A Study of Comorbidities, Lifestyle Risk Factors and Fatigue of Patients with Multiple Sclerosis in South Africa

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DECLARATION

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List of Abbreviations

MS	Multiple Sclerosis
CNS	Central Nervous System
PwMS	Persons with MS
EBV	Epstein - Barr virus
SA	South Africa
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols
DM	Desirèe Maartens
MH	Martin Heine
MSSA	MS Society of South Africa
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
REDCap	Research Electronic Data Capture
BMI	Body Mass Index
ICF	International Classification of Functioning
PDDS	Patient Determined Disease Steps
MSWS-12	MS Walking Scale
PROMIS SF	PROMIS Short Form
IPAQ	International Physical Activity Questionnaire
METs	Metabolic Equivalents
PPP	Purchasing Power Parity
FSS	Fatigue Severity Scale
FSMC	Fatigue Scale for Motor and Cognitive
95% CI	95% Confidence Interval
IQR	Inter Quartile Range
SES	Socioeconomic Status
ROC	Receiving Operating Characteristics
AUC	Area Under the Curve

Abstract

Background: Multiple Sclerosis (MS) affects approximately 2.3 million people globally. A geographical gradient in the prevalence of MS has been reported, with the lowest prevalence reported for sub-Saharan Africa. The vast contextual differences between sub-Saharan Africa and developing countries may argue for a better understanding of MS in an African setting specifically.

Aims and Objectives: The main aims of this thesis were to better understand MS in an African context by reviewing research conducted in Sub-Saharan Africa in the past, and build upon that knowledge by evaluating demographics and characteristics of pwMS in an African country (South Africa [SA]). The objectives were to;

(i) scope the existing literature on MS, originating from sub-Saharan Africa (Chapter 2)

(ii) evaluate the characteristics and key symptoms of pwMS in SA (Chapter 3), and

(iii) investigate the agreement between the reported cut-off values for categorising severe fatigue, one of the key symptoms reported by patients with MS globally, by using three different questionnaires (Chapter 4).

Methods:

(i) A scoping review of the literature on MS from sub-Saharan Africa was undertaken.

(ii) A cross-sectional online survey was developed and distributed to all pwMS in SA affiliated with the Multiple Sclerosis Society of SA (n=1048). Measures were included across all domains of the International Classification of Functioning model.

(iii) The fatigue questionnaires (Fatigue Severity Scale (FSS), Fatigue Scale for Motor and Cognitive Functions (FSMC) and PROMIS Fatigue Short Form (SF)) included in the cross-sectional study were subsequently used to determine their agreement in identifying patients with severe fatigue using previous reported cut-off values, and Receiver Operating Curves were developed to determine new robust cut-off values which acknowledge the unidimensional character of each questionnaire.

Results: Thirty-three studies from sub-Saharan Africa were included for the scoping review. Four themes could be derived to group the included studies; aetiology (n=6), epidemiology (n=9), haematology (n=13) and other (n = 5). Majority of the studies (88%) were conducted in South Africa, and only few reports were from the last decade (9%). No comprehensive report on the characteristics and symptom experience of pwMS in sub-Saharan Africa was identified. Subsequently, 122 pwMS (11.6%) completed the anonymous survey (Age=47±10yrs, Male (%) =14). PwMS were generally moderately disabled (30.2%) according to the Patient Determined Disease Steps. Comorbidity was frequent, with 39.3% of pwMS reporting three or more comorbidities. The most common comorbidities being: depression (36.1%), high blood pressure and high cholesterol (20.5%) respectively, migraines (15.6%) and anxiety disorders (13.9%). The FSS, FSMC and PROMIS Fatigue SF categorised 73.9%, 78.9% and 30% respectively as severely fatigued. Using Cohen's Kappa, a significantly moderate

agreement was found between FSS and FSMC, (k = 0.563, p = 0.000), and not the PROMIS Fatigue SF. Cut-off values of 5.8 out of 7 for the FSS and 88.5 out of 100 for FSMC would provide 100% certainty a patient with these values (or higher) would have classified as having severe fatigue on both fatigue measures.

Conclusion: Despite an increased reporting of MS in sub-Saharan Africa, there is very little recent research on the epidemiology and characteristics of patients with MS in this context. Intervention studies specifically developed for an African context were absent. A triad of poor lifestyle behaviour, low levels of physical activity, and high burden of comorbidity were reported which are concerning in the light of the global burden of disease. Often hampered by the multi-dimensional character of fatigue, the developed robust cut-off values for fatigue could be used in future research where the presence of fatigue is important in for instance evaluating the benefits of interventions to tackle this key symptom. The results of this thesis can be used to set the stage for developing an African specific research agenda for MS.

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Abstrak

Agtergrond: Veelvuldige Sklerose (MS) affekteer ongeveer 2.3 miljoen mense wêreldwyd. 'N Geografiese gradiënt in die voorkoms van MS is aangemeld, met die laagste voorkoms vir Afrika suid van die Sahara gerapporteer. Die groot kontekstuele verskille tussen Afrika suid van die Sahara en ontwikkelende lande kan spesifiek argumenteer vir 'n beter begrip van MS in 'n Afrika-omgewing.

Doelwitte en doelstellings: Die hoofdoelwitte van hierdie proefskrif was om MS in 'n Afrika-konteks beter te verstaan deur navorsing in Afrika suid van die Sahara te hersien, en voort te bou op daardie kennis deur die demografie en eienskappe van pwMS in 'n Afrika-land (Suid-Afrika) te evalueer Afrika [SA]). Die doelwitte was om;
(i) bestudeer die bestaande literatuur oor MS, afkomstig van Afrika suid van die Sahara (Hoofstuk 2)
(ii) die eienskappe en sleutelsimptome van pwMS in SA (hoofstuk 3) te evalueer, en
(iii) die ooreenkoms tussen die gerapporteerde afsnywaardes vir die kategorisering van ernstige moegheid, een van die sleutelsimptome wat deur pasiënte met MS wêreldwyd gerapporteer word, ondersoek deur drie verskillende vraelyste te gebruik (Hoofstuk 4).

