, and relevant persons. Total

score ranged from 12 to 84 points. A higher score means higher levels of perceived social support.

Trait anxiety was assessed by *State-Trait Anxiety Inventory (STAI)* a 20-ítem scale, Spanish version (Spielberger, Cubero, Gorsuch & Lushene, 1982), validated in pwMS by Santagelo et al. (2016). Total score ranged from 0 to 60 points. A higher score means higher level of anxiety. High trait anxiety was considered ≥ 28 in men and ≥ 31 in women (above percentile-75 adjusted for age and gender in standardised Spanish population tables).

Alexithymia was assessed by *Toronto Alexithymia Scale (TAS-20)* a 20-item scale, Spanish version (Martinez-Sanchez, 1996), validated in pwMS by Fernández-Jiménez et al. (2013). It evaluates 3 factors; difficulty identifying feelings, difficulty describing own feelings, and externally oriented thinking. Total score ranged from 20 to 100 points and cut-off scores were ≤ 51 no alexithymia, 52-60 possible alexithymia, ≥ 61 alexithymia.

Early-life stress was assessed by Childhood Trauma Questionnaire-Short Form (CTQ-SF), a 28 item-scale, Spanish version (Hernandez et al., 2012). It evaluates 5 child maltreatment types: emotional, physical and sexual abuse, and physical and emotional neglect. Total score ranged from 0 to 108 points. Higher scores mean higher levels of childhood trauma.

Disease Parameters

Three different measures were used to assess the disease parameters. First, a neurologist rated disease-related impairment by EDSS score (EDSS-tot). EDSS scale (Kurtzke, 1983) ranges from 0 to 10 in 0.5 unit increments that represent higher levels of impairment. A score of 7 and above means daily life support is required. Second, a relative score of EDSS progression was computed by dividing EDSS by years of disease (EDSS-relative). Third, self-reported functionality assessed by the Functional Assessment of MS (FAMS) questionnaire, validated in Spanish pwMS by Chang et al. (2002). FAMS measures 7 subscale symptoms; mobility, symptoms (i.e. pain), emotional state, life satisfaction, mental activity and fatigue, family/social environment, and other preoccupations (i.e. incontinence). The total score range from 0 to 236, higher score means greater functionality.

2.4 Statistical Analysis

The data analyses were conducted using SPSS (version 23.0; SPSS Inc., Chicago, Illinois). To present descriptive data, means and standard deviations were used for continuous variables and absolute frequencies and percentages for

categorical variables. To test the data normality Shapiro-Wilk test was used. To make comparisons between groups Independent T-tests were used for continuous variables and Chi square for categorical variables. To calculate effect size Cohen's d was used for t-test comparisons (Small<0.2, Medium 0.2-0.5, Large>0.8) and Phi coefficient and Cramer's V for Chi square comparisons (Small<0.1, Medium 0.1-0.3, Large>0.3). Two hierarchical regression analyses were conducted in pwMS to determine which of the psychosocial factors were related to disease parameters outcomes after controlling for relevant socio-demographic variables. Significance level was set at 5% ($p \leq .05$).

3. Results

Socio-demographic, lifestyle, and clinical characteristics of the participants are presented in Table 1. No differences were found in socio-demographic data, but groups differed in family history and lifestyle. PwMS showed significantly fewer antecedents in autoimmune diseases (different from MS), but significantly more smoking and drugs consumption (before diagnosis) than controls.

"INSERT TABLE 1 HERE"

Comparisons between pwMS and controls on all the psychosocial factors are presented in Table 2. Coping scores showed that pwMS seek significantly less social support, and use more instinctive action and avoidance coping than controls when facing stressful situations. Moreover, pwMS reported significantly lower perceived social support, mainly explained by the difference in perceived social support from family and relevant persons. Trait anxiety mean scores were significantly higher in pwMS, and 36.7% of pwMS had high trait anxiety, a higher percentage than control group. Regarding Alexithymia, 40% of the pwMS scored higher or equal than cut-off (≥52), whereas only 19.5% of the general population did. Mean scores in alexithymia were also significantly higher in pwMS. This was explained by a significant difference in difficulty identifying feelings, whereas no differences were found for the other alexithymia factors. No significant differences were found in early-life stress but there were a tendency in pwMS to score higher in total score, emotional abuse and neglect.

"INSERT TABLE 2 HERE"

Psychosocial factors and disease parameters

In pwMS all psychosocial factors were correlated at the bivariate level with the disease parameters: EDSS-tot, EDSS-relative and FAMS (Table 3). EDSS-tot showed significant correlations with social joining and avoidance coping styles. FAMS showed significant correlations with social joining, cautious and avoidance coping styles, perceived social support, trait anxiety, alexithymia and early-life stress. EDSS-relative did not show any significant correlations with the psychosocial variables.

"INSERT TABLE 3 HERE"

Two hierarchical regressions were conducted using all the significantly correlated psychosocial factors as predictors and EDSS-tot and FAMS as outcomes adjusting by age, gender and educational level (Table 4). Socio-demographic variables were entered in the first step and psychosocial factors in the second step. The first step of the hierarchical regression showed that socio-demographic variables accounted for 12% ($\triangle F=1.61$, $p=.21$) of the variance in EDSS. Adding psychosocial factors explained a further 23% ($\triangle F=3.569$, $p=.01$). Avoidance was the only significant predictor in the second step (B=0.42, $p=.02$). In the second regression socio-demographic variables accounted for 8% ($\triangle F=0.686$, $p=.57$) of the variance in FAMS. Adding psychosocial factors explained 71% of the variance ($\triangle F=6.66$, $p<.001$). Avoidance (B=-0.30, $p=.05$) and trait anxiety (B=-0.39, $p=.04$) were the only significant predictors in the second step.

"INSERT TABLE 4 HERE"

4. Discussion

There are few studies addressing the study of psychosocial factors related to stress and MS. Our results showed that pwMS tend to use more passive (avoidance) and instinctive approaches to dealing with stress or problems, seek less social support and perceived less social support when compared to healthy controls. PwMS also show higher levels of anxiety and alexithymia but not greater levels of early-life stress. The disease parameters of impairment and functionality were most strongly related to anxiety and avoidance coping.

Previous literature supports our findings that avoidance is a common coping style in pwMS facing stressful situations (Goretti et al., 2009; Hajhashemi, Vaziripour, Baratian, Kajbaf & Etemadifar, 2010), as well as less use of social support and problem-focused strategies (McCabe et al., 2004). However, this is the first study showing that pwMS not only use less social support but also that the perception of support from social network is reduced. Regarding anxiety and alexithymia, higher scores were observed in pwMS than healthy controls, in line with previous studies (Hoang, Laursen, Stenager & Stenager, 2015; Prochnow et al., 2011).

This study showed different patterns of coping and personality between pwMS and healthy controls. Although we do not know if these patterns existed before the diagnosis or are a consequence of either biological or psychological aspects of MS, some hypothesis can be made based on theoretical assumptions.

Following the transactional model (Lazarus & Folkman, 1984, 1987) where stress is considered as an outcome of the interaction individual-environment, we could hypothesise that suffering a chronic illness like MS might modify the coping strategies through altering the cognitive appraisal of stressful situations. Some disease characteristics like the unpredictability or the lack of understanding from social networks could promote these alterations. The coping styles observed (avoidance, instinctive action and less social support seeking) could be related to the perception of less social support but also with the higher levels of alexithymia, especially because pwMS have more difficulties identifying their own feelings. Previous studies in pwMS have shown a deficit in the recognition of emotional facial expressions and instrospection (Prochnow et al., 2011) and an impaired social cognition (Pöttgen, Dziobek, Reh, Heesen & Gold, 2013), which fits with the deficits observed in alexithymia. The lack of ability to identify one's own feelings as well as to recognize emotions from facial expressions are crucial for social functioning and could lead pwMS to misunderstand or be unaware of important social clues, deteriorating the social network.

According to our results, early-life stress seems not to have an important role in MS. The tentative evidence for a higher prevalence of early-life stress in pwMS (Spitzer et al., 2012) suggests that more important than occurrence it is how people deal with stress. The "stress-resilience" hypothesis, defined as an individual's ability to properly adapt to stress and adversity, identified three categories that protect against stress: child dispositional attributes, family cohesion, and external support (Garmezy, 1985). These resilient factors should be considered in future studies about early-life stress. Interestingly, in a recent qualitative study about resilient factors in adjustment to neurological chronic illnesses, McCabe and O'Connor (2012) found that people with

high levels of adjustment showed better social support from family and friends and, this social support was used mainly to assist experiencing enjoyment more than illness-focused help.

Regarding the association between the psychosocial variables and the disease parameters the regression analyses showed that anxiety and avoidance must be the most important ones. In previous studies avoidance behaviour was linked to mental and physical symptoms (Ukueberuwa & Arnett, 2014) and to a poorer adjustment to MS (Pakenham, Stewart & Rogers, 1997) and anxiety was linked to a greater impairment (Jones et al. 2014). Although avoidance behaviour and anxiety are related factors, in the present study they seem to be differently associated to disease parameters. Avoidance predicted both a neurologist rated impairment and a self-reported functionality, whereas anxiety was only related to self-reported functionality. Higher levels of impairment and less functionality may lead to pwMS to use more avoidant strategies or to feel more anxiety when facing stressful situations, worsening the experience to deal with stressors. This deteriorating cycle may, in turn, amplify the stress response dysregulating the neuroendocrine system and worsening the disease progression. There is some modest evidence that coping may be related to disease progression. Mohr, Goodkin, Nelson, Cox & Weiner (2002) measured disease progression through new brain lesions in Magnetic Resonance Imaging scan. They found that emotional preoccupation (focused on emotional consequences) was marginally associated with an increased relationship between stress and disease, whereas use of distraction and instrumental coping was linked to a decreased relationship.

These results have important clinical implications since almost all the psychosocial factors considered are potentially modifiable through psychotherapeutic approaches. A recent randomised controlled trial (Moss-Morris et al., 2013) tested a Cognitive Behavioural Therapy (CBT) for adjustment to MS. In this therapy some coping factors were addressed. Interestingly CBT was more effective for pwMS with low perceived social support and/or clinically defined levels of distress.

In the present study some limitations need to be addressed. The first is the sample size. Osona is a small region and few people met the inclusion criteria. The second is that only people with relapse-remitting type participated and it cannot be generalised to all MS types. The third is the low level of EDSS. Patients were recruited from different spread towns, but difficulties in displacement could have left out the most handicapped people. Finally, we did not measure stress itself. It would be interesting to study the moderating effect of these psychosocial factors in the stress-MS relationship.

Future studies should include large cohort studies, evaluating psychosocial factors in healthy subjects to see their link in the development of chronic illnesses. Moreover, more intervention studies testing psychotherapeutic approaches should be conducted to elucidate its potential benefits on disease progression. Finally, the moderating effect of the resilience factor on early-life stress should be considered to understand this complex process.

In conclusion, there are differences in the psychosocial factors related to appraisal and coping between pwMS and healthy controls and some of them are linked to disease parameters. Psychotherapeutic approaches could help to better adjust to the disease improving functionality, impairment, and quality of life in pwMS.

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Table 1. Socio-demographic, Lifestyle, and Clinical Characteristics of the Participants

	PwMS (n=41)	Controls (n=41)	t-test/ χ^2	*p* value	*d*/*Phi*
Female n (%)	29 (70.7%)	29 (70.7%)	-	-	
Age M (SD)	48.48 (11.85)	48.99 (12.02)	*t*=0.194	0.85	0.04
Marital status n (%)			χ^2=3.973	0.26	0.22
Single	7 (17.1%)	8 (19.5%)			
Married	32 (78%)	26 (63.4%)			
Separated/Divorced	2 (4.9%)	5 (12.2%)			
Widow-er	0 (0%)	2 (4.9%)			
Educational level n (%)			χ^2=9.342	0.053	0.34
Unschooled	0 (0%)	1 (2.4%)			
Elementary	11 (26.8%)	6 (14.6%)			
Secondary	6 (14.6%)	6 (14.6%)			
FP or equivalent	10 (24.4%)	3 (7.3%)			
University	14 (34.1%)	25 (61%)			
Family history (diseases) n (%)					
Multiple Sclerosis	5 (12.2%)	2 (4.9%)	χ^2=1.406	0.24	0.13
Autoimmune	7 (17.1%)	15 (36.6%)	χ^2=3.976	0.05*	0.22
Cancer	25 (61%)	29 (70.7%)	χ^2=0.868	0.35	0.10
Neurodegenerative	16 (39%)	12 (29.3%)	χ^2=0.868	0.35	0.10
Psychopathologic	9 (22%)	4 (9.8%)	χ^2=2.285	0.13	0.17
Lifestyle (before diagnosis) n (%)					
Tobacco consumption (TC)	22 (53.7%)	8 (19.5%)	χ^2=10.303	0.001**	0.36
Alcohol consumption	3 (7.3%)	3 (7.3%)	-	-	
Drugs consumption	4 (9.8%)	0 (0%)	χ^2=4.205	0.04*	0.23
Work activity	40 (97.6%)	37 (90.2%)	χ^2=1.917	0.17	0.12
Physical activity (PA)	28 (68.3%)	35 (85.4%)	χ^2=3.357	0.07	0.20
MS age diagnosis M (SD; range)	35.93 (10.71; 12-62)	-			
MS duration y M (SD; range)	13.46 (7.64; 3-29)	-			
EDSS M (SD; range)	1.96 (1.69; 0-6)	-			

Note. MS = multiple sclerosis; EDSS = Expanded Disability Status Scale; y = years. Significance (two-tailed) = *p<.05, **p<.01

Table 2. Psychosocial Variables Scores Comparing PwMS and Control Participants

	PwMS	Controls			
	M (SD)	**M (SD)**	**t-test/Chi**	***p* value**	**d/Phi**
Coping (SACS)	**n=39**	**n=41**			
Assertive	24.10 (6.12)	25.34 (5.16)	*t*=0.981	0.33	0.22
Social joining	13.10 (3.63)	12.29 (3.66)	*t*=-0.993	0.32	0.22
Seek social support	21.21 (6.93)	25.68 (5.06)	*t*=3.313	0.001**	0.74
Cautious	10.62 (3.29)	10.71 (3.54)	*t*=0.120	0.91	0.03
Instinctive	12.31 (3.44)	10.05 (3.49)	*t*=-2.915	0.005**	0.65
Avoidance	15.10 (7.99)	10.22 (6.28)	*t*=-3.048	0.003**	0.68
Aggressive/Antisocial	8.67 (6.34)	7.05 (5.77)	*t*=-1.195	0.24	0.27
Social Support (MSPSS)	**n=32**	**n=41**			
Family	23.09 (6.24)	26.02 (2.77)	*t*=2.472	0.02*	0.58
Friends	21.72 (5.81)	23.71 (5.14)	*t*=1.549	0.13	0.36
Relevant persons	24.22 (5.53)	26.29 (2.40)	*t*=1.980	0.05*	0.46
Total Score	69.03 (15.74)	76.02 (7.70)	*t*=2.307	0.03*	0.54
Anxiety (STAI-T)	**n=30**	**n=41**			
Anxiety Trait	25.00 (11.79)	17.17 (8.60)	*t*=-3.085	0.003**	0.73
High Anxiety Trait P75 n(%)	11 (36.7%)	3 (7.3%)	χ^2=9.427	0.002**	0.36
Alexithymia (TAS-20)	**n=40**	**n=41**			
Difficulty identifying feelings	17.80 (8.24)	13.88 (6.18)	*t*=-2.418	0.02*	0.54
Difficulty describing feelings	13.05 (4.88)	11.49 (3.26)	*t*=-1.690	0.10	0.38
Externally oriented thinking	20.48 (5.13)	18.49 (4.23)	*t*=-1.904	0.06	0.43
Total Score	51.33 (14.95)	43.85 (10.87)	*t*=-2.577	0.01*	0.58
Score ≥ 52 n(%)	16 (40%)	8 (19.5%)	χ^2=4.076	0.04*	0.22
Early-Life Stress (CTQ-SF)	**n=40**	**n=41**			
Emotional abuse	3.25 (4.53)	1.80 (2.56)	*t*=-1.762	0.08	0.39
Physical abuse	0.98 (3.04)	0.51 (1.36)	*t*=-0.889	0.38	0.20
Sexual abuse	1.13 (3.79)	0.78 (2.34)	*t*=-0.494	0.62	0.11
Emotional neglect	5.00 (4.45)	3.44 (3.42)	*t*=-1.773	0.08	0.39
Physical neglect	1.63 (2.19)	0.98 (1.89)	*t*=-1.429	0.16	0.32
Total Score	12.90 (14.69)	8.10 (8.47)	*t*=-1.808	0.07	0.40

Note. PwMS = people with multiple sclerosis; SACS = Strategic Approach to Coping Scale; MSPSS = Multidimensional Scale of Perceived Social Support; STAI-T = State-Trait Anxiety Inventory; TAS-20 = Toronto Alexithymia Scale; CTQ-SF = Childhood Trauma Questionnaire; P75 = percentile 75. Significance (two-tailed) = *p<.05, **p<.01

Table 3. Psychosocial Correlates of EDSS-tot, EDSS-relative, and FAMS

	EDSS-tot r (95% CI)	EDSS-relative r (95% CI)	FAMS r (95% CI)
Coping (SACS)			
Assertive	0.04 (-0.28 to 0.35)	0.10 (-0.23 to 0.40)	0.16 (-0.17 to 0.45)
Social joining	0.41** (0.11 to 0.65)	0.17 (-0.16 to 0.46)	-0.41** (-0.65 to -0.11)
Seek social support	-0.12 (-0.42 to 0.21)	-0.16 (-0.45 to 0.17)	-0.002 (-0.32 to 0.32)
Cautious	0.11 (-0.22 to 0.42)	0.24 (-0.09 to 0.52)	-0.48** (-0.69 to -0.19)
Instinctive	-0.13 (-0.43 to 0.20)	-0.10 (-0.41 to 0.23)	0.11 (-0.21 to 0.42)
Avoidance	0.48** (0.18 to 0.69)	0.27 (-0.05 to 0.54)	-0.56** (-0.74 to -0.29)
Aggressive/Antisocial	0.07 (-0.25 to 0.38)	0.14 (-0.19 to 0.44)	-0.26 (-0.54 to 0.07)
Social Support (MSPSS)	0.09 (-0.26 to 0.42)	-0.18 (-0.50 to 0.18)	0.70** (0.46 to 0.84)
Trait Anxiety (STAI-T)	0.18 (-0.19 to 0.51)	0.16 (-0.21 to 0.49)	-0.77** (-0.89 to -0.57)
Alexithymia (TAS-20)	0.23 (-0.10 to 0.51)	0.21 (-0.12 to 0.49)	-0.63** (-0.79 to -0.39)
Early-Life Stress (CTQ-SF)	-0.11 (-0.41 to 0.22)	-0.06 (-0.37 to 0.26)	-0.49** (-0.70 to -0.20)

Note: n range 30-40. SACS = Strategic Approach to Coping Scale; MSPSS = Multidimensional Scale of Perceived Social Support; STAI-T = State-Trait Anxiety Inventory; TAS-20 = Toronto Alexithymia Scale; CTQ-SF = Childhood Trauma Questionnaire. Significance (two-tailed) = *p<.05, **p<.01.