Metodes:
(i) 'n Omvangbepalingsoorsig van die literatuur oor MS uit Afrika suid van die Sahara is onderneem.
(ii) 'n Deursnee-opname is ontwikkel en versprei aan alle pwMS in SA wat geaffilieer is by die Multiple Sclerosis Society of SA (n = 1048). Maatreëls is ingesluit in alle domeine van die Internasionale Klassifikasie van Funksionele model.
(iii) Die uitputtingsvraelyste (Fatigue Severity Scale (Fatigue Severity Scale (FSS)), Vermoeidheidskaal vir Motoriese en Kognitiewe Funksies (FSMC) en PROMIS Fatigue Short Form (SF)) wat in die dwarssnitstudie ingesluit is, is later gebruik om hul ooreenkoms te identifiseer om pasiënte te identifiseer met erge moegheid deur gebruik te maak van vorige gerapporteerde afsnywaardes, en Ontvanger Bedryfskurwes is ontwikkel om nuwe robuuste afsnywaardes te bepaal wat die unidimensionele karakter van elke vraelys erken.
Resultate: Drie-en-dertig studies uit Afrika suid van die Sahara is ingesluit vir die omvangsbepaling. Vier temas kan afgelei word om die ingesluit studies te groepeer; etiologie (n = 6), epidemiologie (n = 9), hematologie (n = 13) en ander (n = 5). Meerderheid van die studies (88%) is in Suid-Afrika uitgevoer, en slegs enkele verslae was van die afgelope dekade (...%). Geen omvattende verslag oor die eienskappe en simptome-ervaring van pwMS in Afrika suid van die Sahara is geïdentifiseer nie. Vervolgens het 122 pwMS (11.6%) die anonieme opname voltooi (Ouderdom = 47 ± 10 jaar, Manlik (%) = 14). PwMS was oor die algemeen matig gedeaktiveer (30.2%) volgens die pasiëntbepaalde siektetoestande. Komorbiditeit was gereeld, met 39.3% van PwMS wat drie of meer comorbiditeite rapporteer. Die FSS, FSMC en PROMIS Moegheid SF het onderskeidelik 73.9%, 78.9% en 30% as ernstig vermoeid geraak. Met behulp van Cohen se Kappa is 'n beduidende matige ooreenkoms tussen FSS en FSMC gevind, (k = 0.563, p = 0.000), en nie die PROMIS-moegheid SF nie. Afsnywaardes van

5.8 uit 7 vir die FSS en 88.5 uit 100 vir FSMC sal 100% sekerheid bied. 'N Pasiënt met hierdie waardes (of hoër) sou geklassifiseer het as 'n ernstige moegheid op beide moegheidsmaatreëls.

Gevolgtrekking: Ondanks die toenemende rapportering van MS in Afrika suid van die Sahara, is daar baie min onlangse navorsing oor die epidemiologie en eienskappe van pasiënte met MS in hierdie konteks. Intervensiestudies wat spesifiek vir 'n Afrika-konteks ontwikkel is, was afwesig. 'N triade van swak lewenstyl gedrag, lae vlakke van fisiese aktiwiteit, en 'n hoë las van comorbiditeit is aangemeld wat aangaan in die lig van die wêreldwye las van siekte. Dikwels deur die multidimensionele karakter van moegheid belemmer, kan die ontwikkelde sterk afsnywaardes vir moegheid gebruik word in toekomstige navorsing waar die aanwesigheid van moegheid belangrik is, byvoorbeeld om die voordele van intervensies te evalueer om hierdie belangrike simptoom aan te pak. Die uitslae van hierdie proefskrif kan gebruik word om die verhoog te stel vir die ontwikkeling van 'n Afrika-spesifieke navorsingsagenda vir MS.

CHAPTER 1

Introduction and scope of thesis

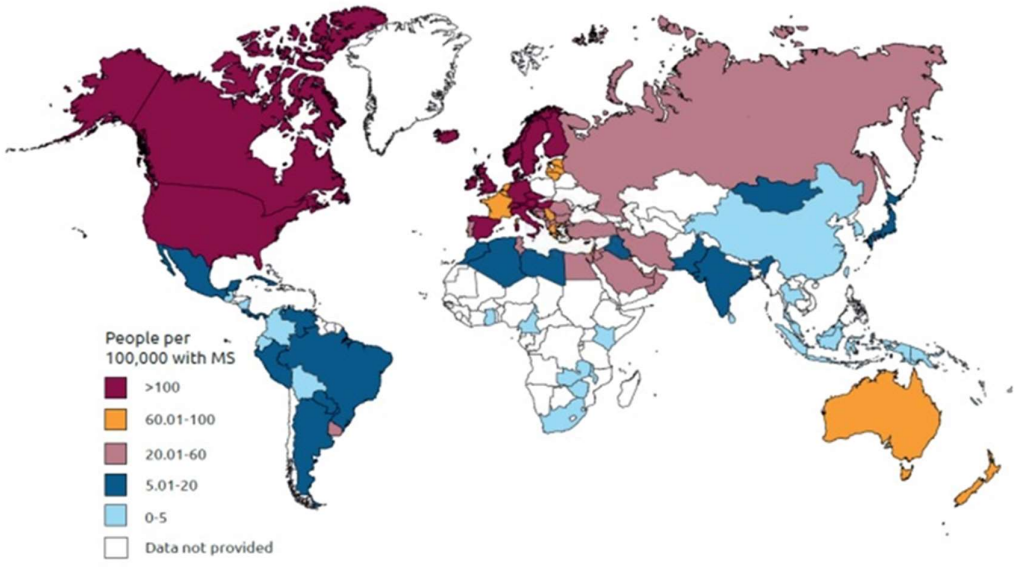
Multiple Sclerosis (MS) is a chronic neurologic disease which has an autoimmune-mediated inflammatory and neurodegenerative impact on the central nervous system (CNS). It predominantly affects individuals in their early adult life, and has a significant impact functionally, financially, and on quality of life.(1) The pathogenesis of MS is not fully understood but it is thought that when lymphocytic infiltration through the blood-brain-barrier into the CNS occurs, this causes inflammation of the myelin, which is the protective sheath of nerves.(2) The inflammation also affects the axons themselves, as well as the oligodendrocytes and microglia which are cells that are important in supporting and protecting the myelin.(2) For the most part, the initial damage to the affected axons, can be repaired through remyelination. Reoccurring inflammation of the myelin will lead to progressive and long term damage of the CNS due to remyelination not being a sustainable solution to repairing the inflamed axons.(3) This results in the overall volume and integrity of the brain being affected. This neurodegeneration of the CNS is thought to be the primary cause of the disability in persons with MS (pwMS). The initial incident of inflammation of the myelin may be due to the interaction between the role of both genetic and environmental factors.(2) The genetic contribution to developing MS, is likely due to the familial recurrence rate of about 20%.(2) The risk reduction changes from 3% in first-degree relatives (siblings, 5%; parents, 2%; and children, 2%), to 1% in second-degree and third-degree relatives.(1,2) There are specific genes associated with the development of MS and there is over 200 sequence allelic variants in multiple genes that increase a person's susceptibility to MS.(4)