Table 4. Hierarchical Regressions: Psychosocial Predictors of EDSS and FAMS

	EDSS-tot			FAMS		
	Beta	***p* value**	**△R^2**	**Beta**	***p* value**	**△R^2**
Step 1: Socio-demographic variables			**0.12 (F=1.61, *p*=0.21)**			**0.08 (F=0.686, *p*=0.57)**
			95% CI			**95% CI**
Age	0.37	0.04*	0.07 to 0.61	0.13	0.56	-0.19 to 0.42
Gender	-0.10	0.55	-0.40 to 0.21	-0.15	0.47	-0.44 to 0.16
Educational level	0.03	0.84	-0.28 to 0.34	0.25	0.22	-0.07 to 0.51
Step 2: Socio-demographic and Psychosocial factors			**0.23 (F=3.569, *p*=0.01)**			**0.71 (F=6.66, *p*<0.001)**
			95% CI			**95% CI**
Age	0.26	0.11	-0.05 to 0.52	0.11	0.48	-0.21 to 0.40
Gender	-0.18	0.25	-0.46 to 0.14	0.03	0.80	-0.28 to 0.34
Educational level	0.09	0.53	-0.22 to 0.39	0.05	0.73	-0.26 to 0.35
Coping process (SACS)						
Social joining	0.17	0.31	-0.16 to 0.46	-0.09	0.61	-0.40 to 0.24
Cautious	-	-		-0.22	0.14	-0.51 to 0.11
Avoidance	0.42	0.02*	0.11 to 0.65	-0.30	0.05*	-0.57 to 0.02
Social Support (MSPSS)	-	-		0.30	0.15	-0.05 to 0.59
Trait Anxiety (STAI-T)	-	-		-0.39	0.04*	-0.66 to -0.04
Alexithymia (TAS-20)	-	-		0.14	0.57	-0.19 to 0.44
Early-Life Stress (CTQ-SF)	-	-		-0.08	0.65	-0.39 to 0.25

Note: SACS = Strategic Approach to Coping Scale; MSPSS = Multidimensional Scale of Perceived Social Support; STAI-T = State-Trait Anxiety Inventory; TAS-20 = Toronto Alexithymia Scale; CTQ-SF = Childhood Trauma Questionnaire. Significance (two-tailed) = *p<.05, **p<.01

5. Phase Three

The effect of stress and the role of different psychosocial factors on disease progression

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5.1 Manuscript

The stress effect and the role of coping in relapse occurrence, functionality and impairment in multiple sclerosis: a prospective study

Title

The stress effect and the role of coping in relapse occurrence, functionality and impairment in multiple sclerosis: a prospective study

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Abstract

Objectives: Studies assessing the stress effect on Multiple Sclerosis (MS) yielded disparate results. The current study investigated how stress and MS may be related over time considering different stress and disease progression measures, and the potential moderator role of coping.

Design: A one year follow-up longitudinal observational study.

Methods: Twenty-six MS patients were interviewed at baseline and trimonthly during one year. The following data was collected: coping style through the Strategic Approach to Coping Scale of Hobfoll; weekly, self-reported diaries of stressful events, coping and discomfort; monthly, the Perceived Stress Scale (PSS), and trimonthly, the self-reported Functionality Assessment of MS (FAMS) questionnaire. Neurologist rated impairment (EDSS) at baseline and at the end, and relapse occurrence were also measured. Hierarchical mixed models were conducted to test the stress effect on MS outcome and viceversa (bidirectional hypothesis).

Results:. Perceived stress and functionality were negatively related in both directions. Moreover, functionality was related to a greater number of stressful events. Active coping showed a moderator role: its use increased the functionality only witht high levels of perceived stress but not with low levels. Comparing the risk periods before and after the relapses no differences were found in perceived stress, stressful events or discomfort but patients who had relapses showed more passive coping.

Conclusions: The bidirectional hypothesis was confirmed only with self-reported measures of stress and functionality. Psychotherapeutic interventions at early stages of MS may help pwMS to deal with stress and MS before getting into a possible deteriorating cycle.

Keywords: Multiple Sclerosis; Stress; Coping; Functionality; Impairment; Relapse

1. Introduction

Multiple Sclerosis (MS) is an autoimmune neurological disease that affects 2.3 million people around the world. The global median prevalence is increasing from 30 in 2008 to 33 per 100.000 in 2013, being more prevalent in women than men with a ratio of 2:1 (Browne et al., 2014). There are two main types of MS: relapsing-remitting type and progressive type, but the 85% of the people with Multiple Sclerosis (pwMS) starts with the first one (Reyes, Olascoaga & Arias, 2010). The relapsing-remitting type is characterized by inflammatory episodes which cause neurological deficits, called relapses, followed by a partial or total recovery. The most common deficits are motor impairment, sensory disturbances and optic nerve disorders. MS also causes other symptoms like fatigue, pain, cognitive deficits, mood changes or bladder and bowel disorders among others (Reyes et al., 2010).

Stress has been proposed to have an effect on the course of MS (Goodin et al., 1999). During a stressful period the homeostasis is threatened or perceived to be so and adaptive responses are needed to re-establish it (Chrousos, 2009). These responses can lead to immune deregulation altering or amplifying cytokine production through the stress-triggered neuroendocrine hormones, which may affect autoimmune diseases like MS (Stojanovich & Marisavljevich, 2008). Studies assessing stress as a trigger factor for disease progression in MS yielded disparate results, but most showed some kind of association (Mohr, Hart, Julian, Cox & Pelletier, 2004). As Artemiadis, Anagnostouli and Alexopoulos (2011) pointed out the heterogeneity in disease progression' and stress assessments could explain these disparate results.

Disease progression can be measured at different levels: first, at a biological level, inflammation and new lesions in the brain can be measured through Magnetic Resonance Imaging scan (MRI); second, at a clinical level, relapses or different symptoms can be neurologist rated or self-reported through a questionnaire; and finally, changes in impairment level can be measured by the Expanded Disability Status Scale (EDSS; Mohr & Pelletier, 2006). Most studies assessed relapse occurrence and symptoms. Some studies found an increased risk for relapse after stressful events (Buljevac et al., 2003; Mitsonis et al., 2008; Potagas et al., 2008) whereas other studies did not (Gasperini et al., 1995; Oveisgharan, Hosseini, Arbabi & Nafisi, 2014). Few studies used biological criteria. Mohr et al. (2000) recorded new brain lesions through MRI, finding a weak but significant association with stressful events.

Stress assessments were also heterogeneous across studies. Some studies used self-reported diaries (Buljevac et al., 2003; Potagas et al., 2008), whereas other studies used questionnaires and scales (Brown et al. 2006; Ackerman et al. 2002; 2003), and semi-structured interviews (Gasperini et al., 1995). A few studies used physiological stress

measures like cardiovascular reactivity but only in “artificial” stressful situations like the Stroop task (Ackerman et al., 2003).

To our knowledge, none of these studies analysed the stress effects considering different measures of stress and disease progression at the same time. Moreover, as it was mentioned in a previous study (Briones-Buixassa et al., 2015) stress response depends in part on potential psychosocial moderators related to cognitive appraisal and coping processes.

The aim of the present study was to analyse how stress and disease progression relate over time in a sample of pwMS and to explore the role of coping on this relationship. The specific aims were (i) to take several and different measures of stress, (ii) to assess disease progression at different levels, (iii) to test the stress-MS bidirectional hypothesis in which stress affects the disease and vice versa, and (iv) to analyse the interaction of active-passive coping in the stress-MS relationship. This knowledge may help us to better understand the relationship between stress and MS and the role of coping on this relationship. This, in turn, may help to develop more accurate psychotherapeutic interventions to improve the course and symptoms of MS.

2. Methods

2.1 Participants

Twenty-six MS patients participated in the study from May 2014 to September 2015. Participants were recruited from the Neurology Department of the Consorci Hospitalari de Vic. From 121 pwMS, 62 met the inclusion criteria, from those 8 were not contactable, 22 refused to participate, and 34 agreed to participate but 8 changed their mind. During the follow-up, 1 patient became pregnant, 2 moved to another place to live, and 2 left the study for health reasons but their data was used in the period covered. A total of 21 patients completed the one year follow-up. All adult patients had clinically definite relapsing-remitting MS (McDonald criteria: Polman et al., 2005). Potential modifiers of disease progression or cognitive function were excluded. Exclusion criteria were: a) under 18 years old, b) pregnant, c) abuse of alcohol or drugs, d) EDSS ≥7, e) diagnosis of other neurologic or psychopathological diseases. Statistical power was estimated close to 60% assuming a correlation higher than 0.5, an alpha risk of 5% and a sample loss of 25%.

2.2 Study design

It is an observational, one year follow-up study nested within the project *“PsychoMSS Study: Stress and Psychosocial Factors in Multiple Sclerosis”*. A total of 5 interviews were conducted by a trained psychologist in the Consorci Hospitalari de Vic, one at baseline and

every three months at 3, 6, 9 and 12 months. In the first interview the psychologist ask for socio-demographic and lifestyle data, administered standardised questionnaires, and gave the instructions to complete the follow-up. During the follow-up patients carried out a self-reported diary and monthly questionnaire about stress. In the following interviews the diaries were collected and new questionnaires were administered to measure changes in functionality.

The study was approved by the local ethics committee, FORES Foundation (23 July 2013, register number 2013841-PR71), and conducted according to the Declaration of Helsinki (World Medical Association, 2009). All of the participants gave written informed consent.

2.3 Measures

Socio-demographic, lifestyle, and medical record data

Information about age, gender, marital status, educational level, lifestyle, and family history of diseases was obtained through the interview. Year of diagnosis, type of MS, EDDS score, MS treatment, and other diagnosed diseases were obtained through medical record.

Stress and coping

Stress was assessed through two measures: a self-reported diary and the Perceived Stress Scale (PSS) questionnaire.

The self-reported diary was completed weekly during the 52 weeks of follow-up. Every person completed a register with 1) if they had, the stressful events occurred during the week, 2) the coping strategy used to deal with each stressful event, and 3) the discomfort level triggered by each stressful event, scored from 0 (no discomfort) to 10 (maximum discomfort). Coping strategies were categorised in active/passive according to the axis of the Strategic Approach to Coping Scale of Hobfoll (SACS; Pedrero, Santed & Pérez, 2011).

The PSS, Spanish version (Remor, 2006) was completed every 4 weeks during the 52 weeks of follow-up, a total of 13 times. The PSS measures the stress perceived in the last month but, to facilitate its completion we considered “a month” every period of 4 weeks. The score ranged from 0 to 56, higher score means higher perceived stress.

Coping strategies were assessed through two measures: the self-reported diary (as mentioned above) and the SACS questionnaire, Spanish version (Pedrero et al., 2011). The self-reported diary provided the strategy used with every stressful event at every point in time. The SACS questionnaire showed the main tendency when using coping strategies. SACS assess 7 strategies: assertiveness, social joining, seeking social support, cautious

action, instinctive action, avoidance, and aggressive/antisocial action. Higher scores mean higher use of a particular coping strategy.

Disease progression

To assess disease progression three measures were obtained: impairment score through EDSS, relapse occurrence, and functionality through the Functional Assessment of MS (FAMS) questionnaire.