The environmental factors that are known to contribute to the development of MS are a deficiency in Vitamin D, obesity in early life and cigarette smoking.(5–7) Checking and correcting Vitamin D concentrations may be an important prevention for developing MS.(1) Cigarette smoking risk associated with MS increases with duration and intensity and the risk is higher for men than woman.(1) There is a twofold increase in risk for men and woman who are obese early in life and may also be associated with lower vitamin D concentrations in obese individuals.(1) The involvement of the Epstein-Barr virus (EBV) as a contributing factor to the development of MS has been extensively studied. Studies have shown that people are at a higher risk of developing MS that have high concentrations of anti-EBV antibodies,(8) the association between MS development and EBV infection in children has also been found,(9) and there is a hypothesis that the EBV infects B cells which then produce autoantibodies and produce antigens to self-reactive T-cells.(10,11) These studies show that there are strong arguments pointing towards EBV's involvement in MS but as to how to deter its involvement (such as a vaccine development) is still up for discussion.(12)

Signs and symptoms of MS vary widely and depend on the amount of nerve damage and which areas of the CNS are affected. Some people with severe MS may lose their ability to walk independently or even are unable to walk at all, while others may experience long periods of remission without any new symptoms. Overtime, there is an accumulation of disability including comorbidities such as

hypercholesterolemia and hypertension, as well as fatigue, depression and cognitive dysfunction which affect the patient's quality of life and societal participation.(2,13–16)

Figure 1.1: Prevalence of Multiple Sclerosis per country (2013)(17)



©The MSIF Atlas of MS 2013

There are an estimated 2.3 million people living with MS globally.(14) Figure 1.1 shows the prevalence of MS per country globally. MS is common in regions populated by northern Europeans,(2) but this effect can be redistributed according to where people live early on in life.(1) Migration from high-risk to low-risk regions as a child is associated with a reduced risk and migrating from a low to a high prevalence part of the world increases the risk of developing MS.(2,18)

The information available of pwMS in sub-Saharan Africa is limited as historically, it has been thought that MS is not a disease of a predominant black population. Furthermore, a black patient that presents with an apparent MS phenotype is investigated for possible alternative explanations and often left with an unclear diagnosis or idiopathic/nonspecific CNS demyelination.(19) In a country such as South Africa (SA), the prevalence of MS is low (4 to 5 per 100 000) relative to the worldwide prevalence of MS which is 33 per 100 000.(13,14) It is perhaps due to the low prevalence of MS in SA, that there is a very little research on MS beyond the level of basic epidemiology.

While the profile of pwMS in the northern hemisphere is well documented, and factors contributing to the health state such as fatigue, depression, sleep issues, cognitive and motor function problems are well documented, it can be hypothesized that their relative contribution might to some extend be context specific. For example; this could be on a micro level (e.g. rural versus peri-urban setting), macro level (e.g. latitude, exposure to vitamin D), as well as country-specific (e.g. medical insurance which gives one access to private medical care vs use of the public health care system). Therefore, the main aims

of this thesis were to better understand MS in an African context by reviewing research conducted in Sub-Saharan Africa in the past, and build upon that knowledge by evaluating demographics and characteristics of pwMS in an African country (South Africa).

The research question for the first part of this MSc thesis was: what does the existing literature on MS in sub-Saharan African reveal about the epidemiology and symptoms of MS? The objective of this question was to gain a better understanding of the prevalence of MS in sub-Saharan Africa through a scoping review which will give knowledge of the current research of MS in sub-Saharan Africa and reveal gaps which can lead to future studies. The scoping review of MS in Sub-Saharan Africa is presented in Chapter 2.

The second research question was: how does MS present in an African country and do the symptoms and experiences of pwMS differ from pwMS in the northern hemisphere? The second objective was to gain insight into the specific characteristics and symptoms of persons living with MS in South Africa (SA). To that extent, a national cross-sectional online survey has been performed to describe the characteristics and symptoms experienced by pwMS in SA and identify the key gaps in our knowledge and give direction for future studies. The results from the cross-sectional study are presented in Chapter 3.

The third research question was: how can the fatigue questionnaires used in the online survey in Chapter 3, identify and explain fatigue in pwMS and be more relevant to pwMS who experience severe fatigue? In studying MS, the symptoms that a pwMS experiences becomes increasingly important to understand. The symptoms can be debilitating such as pain and fatigue and can affect every aspect of life. The symptoms can interfere in one's ability to work, interact socially and even sleep and eat. Fatigue is such a symptom experienced by majority of pwMS and is often hard to fully define as it's a subjective experience and therefore difficult to do research interventions. There is much research on fatigue in pwMS but there are studies showing that the evidence to support fatigue interventions is not methodologically robust to be able to use that information for the evidence-based management of fatigue in pwMS.

There are many questionnaires used in research and clinical practice to assess fatigue and its severity. It has been argued that often these questionnaires only assess a single aspect or dimension of fatigue, (20) and hence the use of more than one questionnaire in clinical research has been suggested to cover a broader aspect of the fatigue construct. Despite each questionnaire having specific, validated, cut-offs to identify "severe" fatigue, we're uncertain that if different questionnaires are used to assess severe fatigue, one would be 100% certain that all pwMS categorised as severely fatigued on one questionnaire would be also categorised as severely fatigued on another? Therefore, this leads to the third objective of this thesis, which was to describe new cut off points for three frequently used fatigue self-reporting questionnaires. These new cut-offs will then assist researchers in including all pwMS that suffer with

severe fatigue across multiple questionnaires in clinical research. The results for these new cut-offs are presented in Chapter 4.

Then finally, in Chapter 5 the joint findings of chapter 2 – 4 are discussed and recommendations for future research provided.