EDSS score was rated at the beginning and at the end of the follow-up by a neurologist. EDSS is the most widely used scale to measure impairment in MS (Kurtzke, 1983). It ranges from 0 (no impairment) to 10 (death from MS complications). A score of 7 and above means daily life support is required.

Relapse occurrence was evaluated by a neurologist according to these clinical criteria: worsening of existing symptoms or appearance of new ones lasting more than 24 hours after at least 30 days of improvement or stability not associated with fever.

FAMS questionnaire was administered at baseline and at every trimonthly interview, a total of 5 times (Conway et al., 1998). FAMS measures 7 subscales of different symptoms: mobility, symptoms (i.e.: pain), emotional state, life satisfaction, mental activity and fatigue, family and social environment, and other preoccupations (i.e. incontinence). The score ranges from 0 to 236, higher score mean higher functionality and fewer symptoms.

2.4 Statistical analysis

The data analyses were conducted using SPSS (version 23.0; SPSS Inc., Chicago, Illinois). To present descriptive data, means and standard deviations were used for continuous variables and absolute frequencies and percentages for categorical variables. To test the data normality Shapiro-Wilk test was used. To make comparisons Independent T-tests were used for continuous variables and Chi square for categorical variables. To calculate effect size Cohen's d was used for t-test comparisons (Small 0.2, Medium 0.5, Large 0.8) and Phi coefficient and Cramer's V for Chi square comparisons (Small 0.1, Medium 0.1-0.3, Large 0.3). Bivariate correlations were calculated between the stress measures and disease progression assessments. Data were transformed in long format and hierarchical mixed regression models were conducted to test the bidirectional hypothesis after controlling for relevant socio-demographic variables. Coping style categorised as active or passive, was entered into the models to see the main and the interaction effect. Significance level was set at 5% ($p \leq .05$).

3. Results

Socio-demographic and clinical data of the participants are presented in Table 1.

"INSERT TABLE 1 HERE"

Participants were mainly female (73.1%), married (84.6%) and with higher educational levels (69.3%). The summary of descriptive statistics for all the stress assessments and disease progression measures at different time points are presented in Table 2.

"INSERT TABLE 2 HERE"

3.1 Relapses

Only 7 people had relapses during the follow-up. In line with Mohr and Pelletier (2006) a risk period for stress was considered 4 weeks before the relapse. This risk period was then compared with a period of 4 weeks after the relapse. No significant differences were found in the perceived stress [x=36.77 (9.54) vs. x=36.63 (8.52); t(4)=.033; *p*=.98; *d*=.015], in the number of stressful situations [x=2.63 (1.73) vs. x=2.20 (2.05); t(4)=2.231; *p*=.09; *d*=.23] or in the discomfort level [x=5.07 (3.88) vs. x=4.68 (4.64); t(4)=.763; *p*=.488; *d*=.09] before and after the relapse period.

Classifying people according to the occurrence of a relapse in the follow-up (people with relapse vs. people without relapse) and considering coping measures no significant differences were found in any category of SACS questionnaire (all *p*s>.05). However, regarding the self-reported diaries it was observed that people who had one or more relapses during the follow-up used more passive coping strategies than people who hadn't had any relapse (85.7% vs. 36.89%; chi=4.887; *p*=.037; *r*=.43).

3.2 Impairment and functionality

Bivariate correlations were conducted between the hypothesized predictors and MS outcomes. Perceived stress and stressful events scores were correlated with the temporary equivalent assessments of EDSS and FAMS (Table 3). EDSS did not show any significant correlation. FAMS was inversely correlated with stress measures, indicating that higher stress scores were related to lower functionality and higher symptomatology. FAMS showed low negative correlations with stressful events (-.30 to -.50) and moderate (-50 to-.70) and high (-.70 to -.90) negative correlations with all the PSS scores (correlations criteria in Mukaka, 2012).

"INSERT TABLE 3 HERE"

Four hierarchical mixed models were estimated to test the bidirectional hypothesis (Table 4). Two were conducted using PSS and stressful events as predictors and FAMS as the outcome, and the other two, using FAMS as the predictor and PSS and stressful events as outcomes. All the models were conducted following the same steps. First, age and gender were entered at step 1. Second, the predictor: PSS, stressful events or FAMS was entered at step 2. Third, the coping style categorised as passive or active was entered at step 3. Finally, the interaction between the predictor and coping was entered at step 4.

The first model took PSS as predictor and FAMS as outcome. This model showed an inverse relationship between PSS and FAMS. An increase in the self-reported PSS score was related with a decrease in the FAMS score. The coping style (passive/active) did not show any significant relationship with FAMS but the interaction between PSS and coping was significant. With low levels of stress active coping was related with a decreased functionality, but with high levels of stress active coping was related to an increased functionality.

The second model took FAMS as predictor and PSS as outcome. This model showed also an inverse relationship between FAMS and PSS. An increase in the FAMS score was related to a decrease in the PSS score. Coping and its interaction with FAMS was not significantly related.

The third model took stressful events as predictor and FAMS as outcome. This model showed no significant relationships.

The fourth model took FAMS as predictor and stressful events as outcome. This model showed an inverse relationship between FAMS and stressful events. An increase in the FAMS score was related to a decrease in the stressful events number. Coping and its interaction with FAMS was not significantly related.

“INSERT TABLE 4 HERE”

4. Discussion

This is the first prospective study where different measures of stress and disease progression were analysed together to test the bidirectional relationship between stress and MS considering also the coping process. The bidirectional hypothesis was confirmed only with self-reported measures of perceived stress and functionality. Neurologist rated impairment did not show any relationship with stress. PwMS who had relapses during the one year follow-up had a tendency to use more passive strategies compared to those without. However, coping style measured through SACS questionnaire did not differ among people with or without relapses. Active coping showed an interaction effect between stress

and functionality outcome. Those with high perceived stress who used active coping had better self-reported functionality than those with high stress and lower on active coping.

Previous studies showed negative associations between stress and disease progression (Buljevac et al., 2003; Mitsonis et al., 2008) and a meta-analysis (Mohr et al. 2004) showed that stress was associated with exacerbation with an effect size of d=0.53 (95% CI 0.40 to 0.65), p<0.0001. Few studies tested the bidirectional hypothesis i.e. it maybe that exacerbation results in greater stress rather than the other way round. Schwartz et al. (1999) found that there was almost twice the risk of stress following physical deterioration than the risk of functional deterioration given a particular level of self-reported stress. Otherwise, Brown et al. (2006) found that the strength of the stress-relapse relationship was similar to the strength of the relapse-stress relationship, for both acute (<6 months) and chronic stressors (>6 months).

In the present study, the bidirectional hypothesis was tested with different stress scores; perceived stress and stressful events, and different disease progression measures; neurologist rated impairment (EDSS) and self-reported functionality. Only perceived stress and self-reported functionality supported the bidirectional hypothesis. A worsening in the functionality increased both the perceived stress and the occurrence of more stressful events. According to this, self-reported measures of perceived stress would be more appropriate than stressful events to predict self-reported functionality and disabling symptoms in MS. It may be due to the fact that perceived stress and self-reported functionality may share much of the variance i.e. people who perceive or self-report more stress may also report more symptoms and functional problems related to stress, even if they think that are related to MS. Moreover, more symptoms and functional problems may, in turn, increase the perception of stress. Regarding relapses, only 7 individuals had 1 or more relapses in the follow-up, and this fact, along with the small sample size, did not allow us to do proper analysis with enough statistical power. Nevertheless, in many other studies stressful events were linked to an increase in the relapse risk (Buljevac et al., 2003; Potagas et al., 2008; Mitsonis et al., 2010).

These results pointed to the difference in the use of self-reported measures of disease change or progression versus standard objective measures. EDSS gives a general perception of the disease stage and it only changes after a substantial deterioration. In turn, a relapse sometimes occurs once in a while. However, other symptoms like fatigue, cognitive deficits or bladder dysfunction are frequent and often more disabling in the daily life of pwMS. For this reason, self-reported measures of symptoms and functionality may be more useful to determine the immediate effect of stress and other related psychosocial factors in the daily life of pwMS.

Coping has been proposed as a moderator of the relationship between stress and MS inflammation (Mohr, Goodkin, Nelson, Cox & Weiner, 2002; Mohr & Pelletier, 2006). Several studies have shown positive effects for adaptive or problem-focused coping in pwMS. Adaptive coping prevented the occurrence of different types of stressors, reduced the stressful experience of the unavoidable stressors and influenced cognitions that may be related to MS inflammation (Mohr, Goodkin, Gatto & Van Der Wende, 1997). Problem-focused coping, in turn, was linked to a better adjustment to MS (Pakenham, Stewart & Rogers, 1997). In the present study, active coping showed an interaction effect between stress and functionality outcome. In a situation of high perceived stress those who used active coping had better self-reported functionality. However, active coping did not show a positive effect with low levels of stress. A possible explanation may be that although active coping empowers people, increase self-esteem, and gives a feeling of control, especially when it succeeds solving the problem, it requires an effort that it is likely to result in more stress perception at short-term. On the other hand, avoidance, denial or escape from the stressful situation reduces the experience to cope at short term, but it decreases also the self-confidence in own resources to deal with the stressful situation (Kobasa, Maddi, Donner, Merrick & White, 1984). For this reason, in situations of low levels of stress some passive or emotion-focused types of coping like avoidance or escape may be more useful; even if they have negative consequences at long-term.

In line with our results, Warren, Warren and Cockerill (1991) found that people in a relapse phase used more passive strategies than people in a remission phase. However, we found that pwMS with relapses showed more passive coping not only in a relapse phase but also during the whole follow-up period. Suffering a relapse is an invalidating experience that may generate feelings of impotence and inability to deal actively with stressful events and, people with a higher relapse rate could have adopted this pattern over time. On the other hand, we can hypothesise that passive coping could be a stable trait that promotes higher levels of perceived stress and ultimately predisposes to a higher relapse rate. However, the SACS questionnaire did not show any differences between people with and without relapses in their general coping pattern, so the first explanation seems to be more plausible. For this reason it may be especially important to develop psychotherapy interventions in the early stages of MS, to provide the patients different strategies to deal with MS before getting into a possible deteriorating cycle.