CHAPTER 2

A Scoping Review of Multiple Sclerosis Research in sub-Saharan Africa between 1967 and 2018

Abstract

Background: Multiple Sclerosis (MS) affects approximately 2.3 million people globally, with the prevalence of MS being highest in Europe and North America, and lowest in sub-Saharan Africa. However, despite the low prevalence, an increasing incidence of MS in sub-Saharan Africa in observed. The objective of this scoping review is to provide a synthesis of original studies in patients with MS (pwMS), originating from sub-Saharan Africa. This review facilitates a better understanding of the academic and health landscape involving patients with MS in Sub-Saharan Africa, and would assist identification of research gaps which can help inform future studies.

Methods: A scoping review was conducted on the 7th of September 2018 in the online databases PubMed, SCOPUS, Web of Science, and EBSCO Host. A descriptive analysis along with a qualitative synthesis of the included studies was conducted.

Results: Thirty-three studies from sub-Saharan Africa were included. The majority of identified studies (n = 29 [88%]) was conducted in South Africa. The studies were predominantly of cross-sectional design (n = 28 [85%]); no randomized clinical trials were identified. Furthermore, most studies (n = 23; 70%) focused on Caucasian pwMS. Three studies (9%) originated from the last decade. The objectives of the included studies could be grouped under four themes: aetiology (n = 6), epidemiology (n = 9), haematology (n = 13) and other (n = 5).

Conclusion: Most studies conducted in sub-Saharan Africa have focussed on increasing understanding of the aetiology and working mechanism of MS, predominantly in the context of the high incidence rates of MS in developed countries. Only few studies have been conducted with the primary aim of understanding MS patient care across the continuum, and management of MS in an African context. A better understanding of the working mechanisms behind the apparent increase of MS prevalence in sub-Saharan Africa, can inform academic and health systems, to facilitate evidence-based and contextualized management of MS.

2.1 Introduction

There are an estimated 2.3 million people living with Multiple Sclerosis (MS) globally.(14) The majority of persons with MS (pwMS) live in Europe and North America, (108 and 140 per 100,000 respectively) and the lowest incidence is in sub-Saharan Africa and East Asia, at 2.1 and 2.2 per 100,000 respectively.(17) The prevalence of MS in sub-Saharan Africa has not been fully investigated as historically, it has been thought that MS is not a disease of the black population.(21) A black patient that presented with an apparent MS phenotype has historically been investigated for possible alternative pathological explanations and often left with an unclear diagnosis or idiopathic/nonspecific central nervous system (CNS) demyelination.(21)

The earliest cases of MS recorded in sub- Saharan Africa were reported by Dean in a review in 1949, yet these were in Caucasian South Africans.(22) Subsequently, the first cases of MS in black Africans were recorded in 1970. Foster and Harries confirmed two cases in Kenya,(23) and in the timespan of a decade, 10 cases were confirmed in Uganda in between 1970 and 1980.(24) Since the 1980's only a handful of studies have reported cases of MS in black Africans,(13,25–30) which may indicate the low prevalence of pwMS in sub-Saharan Africa. However, more recent studies show increasingly that MS does occur, albeit rarely, in black Africans.(13,17,30) The Atlas of MS survey conducted in 2008, listed 3341 known cases of MS in sub-Saharan Africa which subsequently increased to 3992 cases by 2013.(17) The reasons for this increase in the prevalence of MS in sub-Saharan Africa may be multifactorial, and may include a growing awareness of MS, increased access to medical care, increased local medical expertise, increased number of neurologists, accessibility and availability of new diagnostic procedures, and resources.(31) Despite the apparent increasing incidence, little research has been conducted that focuses on the management of patients with MS in an African context. Hence, the objective of this scoping review is to provide an overview of original studies in patients with MS, originating from sub-Saharan Africa; with the aim to facilitate a better understanding of the academic landscape involving patients with MS in Sub-Saharan Africa, and would help to identify any research gaps which may help inform future studies.

2.2 Methods

This protocol was drafted using the PRISMA Extension for Scoping Reviews (PRISMA-ScR) [Please see Appendix F for the checklist].(32). A scoping review is used to assess broad topics in a specific area of research and the area of research has many different study designs. A scoping review is helpful when the research question is not very specific nor is assessing the quality of the included studies a priority.(33) Therefore, the scoping review was chosen due to the objective of this chapter which was to give an overview of studies of pwMS in sub-Saharan Africa so that research gaps can be identified to inform future studies. The following bibliographic databases were searched on the 7th of September 2018: PubMed, SCOPUS, Web of Science and EBSCO Host. The search strategies were discussed with an experienced librarian from the University of Stellenbosch, and further refined through discussion between the two reviewers. The final search strategy for PubMed can be found in Appendix A.

2.2.1 In/Exclusion criteria

Studies on multiple sclerosis that were: peer-reviewed, original research in humans, written in English, and conducted in sub-Saharan Africa were included. Non-original research (e.g. conference proceedings, letters, reviews, and guidelines) as well as case studies were excluded. Case studies were excluded due to them predominantly referring to uncertainty in the diagnostic process of MS in specific subsamples. The case studies provide little information on the study design or methods and some information on the practice of diagnosing MS at the time of the case studies. A single reviewer (DM) reviewed, removed duplicates and screened titles. Subsequently, two reviewers, (DM and MH), independently screened the titles and abstracts (if available) to determine if the articles fitted the inclusion framework for the review. Any disagreements were discussed until consensus was reached. Finally, full-text articles were sourced, and data was charted by a single reviewer (DM), and data extraction was verified by a second reviewer (MH).

2.2.2 Data extraction

The data-charting form was jointly developed by the research team, and the form was continuously updated through an iterative process. Any disagreements were resolved through discussion between the two reviewers. We extracted data on article characteristics (e.g., country of origin, year of publication), type of study (e.g., cross-sectional, prospective cohort or retrospective cohort), divided the articles into themes (e.g., epidemiology, aetiology, haematology etc.), study population, aim of the study, methodology and important results. Methodological quality of RCTs is determined using the Cochrane Risk of Bias tool if applicable.(34) No random controlled trials (RCTs) were identified in this review and therefore no critical appraisal of RCTs were required.

2.3 Results

After duplicates were removed, a total of 117 citations were identified from searches of electronic databases. Based on the title and the abstract, 50 were excluded, with 67 full text articles to be retrieved and assessed for eligibility. After the 67 full text articles were retrieved 33 studies were considered eligible for this review (see Figure 2.1). The included studies are presented in Table 2.1, and could be grouped according to the following themes: aetiology, epidemiology, haematology, and other. Under each theme, summaries of the country of origin, population, study design, aim, methodology and broad findings of each study were analyzed.

2.3.1 Study characteristics

The majority of the studies were conducted in South Africa (n=29; 88%), followed by Kenya (n=2; 6%), Uganda (n=1; 3%) and Zimbabwe (n=1; 3%). There were six studies related to the aetiology of MS, nine studies reported on the epidemiology of MS, thirteen studies reported on haematology in MS, and five studies could not be classified under the previous three groupings (i.e. other). The vast majority of the studies used a cross-sectional design (n=28), retrospective cohort analyses (n=4) and prospective

cohort analyses (n=1). The studies that were included in this review were published from 1967 to 2018 with 21 research papers published in the last decade. There was only one intervention study.(35) The majority of the studies focused on Caucasian pwMS (n=23; 70%), followed by pwMS from different ethnic backgrounds (n=7; 21%), studies on only black pwMS specifically (n=2; 6%) and mixed ancestry (n=1; 3%).

Table 1.1 Overview of included studies per subcategory, and ordered alphabetically.

Citation, author, date	CO	ST	Demographics	Aims of the study	Methodology	Key findings
				Aetiology		
(36) Davis 2014	ZA	CS	114 unrelated Caucasian ZA pwMS (98 females). 195 unrelated Caucasian controls without neurological diseases (128 females)	To investigate the mechanism underlying homocysteine accumulation in MS patients as there is a link between homocysteine and obesity as risk factors for MS	A total of 114 patients and 195 population-matched controls were analysed for the FTO rs9939609 polymorphism through DNA analysis Homocysteine concentrations were measured in a subgroup of 60 patients and 87 controls screened for multiple vascular risk factors through biochemical analysis. A questionnaire to determine diet scores and lifestyle factors	The risk-associated FTO rs9939609 A-allele was associated with raised homocysteine concentrations in pwMS, but not in controls. Homocysteine concentrations correlated positively with BMI and total cholesterol concentrations. Identifying the FTO rs9939609 means adequate fruit, vegetables and folate and a diet low in saturated fats is important.
(37) de Villiers 2006	ZA	CS	49 unrelated Caucasian ZA pwMS of European decent and 33 of their close relatives all with the SLC11A1 gene and 39 controls same age and population group.	To investigate the role of viral infection in ZA in pwMS in relation to specific SLC11A1 genotypes	Serum and peripheral blood mononuclear cells were screened for the presence of MS-associated retrovirus (MSRV) and two herpes virus (HHV-6 and EBV) sequences	MSRV had a significantly higher frequency HHV-6 and EBV less significant Viral sequences detected in the unaffected close relatives of pwMS MSRV primary causative for MS in ZA population
(38) Dean 1971	ZA	CS	123 Caucasian pwMS not born in ZA	To identify the age at which immigrants entered ZA and therefore determine the age of risk for developing MS	Survey of all British and Northern Europeans who entered ZA between 1900 to 1968	91 (53 British and 38 other Europeans) developed MS after immigration.12/91 were under 15 on arrival. Suggests early immigration to a low risk area reduces the risk of MS Mean onset is 37 years
(39) Fewster 1979	ZA	CS	74 Caucasian (46 born in ZA); 55 females and 12 Mixed ancestry; 10 females of ZA pwMS. 73 Caucasian and 11 Mixed ancestry sex matched controls	To determine the relationship of higher measles antibody titres and certain HLA antigens in pwMS in a low incidence setting (ZA)	Diagnosis of MS used Schumacher criteria Measles antibody titres were determined by the hemaglutination inhibition test and HLA antigens were determined serologically by a microlymphocytotoxicity test	52.1% Caucasian pwMS had significantly higher titres 57.1% Caucasian born pwMS had significantly higher titres No difference in the Mixed ancestry No significant differences in the tissue typing
(40) Fewster 1984	ZA	CS	24 unrelated Mixed ancestry ZA pwMS. 190 healthy, unrelated mixed ancestry controls with HLA-A, HLA-B and HLA-DR antigens	To determine HLA antigens in mixed ancestry pwMS in ZA	Diagnosis of MS used Poser criteria Lymphocyte typing used to test for the antigens	No significant difference between the pwMS and the controls for HLA-A and HLA-B antigens. A trend towards an association between HLA-DR2 Overall the HLA antigens significantly lower than the Caucasian pwMS (Fewster 1979) (39)
(41) Lowe 1980	ZW	CS	40 Caucasian ZW pwMS 35 immigrants, 5 born in Africa 705 Caucasian ZA controls	To determine HLA antigen in Caucasian ZW pwMS	Lymphocyte typing of 29 antigens	6/29 significant differences to the controls;HLA-A9 had the highest significant frequency HLA-A29, B7, B17 were also increased; HLA-A1 was higher in the controls; HLA-A28 was completely absent in pwMS