In general, stress-managing therapies, especially those based on Cognitive Behavioural Therapy (CBT) and relaxation techniques, have shown improvements on disease biological outcomes (Mohr et al., 2012), mental health symptoms (Artemiadis et al., 2012; Foley, Bedell, LaRocca, Scheinberg & Reznikoff, 1987), and better quality of life with lower stress levels (Hughes, Robinson-Whelen, Taylor & Hall, 2006). Moreover, a specific

CBT trial focused on the management of symptoms at early stages of MS promoted a better adjustment to the disease, especially in those patients with clinically defined levels of distress (Moss-Morris et al., 2013). However, due to the unpredictable course of MS another type of interventions like Mindfulness or Acceptance and Commitment Therapy may be useful to deal with MS, especially in relapsing phases or progressive forms of the disease. These new therapies have shown improvements in anxiety, depression or stress symptoms in pwMS (Muñoz et al., 2016), but further interventional studies are needed to elucidate their potential benefit on disease progression parameters.

Limitations

The small sample size limits the generalization of the results. Osona is a small region and few pwMS met the inclusion criteria. Although 1 year of follow-up was sufficient to see the association between stress and functionality; other parameters like EDSS or relapses would need a greater period of time to observe reliable results. To complete our study biological measures could have been measured. However, the lack of funding prevented us to carry out these complex assessments.

Conclusions and future directions

In summary, the results supported the bidirectional hypothesis (stress affects disease progression, and vice versa) but only with self-reported measures of perceived stress and functionality. Perceived stress seems to be better than stressful events testing the immediate stress effect on self-reported disease outcome, but not in other neurologist rated disease parameters. Self-reported functionality is a good predictor of perceived stress and stressful events. Active coping appear to be useful to increase functionality with high levels of stress, whereas in low levels may not be appropriate or even counterproductive at short-term. Future studies should test different types of psychotherapeutic interventions in the early stages of MS to see their beneficial on disease progression at long-term.

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Table 1. Sociodemographic and Clinical Data of PwMS

	PwMS (n=26)
Female n (%)	19 (73.1%)
Age y M (SD; range)	47.10 (11.89; 25-67)
MS age diagnosis M (SD; range)	34.38 (10.61; 12-51)
MS duration y M (SD; range)	13.77 (7.53; 4-29)
EDSS M (SD; range) baseline	1.96 (1.84; 0-6)
EDSS M (SD; range) final	2.17 (1.92; 0-6)
Marital status n (%)	
Single	4 (15.4%)
Married	22 (84.6%)
Educational level n (%)	
Elementary	5 (19.2%)
Secondary	3 (11.5%)
FP or equivalent	8 (30.8%)
University	10 (38.5%)
Family history (diseases) n (%)	
Multiple Sclerosis	3 (11.5%)
Autoimmune	5 (19.2%)
Neurodegenerative	11 (42.3%)
Psychopathologic	7 (26.9%)

Note: MS=multiple sclerosis; M=mean; SD=standard deviation; EDSS=Expanded Disability Status Scale; y=years;

Table 2. Summary of Descriptive Statistics for all the Measures at Different Time Points

Mean(SD)	T0-Baseline	T1	T2	T3	T4/Final	Total/M
Predictors						
SEs	-	8.69(3.27)	6.74(4.02)	6.90(3.96)	9.30(5.26)	27.50(15.23)
PSS	-	26.55(10.02)	27.20(9.34)	24.90(9.37)	27.59(10.18)	26.53(8.61)
Outcomes						
EDSS	1.96(1.84)	-	-	-	2.17 (1.92)	2.07(1.85)
FAMS	153.88(42.07)	156.62(40.88)	156.57(42.90)	157.19(40.48)	152.58(43.80)	157.19(41.40)
Relapses	-	Σ=2	Σ=1	Σ=5	Σ=2	Σ=10

Note: SEs=Stressful Events; PSS=Perceived Stress Scale; EDSS=Expanded Disability Status Scale; FAMS=Functional Assessment of MS; T1=Trimester 1; T2=Trimester 2; T3=Trimester 3; T4=Trimester 4; M=Mean; SD=Standard Deviation

Table 3. Bivariate Correlations among Predictor and Outcome Variables

	EDSS (baseline and final)	FAMS (baseline and total)	FAMS (T1, T2, T3 & T4)
PSS T1	**EDSS base** .09 (-0.31 to 0.46)	**FAMS base** -.70*** (-0.86 to -0.43)	**FAMS T1** -.74*** (-0.87 to -0.49)
PSS T2	-	-	**FAMS T2** -.56** (-0.80 to -0.16)
PSS T3	-	-	**FAMS T3** -.70*** (-0.87 to -0.38)
PSS T4	**EDSS final** .04 (-0.41 to 0.48)	-	**FAMS T4** .84*** (-0.94 to -0.62)
PSS total	**EDSS final** .09 (-0.31 to 0.46)	**FAMS total** -.75*** (-0.88 to -0.51)	-
SEs_T1	**EDSS base** -.03 (-0.41 to 0.37)	**FAMS base** -.40* (-0.68 to -0.01)	**FAMS T1** -.27 (-0.60 to 0.13)
SEs_T2	-	-	**FAMS T2** -.36 (-0.69 to 0.08)
SEs_T3	-	-	**FAMS T3** -.43 (-0.73 to 0.00)
SEs_T4	**EDSS final** -.04 (-0.47 to 0.41)	-	**FAMS T4** .49* (-0.77 to -0.05)
SEs_total	**EDSS final** .06 (-0.33 to 0.44)	**FAMS total** -.42* (-0.69 to -0.04)	-

Note: PSS=Perceived Stress Scale; SEs=Stressful Events; EDSS=Expanded Disability Status Scale; FAMS=Functional Assessment of MS; T1=Trimester 1; T2=Trimester 2; T3=Trimester 3; T4=Trimester 4; base=baseline. Significance (two-tailed) = *p<.05, **p<.01, ***p<.001

Table 4. Hierarchical Mixed Regression Models to test Bidirectional Hypothesis

Model 1	**Outcome: FAMS**			**Model 2**	**Outcome: PSS**		
Predictor: PSS	βi (CI)	AIC	*p* value	**Predictor: FAMS**	βi (CI)	AIC	*p* value
Step 1 Age Gender	-17.86 (-118.71 to 82.99) -1.30 (-3.61 to 1.01)	798.36	.73 .27	**Step 1** Age Gender	-1.33 (-9.99 to 7.34) 0.03 (-0.31 to 0.37)	609.04	.76 .86
Step 2 PSS	-1.38 (-2.21 to 0.56)	790.35	.002**	**Step 2** FAMS	-0.18 (-0.22 to -0.13)	568.26	<.001***
Step 3 Coping	3.59 (-2.01 to 9.18)	746.72	.19	**Step 3** Coping	-1.59 (-4.29 to 1.11)	521.72	.24
Step 4 PSS x Coping	0.96 (0.19 to 1.72)	739.57	.01**	**Step 4** FAMS x Coping	-0.01 (-0.08 to 0.05)	526.63	.70
Model 3	**Outcome: FAMS**			**Model 4**	**Outcome: SEs**		
Predictor: SEs	βi (CI)	AIC	*p* value	**Predictor: FAMS**	βi (CI)	AIC	*p* value
Step 1 Age Gender	-13.71 (-54.82 to 27.40) -0.78 (-2.35 to 0.79)	779.17	.50 .31	**Step 1** Age Gender	1.59 (-1.38 to 4.57) 0.04 (-0.07 to 0.16)	493.29	.28 .44
Step 2 SEs	-0.56 (-1.67 to 0.55)	777.56	.32	**Step 2** FAMS	-0.03 (-0.05 to -0.00)	476.28	.04*
Step 3 Coping	3.45 (-5.46 to 12.35)	724.71	.44	**Step 3** Coping	1.23 (-0.18 to 2.65)	423.98	.09
Step 4 SEs x Coping	1.13 (-1.26 to 3.52)	721.68	.35	**Step 4** FAMS x Coping	0.02 (-0.2 to 0.05)	429.35	.35

Note: PSS=Perceived Stress Scale; SEs=Stressful Events; FAMS=Functional Assessment of MS. Significance (two-tailed) = *p<.05, **p<.01, ***p<.001

5.2 Complementary analyses

In order to test the moderator effects of all the psychosocial factors, complementary analyses were conducted with social support, anxiety, alexithymia and early-life stress.

5.2.1 Statistical analyses

The data analyses were conducted using SPSS (version 23.0; SPSS Inc., Chicago, Illinois). Following the results of the correlations and models conducted in Phase 3, new multiple hierarchical mixed regression models were carried out to test the main and moderator effects of these variables in the stress-MS relationship. Three models were developed. First, considering PSS as predictor and FAMS as outcome; second, considering FAMS as predictor and PSS as outcome; and third, considering FAMS as predictor and SEs as outcome. Individually in each model, the main effect and moderator effect of social support, anxiety, alexithymia and early-life stress was tested. Anxiety was categorised as low-anxious (≤ 31 in women and ≤ 28 in men) and high-anxious (≥ 31 in women and ≥ 28 in men) following the above percentile-75 adjusted for age and gender in standardised Spanish population tables. Alexithymia was categorised as alexithymia or non-alexithymia following the TAS-20 criteria: non-alexithymia (≤52), possible alexithymia (52-61) and alexithymia (>61), gathering together those with a score of over and under 52. In the first step socio-demographic variables were entered; in the second step the main predictor and outcome (PSS, FAMS or SEs); in the third step the psychosocial variables of social support, anxiety, alexithymia and early-life stress; and in the fourth step the interaction between the main predictor and the psychosocial variables. Significance level was set at 5% (p≤.05).

5.2.2 Results

The results of the complementary analyses are shown in Table 3.

The first model took PSS as predictor and FAMS as outcome. This model showed an inverse relationship between PSS and FAMS. An increase in the PSS score was related with a decrease in the FAMS score. STAI and TAS showed also a significantly positive main effect. It means that low-anxiety and non-alexithymia were related with higher levels of FAMS. Anxiety and PSS also showed a significant interaction effect. Low-anxious people seem to have a better functionality without stress but, with higher levels of stress, functionality decreases almost at the same level as the whole sample.

The second model took FAMS as predictor and PSS as outcome. This model showed also an inverse relationship between FAMS and PSS. An increase in the FAMS score was related to a decrease in the PSS score. STAI also showed a negative main effect. It means that low-anxious people were related to lower levels of perceived stress.