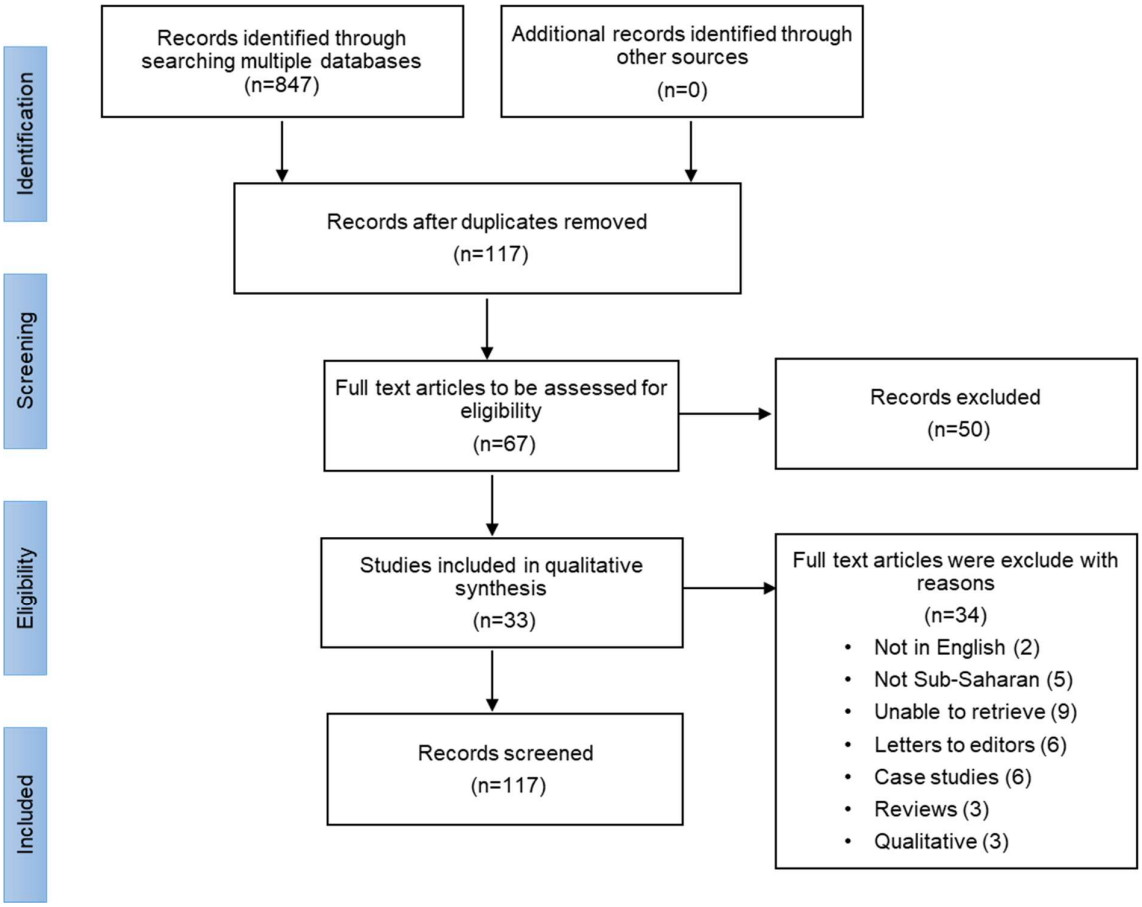
Citation, author, date	CO	ST	Demographics	Aims of the study	Methodology	Key findings
Epidemiology						
(25) Adam 1989	KE	PC	6 Black Kenyans (4 females)	Identify MS in the Black Kenyan population	Cases diagnosed by Poser criteria between Nov 1983-Oct 1988 at the Kenyatta National Hospital	Age of onset 12-30 years. No difference in the clinical presentation of MS to northern latitudes. Theory that MS is a childhood viral infection that is brought into the areas of low risk by the settlers from Europe.
(28) Bhigjee 2007	ZA	CS	167 medical charts of ZA (123 females)	To determine the period prevalence of MS in KZN in the different racial groups, using the revised McDonald's criteria.	All patients were contacted telephonically over a period of one month (July 2005) to determine whether they were still alive and still resident in KZN. Clinical, laboratory and treatment data were also extracted from the charts	MS in KZN is more frequent than previously believed. Occurs in all racial groups: Caucasians (105), Indians (48), Blacks (12) and mixed ancestry (2). Optic neuritis found in 26% of the pwMS. Age at onset ranged 15-75years. The clinical features were similar to the Western world
(42) Bird 1969	ZA	RC	42 Caucasian ZA pwMS (25 females)	To show the incidence of MS in ZA	PwMS records from a private consulting neurological practice in Johannesburg during the years 1959-July 1968. Diagnosis was a clinical using McAlpine criteria.	38 were born in ZA. The average age was 39.9 years. No Black ZA diagnosed. Theory of an infective basis is the cause of the increased incidence.
(43) Bird 1975	ZA	RC	53Caucasian ZA pwMS (33 females)	To compare environmental factors in ZA and Japan and the changes that took place for the increased incidence of MS	PwMS records from a private consulting neurological practice in Johannesburg during the years 1959-70	49 were born in ZA. Incidence rose from 5.46/1000 in 1962 to 7.69/1000 in 1970. Increased incidence of MS among the Caucasian ZA. No Black South Africans reported with MS. Theory: an infective element-probably from a high- risk area is the cause
(44) Dean 1967	ZA	CS	281 Caucasian ZA pwMS (158 born in ZA and 123 immigrants)	To show the incidence, prevalence and mortality of Caucasian pwMS in ZA	Patient records including death certificates from all over ZA from 1958 to 1966 were sought through doctors, hospitals, and the MS society.	101of the pwMS born in ZA were English speaking. 40/101 had both parents born in Europe. 22/101 had one parent born in Europe. Incidence was 0.6/100,000 for 1945-54. The prevalence rate for Caucasian ZA of 9.1/100,000 (males 5.4, females 12.8). English speaking 10.9/100,000. Mean age of onset was 31 years. The mean from onset to diagnosis was 8 years.
(12) Kanyerezi 1980	UG	RC	10 UG Africans (6 females)	To report cases of pwMS	Medical records from July 1969 – July 1979	Mean age 29 years 5 cases found in 1978-1979 Disease presents similarly to Europe
(27) Kioy 2001	KE	RC	9 KE; 7 females (2 Indo-Asian ethnicity)	To report the occurrence of MS among Black Kenyans who have never been out of the country	Patients referred to a private neurology and clinical electrophysiology clinic	Mean age of onset: 24years Mean duration since onset: 4 years MS had similar presentation to western countries Mean EDSS:4.5
(13) Modi 2008	ZA	CS	430 ZA pwMS	To determine qualitative data of pwMS in ZA	Country wide survey on the Multiple Sclerosis Society of ZA website	73% female; 3:1 female ratio; 71% 30-59 years old; 46% RRMS 89% Caucasian, 3% Mixed ancestry, 3% Indian, <1% Black 91% diagnosed by a neurologist
(45)Rosman 1985	ZA	CS	Caucasian ZA Afrikaans pwMS	Pilot study of incidence of MS in Caucasian Afrikaans	Study ran from 1 March 1984 to 28 February 1985. Poser et al. criteria used to diagnose	5 new cases diagnosed in 12 months. Annual incidence of 1.6/100 000.Significant rise in the incidence of MS in Caucasian Afrikaans-speaking South Africans