The third model took FAMS as predictor and SEs as outcome. This model showed an inverse relationship between FAMS and SEs. An increase in the FAMS score was related to a decrease in the SEs number. MSPSS and STAI also showed a negative main effect. Higher levels of perceived social support and the low-anxious group were related to lower levels of perceived stress.

Table 3. Multiple Hierarchical Mixed Regression Models to Test the Role of Social Support, Anxiety, Alexithymia and Early-Life Stress in the stress-MS relationship

Model 1	**Outcome: FAMS**			**Model 2**	**Outcome: PSS**			**Model 3**	**Outcome: SEs**		
Predictor: PSS	βi (CI)	AIC	*p* value	**Predictor: FAMS**	βi (CI)	AIC	*p* value	**Predictor: FAMS**	βi (CI)	AIC	*p* value
Step 1 Age Gender	-17.86 (-118.71 to 82.99) -1.30 (-3.61 to 1.01)	798.36	.73 .27	**Step 1** Age Gender	-1.33 (-9.99 to 7.34) 0.03 (-0.31 to 0.37)	609.04	.76 .86	**Step 1** Age Gender	1.59 (-1.38 to 4.57) 0.04 (-0.07 to 0.16)	493.29	.28 .44
Step 2 PSS	-1.38 (-2.21 to 0.56)	790.35	.002**	**Step 2** FAMS	-0.18 (-0.22 to -0.13)	568.26	<.001***	**Step 2** FAMS	-0.03 (-0.05 to -0.00)	476.28	.04*
Step 3a MSPSS	0.62 (-0.17 to 1.40)	808.71	.12	**Step 3a** MSPSS	-0.24 (-0.67 to 0.19)	670.22	.28	**Step 3a** MSPSS	-0.09 (-0.16 to -0.02)	495.49	.02*
Step 4a PSS x MSPSS	-0.20 (-1.22 to 0.83)	1049.63	.71	**Step 4a** FAMS x MSPSS	0.002 (-0.07 to 0.08)	876.42	.97	**Step 4a** FAMS x MSPSS	4.78 (-0.002 to 0.002)	520.71	.96
Step 3b STAI	31.75 (12.55 to 50.95)	812.91	.01*	**Step 3b** STAI	-4.27 (-8.44 to -0.10)	557.15	.05*	**Step 3b** STAI	-4.06 (-6.84 to -1.27)	470.68	.004**
Step 4b PSS x STAI	-1.60 (-2.90 to -0.29)	738.18	.01*	**Step 4b** FAMS x STAI	0.03 (-0.05 to 0.12)	793.60	.41	**Step 4b** FAMS x STAI	0.02 (-0.03 to 0.08)	715.16	.36
Step 3c TAS	24.63 (5.45 to 43.82)	779.92	.01*	**Step 3c** TAS	-1.03 (-4.96 to 2.91)	569.68	.60	**Step 3c** TAS	0.76 (-2.53 to 4.05)	487.19	.64
Step 4c PSS x TAS	-0.41 (-1.82 to 1.00)	778.27	.57	**Step 4c** FAMS x TAS	-0.10 (-0.46 to 0.27)	692.47	.60	**Step 4c** FAMS x TAS	0.006 (-0.05 to 0.04)	709.56	.77
Step 3d CTQ	-0.49 (-2.33 to 1.36)	780.77	.50	**Step 3d** CTQ	-0.04 (-0.25 to 0.17)	617.85	.69	**Step 3d** CTQ	0.06 (-0.02 to 0.14)	485.87	.15
Step 4d PSS x CTQ	0.11 (-0.54 to 0.77)	933.67	.73	**Step 4d** FAMS x CTQ	0.002 (-0.04 to 0.05)	811.83	.92	**Step 4d** FAMS x CTQ	0.001 (-0.003 to 0.005)	556.36	.58

6. Discussion

Discussion

6.1 Main findings

The aim of the present thesis was to investigate the effect of stress on MS and the potential moderating role of the psychosocial factors of coping, social support, anxiety, alexithymia and early-life stress. To do so, the project *"PsychoMSS Study: Stress and Psychosocial Factors in MS"* was developed. This study was carried out in three phases: a systematic review, a case-control study and a longitudinal follow-up study.

The provided findings make an original contribution to the knowledge about the complex relationship between stress and MS, highlighting the importance of some psychosocial moderating and mediating factors on this relationship. Phase One, a complete qualitative systematic review, is a starting point to develop new research. It summarizes the main findings and knowledge on this field, providing a new insight about the methods used to measure the stress effect on MS and the potential moderators and mediators of this relationship. Phase Two, a case-control study, provides new data about the differences between pwMS and people without MS in some selected psychosocial factors, and the association of these factors with disease parameters. Phase Three, a one year follow-up study, contributes to clarifying the relationship between stress and MS. It confirms the bidirectional hypothesis between stress and MS and, at the same time, it elucidates which psychosocial factors are more related to disease progression parameters.

The main results in phase one indicated that prospective designed studies with repeated measures over time and self-reported evaluations showed the most consistent results when studying the relationship between stress and MS. Although stress seems not to be a risk factor to develop the disease, almost all the studies reviewed showed a positive association between stress and the progression of MS. From all the psychosocial factors reviewed in the studies, those more related to the stress-MS relationship were those associated to the duration and severity of stress, the autonomic nervous system reactivity and anxiety, and the social support provided.

The main results in Phase Two showed that pwMS used different coping patterns in dealing with stressful situations compared to people without MS. Specifically; pwMS use more passive coping, avoidance and instinctive actions, and seek and perceive less social support from their social environment. Moreover, pwMS

presented higher levels of anxiety and alexithymia, but not more stressful or traumatic events in early-life. Considering the disease parameters, only anxiety and avoidance coping were related to self-reported functionality and neurologist rated impairment.

The main results in Phase Three indicated that there is a positive bidirectional relationship between stress and disease progression, but only with self-reported measures of stress and functionality. The greater the perceived stress was, the lower the functionality level. Lower levels of functionality, in turn, may predict more stressful events but the occurrence of stressful events itself does not dispose to a worse functionality. Considering relapses, pwMS did not show differences comparing the period before and after the relapse in perceived stress level, discomfort or number of stressful situations, but patients in a relapsing phase did show more passive coping than those in a remitting phase. Regarding psychosocial factors, active coping and anxiety showed an interaction effect with stress and functionality. Active coping seems to be adaptive with high levels of stress, but with low levels of stress it might be even counterproductive in the short term. Low-anxiety individuals showed higher levels of functionality compared to the whole sample, but as stress increased, differences in functionality decreased. Anxiety and alexithymia also showed an effect on functionality; pwMS with high-trait anxiety or alexithymia did show lower levels of functionality. Finally, social support showed an effect on stressful events. The less the perceived social support was, the more the number of stressful events.

6.2 The complex relationship between stress and MS

The stress effect on MS is a complex issue to address. Previous studies pointed out that it is not a causal unidirectional relationship and postulated the *Bidirectional Hypothesis* (Brown et al., 2006a; Schwartz et al., 1999). This hypothesis explains the stress-MS relationship as a vicious deteriorating cycle where stress is related to a worsening in the clinical course of the disease and, at the same time, a worsening in the clinical course is related to more stress (Schwartz et al., 1999). In the present study we confirmed this hypothesis with self-reported measures of perceived stress and functionality but not with other measures like neurologist rated impairment (EDSS) or the number of stressful events. However, one must be cautious with this assessment as the sample size is small and false negative results may appear.

According to Valdés and De Flores (1990), stress activates several body systems that ultimately may deregulate the immune system. This deregulation may affect the disease progression. In turn, difficulties in adapting to the disease, new symptoms, relapses or impairment may worsen the perception of stress or even cause new stressful situations. For this reason, in the treatment of MS it is important to be aware of this deteriorating cycle to provide a suitable therapy from the first stages of the disease, giving resources for a better adaptation to MS and to manage future stressful events successfully. Some interventional psychological therapies have shown improvements in adaptation and the disease progression (for a review, see Reynard et al., 2014).

In the study of the relationship between stress and MS it is also necessary to point out the importance of how stress is evaluated. According to the systematic review carried out in Phase One (Briones-Buixassa et al., 2015), those studies that used self-reported measures of stress and MS progression yielded the most consistent results. However, stress measurement is a controversial topic and its evaluation depends on the paradigm used to define it. Under a transactional approach (Lazarus & Folkman, 1984), stress is considered as an interaction between the individual and the environment and a complete and continued stress evaluation needs to be carried out.

According to Fernández and Blasco (2003), it has to be measured as follows: first, the source of stress or the stressors; second, the immediate effects; third; the coping strategies used to deal with stressors; and fourth the noxious consequences. Moreover, all these factors need to be measured at different points over time (Lazarus, 1990). Phase Three, the longitudinal follow-up study, was developed in compliance with these criteria. This complete evaluation assured a great number of evaluations during the period of study and allowed us to draw a good picture of the stress process and its relationship with MS. Future studies should evaluate stress in a similar way, as a state which changes over time, to see the whole dimension of this construct.

Apart from that, psychosocial moderators and mediators of this relationship need to be considered. Only coping and anxiety have shown a moderator effect between perceived stress and functionality. However, other psychosocial factors like alexithymia and social support seem to play an important role in the disease i.e. pwMS had higher levels of alexithymia and lower levels of perceived social support. Although we cannot know if differences in these psychosocial factors are prior to, or a consequence of, the disease, either biologic or psychological, we do know that almost all of these factors are potentially modifiable through therapeutic approaches, and this may help also to break the deteriorating cycle between stress and MS.

6.3 Coping with stress in people with MS

The appraisal and coping processes to deal with stress depend on different individual features, resilient factors, stressful characteristics, and so on. The transactional theory (Lazarus & Folkman, 1984) considers these two processes as key elements in the management of stressful conditions. The way one copes with stress and the consequence of the coping behaviour will determine how one will face future stressful situations. In relation to this, the present thesis has shown the following; a) pwMS tend to use more avoidance and instinctive coping and to seek less social support from their social network compared to people without MS; b) people in a relapse phase tend to use more avoidance coping than people in a remitting phase; and c) in pwMS active coping seems to be effective to improve functionality with high levels of stress, but with low levels of stress it may even be counterproductive. According to Olff, Brosschot and Godaert (1993), avoidance, denial or escape from the stressful situation is considered to reduce the experience to cope in the short term, but it also decreases self-confidence in one's own resources to deal with the stressful situation. Active coping seems to be better to deal with stress in general (Afshar et al., 2015) and to adapt to MS (Pakenham, 1999; Pakenham, Stewart & Rogers, 1997), but it may temporarily increase the stress experience in the short term. In this regard, it would be interesting to investigate in a chronic and unpredictable disease like MS whether active coping is advisable in all situations or not, especially in the relapse phase, in progressive forms of the disease or in those situations of greater disability. In these situations some forms of passive coping like emotional coping or mindfulness could be more appropriate (Brooks and Matson, 1982; Senders, Bourdette, Hanes, Yadav and Shinto, 2014).