Citation, author, date	CO	ST	Demographics	Aims of the study	Methodology	Key findings
Haematology						
(16,18, 19,23–25) Hon * 2009; 2009c; 2009d; 2012c; 2013; 2014	ZA	CS	31 Caucasian ZA females pwMS and 30 Caucasian female controls	To determine in pwMS: the erythrocyte membrane fatty acid concentrations and correlate with EDSS; the fatty acid composition within the different phospholipid cell membrane; the differences in RBC membrane fluidity and permeability, as measured by the relationship between membrane phospholipids, fatty acids and cholesterol; the presence of EBV; the decrease in cell membranes fatty acid C20:4n-6 was associated with abnormalities in the prostaglandin E2 pathway and whether the prevalence of human herpesvirus-6 and varicella zoster virus could be associated with different stages of activity of the disease as well as the inflammatory status of the patients all in comparison to healthy controls	FA composition measured by GC Phospholipids measured using a colorimetric assay, Cholesterol by an enzymatic assay CRP by a Beckman nephelometer PCR and ELIZA assays for viral DNA and antibody screening for EBV Enzyme linked immunosorbent assays Polymerase chain reaction assays for human herpesvirus-6 and varicella zoster virus	C20:4n-6 concentrations lower pwMS and correlated inversely with the EDSS Specific long chain SATS may increase risk of developing MS Increased inflammation status in pwMS influences membrane fluidity due to membrane lipid composition Higher prevalence rates for EBV in pwMS, IgM association with relapse episodes showing viral re-activation a contributing factor to relapses in pwMS Increased prostaglandin E2 concentration in plasma decreases C20:4n-6 which could contribute to CNS damage in pwMS Human herpesvirus-6 or varicella zoster virus have no causative role in the aetiology of MS
(52–55) Hon # 2009b; 2011; 2012a; 2012b	ZA	CS	26 Caucasian ZA females pwMS and 30 Caucasian female controls	To investigate in pwMS: the fatty acid composition within the different membrane phospholipid fractions in peripheral blood mononuclear cells; whether the blood cell membrane monounsaturated fatty acids were associated with inflammation and disease outcome; the relationship between peripheral blood mononuclear cell membrane fluidity, permeability status, and disease outcome measured by EDSS; NEFA concentrations in blood cell membranes and to correlate possible changes with disease outcome all in comparison to healthy controls	Fatty acid composition and RBC membranes measured by GC; Phospholipids, FA and cholesterol composition in peripheral blood mononuclear cells determined by colorimetric assay, GC and enzymatic assays;	The elongation product of 20: 4n-6, 22: 4n-6, was significantly decreased in membrane phosphatidylethanolamine and phosphatidylserine and correlated inversely with severity of EDSS and CRP. The inflammatory aspect of MS may be connected to n-9 and n-7 FA and polyunsaturated FA Correlation studies showed lipid metabolic abnormalities between membrane fluidity which may show immune cell membranes involvement in disease progression. Decrease in NEFA results in metabolic abnormalities and in immune cell membranes would influence the cell function and have a positive correlation between FAs and MS progression.
(56) Kotze 2001	ZA	CS	104 Caucasian ZA Afrikaans pwMS and 522 Caucasian controls	To investigate the likelihood that iron dysregulation in association with infectious and/or autoimmune disease susceptibility may underlie the MS phenotype in a subgroup of patients	The functional Z-DNA forming repeat polymorphism of the NRAMP1 gene was analysed	Allele 5 of the NRAMP 1 is maintained in this population group but if it related to dysregulation of iron or modified susceptibility to viral infection and/or autoimmunity is unknown
(57) Kotze 2006	ZA	CS	118 Caucasian ZA pwMS and 102 healthy controls	To determine the impact of iron overload on clinical outcome of MS through HH mutations, H63D and C282Y	DNA screening	No significant difference between pwMS and controls for the mutations. 17 pwMS 17pwms heterozygous for C2827, 3 had below normal and none had above normal transferrin saturation concentrations
(35) van Rensburg 2006	ZA	CS	41 ZA pwMS; 32 Caucasians, 7 mixed ancestry, 2 Black (37 females) and 30 healthy matched controls	To determine iron status, folate and homocysteine in pwMS and to evaluate the effect of MS symptoms if deficiencies are addressed	In Caucasian females' serum	In Caucasian female's serum iron and ferritin concentrations were significantly lower than controls After 6-month intervention of nutritional supplements improvement on EDSS, reduced homocysteine concentrations at 6 months
Hon et al. used the same female sample which was divided into two groups: 31 female Caucasians* and 26 female Caucasians#. Five were excluded because they were using fatty acid supplements, interferon, or cortisone.						

Citation, author, date	CO	ST	Demographics	Aims of the study	Methodology	Key findings
Other						
(58) Roos 2016	ZA	CS	19 pwMS (16 female); 11 Indian, 4 Caucasian British, 3 Caucasian Dutch, 1 Mixed ancestry; 15 ZA born; 4 ZW born	To determine the role and usefulness of OCT in a local cohort of MS patients	PwMS being treated with interferon b-1B underwent OCT exam of both eyes. RNFL thickness and macular volume were measured and correlated with clinical disease characteristic, history of optic neuritis and level of disability	No significant difference in mean RNFL in eyes with a history of ON and those without Eyes with a history of ON did have significantly thinner RNFL Strong correlation between TMV and RNFL No correlation between RNFL and disability scores
(59) Shannon 1994	ZA	CS	24 ZA pwMS (21 females) (22 Caucasians; 2 Indian)	To identify the deficits underlying observed behavioural performance difficulties regarding the behavioural sequelae accompanying pwMS	Qualitative and quantitative assessment instruments used	Two subgroups: Subgroup 1 displayed fatigability, information overload and disturbed fine control and integration of skilled motor movement Subgroup 2 displayed disturbed attention, concentration and tracking and disturbed executive skills
(60) Herbert 2018	ZA	CS	107 Caucasians ZA pwMS (93 females)	To investigate the relationship between FA and disability and blood iron parameters associated with FA and/or disability	PwMS confirmed according to McDonald et al. Criteria. 11 of the females underwent DTI studies, EDDS assessment and MRI. Only EDSS ≤ 3 and ≥6 grouped and data analysed. Control of 12 healthy females.	Patients with high EDSS scores the mean FA was significantly lower than controls. Patients with low EDSS scores had similar mean FA values to controls. Positive association between FA and the iron parameters in all the white matter tracts. Whole patient group found inverse association between the EDSS and the %Tfsat showing reduced disability in the presence of higher blood iron parameters. Significant inverse association between disease duration and haemoglobin and %Tfsat
(61) Temlett 1988	ZA	CS	24 Caucasian ZA born pwMS (14 females)	To establish the diagnosis of MS in a group of patients with clinically acceptable criteria of the disease can be confirmed by MRI	Using the criteria of Rose and Poser the pwMS subdivided in clinically definite, probable or possible MS and then underwent MRI	9 clinically definite MS; 9 probable, 6 possible
(62) Klugman 2002	ZA	CS	30 ZA pwMS (29 Caucasian); 2:1 female ratio	To investigate the self-reports or perceptions of a group of ZA pwMS regarding the nature of any speech, language, hearing and swallowing difficulties experienced as well as the impact of these problems on QoL	Cross-sectional survey	70% of pwMS experienced speech and/or language problems; 61.9% of the 70% felt the speech/language impacted significantly on their QoL. 50% of pwMS experienced swallowing difficulties; 53.4% of the 50% say it impacted their QoL. 23.3% experienced hearing difficulties; 42.8% of these pwMS say hearing impacted their QoL