Considering social support, it was postulated that seeking social support buffers the experience of stress (Cohen & Willis, 1985) and it seems to be useful to improve physical and mental status in pwMS (Costa et al., 2012; Krokavcova et al., 2008). However, social support may be a double-edged sword. In a recent qualitative study, McCabe and O'Connor (2012) found that people with high levels of adjustment showed better social support from family and friends, but that this social support was used mainly to assist experiencing enjoyment in life and not merely illness-focused help.

Although in general social support helps to better manage stress and adapt to the disease, some kind of illness-focused support may be a constant reminder of the disease or disability state for the individuals. This could be one of the reasons why social support is less used among pwMS. On the other hand, in pwMS the low perception of social support may be related to the higher levels of alexithymia. People with alexithymia have difficulties to identify and express their feelings, and to read emotions from other people (Grynberg, Luminet, Corneille, Grèzes & Berthoz, 2010). At the same time, pwMS have shown higher levels of alexithymia along with deficits in the recognition of emotional facial expressions and introspection (Prochnow et al., 2011) and an impaired social cognition (Pöttgen, Dziobek, Reh, Heesen & Gold, 2013). These deficits may make social interaction more difficult and, as a result, affect the perception of social support from their social environment.

Finally, social support has been related also with early-life stress. Under a stressful situation people with more secure attachment bonds tend to seek more social support, whereas people with detached bonds tend to seek less social support (Feeney & Kirkpatrick, 1996). In the present study, early-life stress did not show any relationship with MS or a higher prevalence among pwMS. However, other studies did find higher levels of early-life stress in pwMS, and a negative association to the disease progression (Spitzer et al., 2012) or a quasi-significant association to disease onset (Riise et al., 2011). Possible explanations for these disparate results may be the following. First, some resilient factors are mediating on this relationship like child dispositional attributes, family cohesion, or external support (Garmezy, 1985). Second, due to the small sample size our results do not have enough statistical power to detect differences or associations. Third, according to the results of Feeney and Kirkpatrick (1996), pwMS may not have had more traumatic experiences in early-life like sexual or emotional abuse, but perhaps some kind of deficit in the attachment bonds.

6.4 The role of anxiety

Anxiety seems to play an important role in the disease of MS, and also in the relationship between stress and MS. First, pwMS have higher levels of trait anxiety than people without MS. Second, high anxiety has been related to low levels of functionality in both phases of the study, at cross-sectional and long-term levels. Third, high anxiety has been related to a greater perceived stress and to more stressful events. Finally, through the systematic review, we have seen that anxiety, and in general autonomic nervous system reactivity, is one of the main factors related to stress and MS.

Anxiety is a normal reaction of the body in situations where a kind of threat is perceived and a “fight or flight” response needs to be activated to deal with this. It is an evolutionary, mainly physiologic response that activates the sympathetic branch of the autonomous nervous system preparing the body to act. However, this survival mechanism may not be adaptive to live in a modern society. Although the highest prevalence of anxiety in pwMS may respond to the diagnosis of a chronic and disabling disease, some patients reported they had high levels of anxiety many years before the diagnosis or referred to a high trait anxiety during all their lives. This fact makes us think about a biological link between MS and a disposition to suffer high trait anxiety. Further studies should investigate this potential link through the analysis of the serotonin transporter gen (5-HTT), a genetic link to anxiety (Lesch, Bengel, Heils & Sabol, 1996), or through the study of the brain structures involved in anxiety response like the limbic system (amygdala, hypothalamus, thalamus) or the pre-frontal cortex (Davidson, 2002). It would be also useful to carry on with the study of physiological measures of anxiety like the startle reflex, the electrodermal activity or the heart rate, in a similar way to the study of Ackerman et al. (2003).

On the other hand, it is important to highlight the strong association between stress and anxiety. Both factors are part of the appraisal process of threats, but whereas anxiety is mainly anticipatory in front of diffuse threats, stress is a response to a highly demanding environment. In any case, there is a lack of control and the intrinsic characteristics of MS may be playing an important role in this issue. According to Grupe and Nitschke (2013), the sense of control reduces the subjective perception of anxiety and predictable threats produce less physiological activation and anxiety. In this sense, MS is a disabling disease characterized by a lack of control over the

disease progression and a completely unpredictable course; one never knows how and when the person will be affected. For this reason, anxiety and stress management should be addressed both in future observational and interventional studies about the stress effect on MS.

6.5 Recommendations and implications

The confirmation of the bidirectional hypothesis between stress and MS highlight the importance of taking into account the psychological aspects of individuals to deal with MS. Considering the disease characteristics of unpredictability and disablement, a diagnosis of MS usually represents a great impact on the emotional state of the individual and it may take a long time to adjust to the disease (Dennison, Yardley, Devereux & Moss-Morris, 2010; Pakenham, 1999). For this reason, it is important to offer psychological treatment in the early stages of MS, in order to empower the patients giving them resources to deal with living with MS from the very beginning. This may prevent them from entering this possible deteriorating cycle of stress and exacerbation. In this sense, the protocol developed by Moss-Morris et al. (2013) is a reliable and complete cognitive-behaviour trial intervention focused on the management of the symptoms and disturbances of MS, with the aim of improving the adjustment to the disease in the early stages after the diagnosis.

In the treatment of MS, and other chronic illnesses, psychological aspects play an important role and the participation of multidisciplinary health professional teams is required. The treatment of MS should include a psychologist from the moment of diagnosis to help patients to adjust to the disease and to provide better strategies to manage stress and emotional resources in order to develop proper coping strategies. As a result, not only is it important to mitigate stress conditions, it is also important to provide resources that build resilience and emotional management to improve appraisal and coping processes in the face of future stressful situations.

Finally, other psychological factors like anxiety, alexithymia or social support have shown to be related to the functionality and symptomatology of the disease. Therefore, it is necessary to develop psychotherapeutic interventions focused on these specific factors, serving as key targets for interventions. Anxiety seems to be one of the most common and important factors in the worsening of the disease. A recent study showed that escitalopram (Mitsonis et al., 2010), a selective serotonin reuptake inhibitor used to treat depression and anxiety, demonstrated beneficial effects for disease progression. The stress-related relapses were lower in patients that were under a medication with escitalopram compared with those that were not. This

suggests that anxiety treatment should be a priority in the treatment of pwMS. At the same time, perceived social support seems to be another key factor related to disease progression. Therapeutic groups may improve social support from other people in the same condition, increasing the therapeutic adherence and providing a space in which pwMS can express not only their fears and worries but also their achievements and positive hopes for the future (Mazaheri, Fanian & Zargham-Boroujeni, 2011; Tesar, Baumhackl, Kopp & Günther, 2003).

6.6 Strengths and limitations

The main strengths and limitations of the three phases of the study are summarized in Table 4.

Table 4. Summary of the Main Strengths and Limitations of Phase One, Two and Three

	Strengths	Limitations
Phase One	The review was extensive and covered a long period, a large number of databases and was done in two important languages: English and Spanish First systematic review of the stress-MS relationship considering stress evaluation and potential psychosocial mediators and moderators	Review limitations: Publication bias, different terms to refer to the same concepts, interventional papers not included Results limitations: generalization (homogenous samples), comparison (different methods, few studies for each moderator/mediator factor)
Phase Two	Wide range of psychosocial factors considered First study to relate several psychosocial factors to different disease parameters	Relatively small simple size Lack of generalization to other forms of MS (only relapsing-remitting form) Lack of other potential moderators and mediators of the stress-MS relationship
Phase Three	Multiple assessments of stress over time following the transactional approach to stress Multiple assessments of coping behaviour (trait and state) Use of different stress measures and different disease progression assessments during the follow-up	Relatively small simple size Short period to see major changes in some disease progression parameters (EDSS or relapses) Lack of physiological stress measures and biologic disease progression assessments

The main strength of the present thesis is that it is a complete study that includes three important phases: a broad systematic review, a case-control study and a longitudinal one-year follow-up study. This allows us to address the same topic from different perspectives that are complementary to each other. Phase One provides a literature review giving some guidelines to develop the following studies. Phases Two and Three provide new knowledge about the same problem from different points of view: a cross-sectional study which provides information at a given point in time, and a longitudinal study which provides information in several assessments during a one-year follow-up.

Another important strength of the present thesis is that it was developed in the Mental Health and Social Innovation Research Group, an inter-institutional research group formed by the Consorci Hospitalari de Vic and the Universitat de Vic – Universitat Central de Catalunya. The opportunity of working in a multidisciplinary team facilitated the access to the patients of the hospital and the development of shared studies. Moreover, two neurologists from the Consorci Hospitalari de Vic, specialized in MS, collaborated in all the phases of the study.

One of the main limitations of the studies is the sample size. Although the incidence of MS is increasing in Osona and the prevalence is one of the highest in Spain (Otero-Romero et al., 2013), it is a small region (approx. 154.554 inhabitants) and not so many people met the inclusion criteria. Moreover, EDSS was unusually low. It could be due to the fact that there are so many towns spread apart with poor transport connections to the hospital and this may have left out the most handicapped people. Another limitation is that only people with the relapsing-remitting type participated in the study. Although this type represents around 85-90% of all diagnosed cases of MS, this fact does not enable us to generalise the results to the progressive forms of MS. Finally, another important limitation of the study was the lack of funding. This fact prevented us from conducting the most expensive assessments like physiological measures of stress, genetic analyses of serotonin transporters or Gd+ MRI scans for the disease progression.

6.7 Future direction for research

The bidirectional effect between stress and MS needs more studies to establish and clarify their complex relationship. Prospective large cohort studies are needed to elucidate their temporal relationship and the effect of stress through the disease progression, and in turn, the effect of the disease progression on perceived stress. Following a transactional approach different measures of stress are needed over time to observe the stress process and development. At the same time, the disease should be assessed from different aspects: symptoms, impairment, functionality, clinical relapses and biological parameters like new Gd+ lesions in the brain or MRI scans to see the functionality of the different brain areas affected.

Psychosocial factors should be taken into account as moderators of this relationship but also as factors that have a major effect on disease progression. It would be advisable to deepen our knowledge of which psychosocial factors are related to stress and disease processes in order to develop more focused psychotherapeutic approaches as almost all of them are potentially modifiable. It might be fruitful to collect data about different psychosocial factors in primary care centres or schools, and to observe the relationship in the long term with different chronic diseases, including MS.

Considering the strong association between stress, disease parameters and anxiety, it would be appropriate to develop genetic studies of serotonin transporters among pwMS, or studies evaluating the functionality of the amygdala and the pre-frontal cortex in MRI scans, to observe if there is some relationship between the disease and the biological bases of anxiety. Furthermore, physiological measures of the autonomic nervous system like electrodermal activity, startle reflex, heart rate or blood pressure may improve our knowledge about the physiological activation of pwMS in the face of stressful situations.

Finally, more interventional studies focused on the treatment of specific psychosocial factors like anxiety, alexithymia or social support, and resources to successfully manage stressful situations are needed to elucidate their potential benefits on the disease progression in pwMS. CBT trials have shown to be effective to adapt to MS (Moss-Morris et al., 2013) or even to reduce brain lesions (Mohr et al., 2012), but other approaches like mindfulness or ACT should be further studied.

7. Conclusions

Conclusions

The present thesis aimed to explore the effect of stress on MS and the role of some potential psychosocial moderators and mediators of this relationship. The three phases of the study described above allow us to draw the following conclusions:

- The relationship between stress and MS is bidirectional in terms of self-reported perceived stress and functionality and it is relevant to highlight the importance of breaking this possible deteriorating cycle from the early stages of the disease.
- The way stress is measured largely determines the results obtained. One of the most complete ways to measure stress is its evaluation under a transactional approach following the established criteria and making repeated assessments over time. Moreover, it is necessary to consider different psychosocial moderators and mediators of this relationship to achieve a holistic view of the stress concept.
- The way disease progression is measured also determines the design, temporality and results of the study. Large prospective studies are needed considering the assessment of several parameters: symptoms, relapses, functionality, impairment and biological measures.
- In general, pwMS have different coping patterns characterised by a more passive style and a lower search for social support. Although active coping usually seems to work better in dealing with stressful situations, in a chronic and unpredictable disease like MS some forms of passive coping like mindfulness could be more appropriate at some points, for example in a relapse phase or progressive forms of the disease.
- Psychosocial factors like coping, social support, anxiety and alexithymia have shown to play an important role in the functionality of the disease, and anxiety especially has been postulated as one of the main factors related to MS and the stress-MS relationship. As almost all of them are potentially modifiable, the psychotherapeutic approaches should include these psychosocial factors as key targets of the intervention.
- Early-life stress is a controversial topic. There are disparate results about the prevalence of childhood traumatic experiences among pwMS and its relationship with the disease progression. Future studies should include the assessment of mediators of this relationship like resilient factors or the attachment bond generated by pwMS with the attached figures.

- In primary health care centres, hospitals and day care centres the treatment of MS should be addressed from a disciplinary team which includes a psychologist. Moreover, adaptation to MS and the treatment of related psychosocial factors should be addressed at the early stages of MS to better adjust to the disease, and to improve directly and indirectly some parameters of the disease like functionality and impairment.

Multiple Sclerosis has been called "*the disease of the thousand faces*" due to the fact that it affects every person who is diagnosed in a different way. One never knows at what point in time the disease will be present, which parts of their body or mind will be affected or which impact the disease will have through their life. For many years research on the treatment of MS has been mainly focused on the biological aspect of the disease. However, under the biopsychosocial model the psychological and social aspects are also equally important and the mind-body connections need to be considered. In this regard, this thesis provides new insights on this issue pointing out the necessity to carry on with the study of stress and related psychosocial factors in the clinical course of MS. According to the main findings of the present study, psychotherapeutic interventions may help to better adapt to this unpredictable disease, especially if they are conducted at early stages. They may act preventing pwMS from entering into a possible deteriorating cycle between stress and exacerbation, modifying some parameters of disease progression and, in general, improving the quality of life in pwMS.

8. References

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9. Annex

Annex

9.1 Study support materials

9.1.1 Informed consent form of the participants with MS

FULL DE CONSENTIMENT INFORMAT

Estudi de recerca compartit entre el Consorci Hospitalari de Vic i la UVic-UCC.

TÍTOL DE L'ESTUDI: Anàlisi de la influència de l'estrès i determinats factors psicosocials en el debut i l'evolució de l'Esclerosi Múltiple.

EXPLICACIÓ DE L'ESTUDI: Aquest és un estudi destinat a conèixer la influència de determinats factors psicosocials en el desenvolupament i l'evolució de l'Esclerosi Múltiple. L'estudi consta de dues parts: una entrevista inicial i quatre entrevistes de seguiment.

La primera part de l'estudi és l'entrevista d'avui on inicialment recollirem dades bàsiques sobre vostè. Després li administrarem quatre qüestionaris d'una duració aproximada de 5-10 minuts cada un. Finalment, li explicarem detalladament en què consisteix la segona part de l'estudi i li facilitarem els instruments necessaris per a dur-la a terme. L'entrevista inicial tindrà una durada d'entre 1h i 1h 30min. Si vostè vol pot realitzar aquesta entrevista en dos dies, només cal que ho digui a l'investigador en qualsevol moment.

La segona part de la investigació es durà a terme a partir d'avui i durant 1 any. En aquesta segona part haurà de dur un registre setmanal sobre les situacions vitals estressants que li ocorrin, les estratègies que utilitza per afrontar-les i el grau de malestar que li generen. Un cop al mes haurà de respondre a un qüestionari sobre estrès, situat a la part posterior del registre. Aquest registre el recollirem en una entrevista que realitzarem aproximadament cada 3 mesos i que tindrà una duració d'uns 30 minuts. En aquestes entrevistes comentarem el registre dut a terme i li administrarem novament el qüestionari de qualitat de vida.

Seria desitjable que participés en ambdues parts de l'estudi però, tanmateix, existeix la possibilitat de realitzar-ne només la primera part, consistent en l'entrevista d'avui.

Les dades que ens faciliti son confidencials: els qüestionaris seran destruïts a la finalització d'aquest estudi i s'esborrarà el nom a les dades perquè no puguin ser identificades.

La seva participació a l'estudi és lliure i voluntària i pot decidir finalitzar-la quan vostè vulgui.

DRETS DELS PARTICIPANTS:

Jo _____
(nom i cognoms) he llegit el text complet d'aquest document de consentiment informat.

M'han estat exposades les característiques de l'estudi i s'ha respost a totes les meves preguntes.

Se m'han comunicat les diferents opcions que tinc alhora de participar-hi.

He comprès que no estic obligat a formar part d'aquest estudi i que en puc interrompre la participació en qualsevol moment.

He entès que es garanteix la confidencialitat respecte la meva participació en aquest estudi per a qualsevol de les dades que puguin extreure's.

He entès els motius de la seva realització i els procediments per dur-lo a terme.

He entès els meus drets com a participant en aquest estudi d'investigació i voluntàriament accedeixo a participar en el mateix.

Signatura:

DNI: _____

Data: _____

9.1.2 Informed consent form of the comparison group

FULL DE CONSENTIMENT INFORMAT

Estudi de recerca compartit entre el Consorci Hospitalari de Vic i la UVic-UCC.

TÍTOL DE L'ESTUDI: Anàlisi de la influència de l'estrès i determinats factors psicosocials en el debut i l'evolució de l'Esclerosi Múltiple.

EXPLICACIÓ DE L'ESTUDI: Aquest és un estudi destinat a conèixer la influència de determinats factors psicosocials en el desenvolupament i l'evolució de l'Esclerosi Múltiple. Vostè participa com a control i, per tant, la seva participació consisteix en realitzar una entrevista de 1 hora de duració on se li passaran una sèrie de qüestionaris sobre vostè, la seva manera de ser i el seu estil de vida.

Les dades que ens faciliti son confidencials: els qüestionaris seran destruïts a la finalització d'aquest estudi i s'esborrarà el nom a les dades perquè no puguin ser identificades.

La seva participació a l'estudi és lliure i voluntària i pot decidir finalitzar-la quan vostè vulgui.

DRETS DELS PARTICIPANTS:

Jo _____
(nom i cognoms) he llegit el text complet d'aquest document.

M'han estat exposades les característiques de l'estudi i s'ha respost a totes les meves preguntes.

He comprès que no estic obligat a formar part d'aquest estudi i que en puc interrompre la participació en qualsevol moment.

He entès que es garanteix la confidencialitat respecte la meva participació en aquest estudi per a qualsevol de les dades que puguin extreure's.

He entès els motius de la seva realització i els procediments per dur-lo a terme.

He entès els meus drets com a participant en aquest estudi d'investigació i voluntàriament accedeixo a participar en el mateix.

Signatura:

DNI: _____

Data: _____

9.2 Certificat of attendance

Research internship at the Institute of Psychiatry, Psychology and Neuroscience (IoPPN) King’s College London

Institute of Psychiatry, Psychology & Neuroscience
Department of Psychology & Systems Sciences (at Guy's)

Professor Rona Moss-Morris
CPsychol AFBPsS

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KING'S College LONDON

08 February 2016

To whom it may concern

CERTIFICATE OF ATTENDANCE

Laia Briones Buixassa ID number **43633088H** (Catalonia, Spain), has been doing a research internship at the Institute of Psychiatry, Psychology and Neuroscience at King's College London (London, United Kingdom) in the framework of her candidature to obtaining a PhD.

Supervisor: Prof Rona Moss-Morris
Research group: Health Psychology
Study period: 12 October 2015 to 1 March 2016

Yours faithfully

Rona Moss-Morris
Head of the Health Psychology Research Group

The disease of the thousand faces.
As the thousand faces of the moon.
Even the shadows.

Laia Briones

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Disseny: Joan Fossas