CO = Country; ST = Study Type; ZA = South Africa; ZW = Zimbabwe; KE = Kenya; UG = Uganda; CS = Cross-sectional study; PC = Perspective Cohort; RC = Retrospective Cohort, MS = Multiple Sclerosis; PwMS = persons with Multiple Sclerosis; EDDS = Expanded Disability Status Scale; RRMS = Remitting and relapsing MS; BMI = Body Mass Index; GC = Gas chromatography; FA = Fractional Anisotropy; DTI = Diffusion Tensor Imaging; RBC = Red Blood Cells; FA = fatty acid; MSRV = MS Retro virus; EBV = Epstein Barr Virus; HLA = human leukocyte antigen; CRP = C-reactive protein; SATS = Saturated fatty acids; CNS = Central nervous system; NEFA = non-esterified fatty acid; NRAMP-1 = natural resistance-associated macrophage protein-1; HH = hereditary haemochromatosis; OCT = Optical Coherence Tomography; RNFL = Retinal Nerve Fibre Layer; ON = Optic Neuritis; TMV = Total Macular Volume; %tfsat = percentage transferrin saturation; QoL = Quality of life .

Figure 2.1 Flow chart of data synthesis



Studies that could be grouped under the “aetiology” theme, focused on the human leukocyte antigen (HLA) presence in certain ethnic groups of pwMS and the presence of certain viruses such as measles and Epstein-Barr virus, (EBV) in pwMS as causes of MS. One study evaluated the link between homocysteine and obesity as risk factors for MS and another that looked at migrating from a high-risk area for MS to a low area of MS as a possible prevention for developing MS.

The studies that were grouped under the ‘epidemiology’ theme, focused on the incidence of MS. The earlier studies on epidemiology by Dean,(44) Bird,(42,43) and Rosman,(45) only identified Caucasians with MS in SA but the later studies by Bhigjee,(28) and Modi,(13) though less prevalent, showed MS in all ethnic groups. There are also more people being reported with MS in all the countries that reported pwMS. The two studies in Kenya reported an increase in the incidence of black pwMS.(25,27)

The studies grouped under the theme of ‘Haematology’ were all conducted in South Africa, and focused on blood parameters potentially involved in various physiological MS processes (e.g. demyelination). These factors were the involvement of fatty acids, phospholipids and cholesterol on the membranes of the red blood cells and the fluidity and permeability of the membranes. Two studies evaluated the association of EBV, Human herpesvirus-6 and varicella zoster virus as causative roles in the aetiology of MS.(49,51) Two studies evaluated the association of iron concentrations to certain genes in pwMS

compared to controls.(56,57) The only intervention study in this review focused on iron status, folate and homocysteine concentrations in pwMS. If any deficiencies in these concentrations were identified, these pwMS would be placed in an intervention group to address these deficiencies with either a multivitamin or specific iron or folate supplements.

The studies grouped under the theme 'other', covered research in Optical Coherence Tomography (OCT);(58) neuropsychology;(59) imaging;(60,61) and perceptions of symptoms.(63)

2.4 Discussion

To our knowledge, this is the first comprehensive scoping review of studies in pwMS that originate from sub-Saharan Africa. This review highlights that there is an increase in the number of reported cases of pwMS in sub-Saharan Africa, even though there have only been a few studies on the epidemiology of MS in sub-Saharan Africa in the last decade. Hence, it seems that despite increased access to diagnostic tools, and increased academic capacity, and potentially increased incidence of MS; interest in MS in the context of sub-Saharan Africa is meagre. The majority of the studies reviewed for this study, focused on the aetiology of MS. Aetiology of MS was of particular interest to earlier researchers due to the notion that MS was not present or less prevalent in black Africans. However, this thinking changed slowly over time as the increased access to diagnostic tools and understanding of MS improved with more research in the aetiology of MS. However, some important gaps in the existing body of evidence were identified that warrant future research.

First, the aetiology of MS in sub-Saharan Africa is difficult to investigate due to the need for laboratory equipment and tests that many sub-Saharan countries would not be able to afford. Thus, the situation might represent a significant under diagnosing (and management) of MS in sub-Saharan Africa. To illustrate, a study by Langer-Gould et al. (64) did not find a different prevalence of MS amongst Caucasian and black males. Hence, the epidemiological differences reported in Africa, could above all, be related to access to resources. This may also partly explain why studies conducted with expensive equipment like neuroimaging were done in South Africa. Increased access to resources in other African countries may further increase our knowledge and understanding of MS in sub-Saharan Africa.

Despite this limitation, there is evidence of an increase in the detection of MS in sub-Saharan Africa.(17) Yet, the most recent studies were conducted in 2008 (in South Africans with MS).(13) Hence, a second important gap relates to aetiology and how it relates to the actuality of research findings. To further illustrate, the studies from Kenya are from 2001,(27) and Uganda from 1980.(24) Hence, recent statistics on the incidence of MS across the entirety of sub-Saharan Africa are lacking. Nonetheless, the Atlas of MS has numbers of pwMS in sub-Saharan Africa which they located through key people investigating MS in a number of countries in sub-Saharan Africa.(17) A comparison of the Atlas data published in 2008 and 2013 indicates a higher prevalence of MS across many ethnic backgrounds. There are various reasons one may postulate for this finding, such as increased awareness and resources to diagnose MS in sub-Saharan Africa. Communicable disease like HIV, TB and more recently non-communicable diseases of lifestyle have been of higher priority in the context of mortality

and disability in sub-Saharan Africa. Logically, resources and funding are diverted to the study of these "colliding epidemics".

In the light of increasing incidence, prevalence, and awareness of MS in sub-Saharan Africa, there were very few studies on fatigue and lifestyle related factors on pwMS, which supports that a stronger focus on research for the management of MS in a sub-Saharan African context is warranted. While there is ample knowledge on the management of pwMS originating from western countries with a high prevalence of MS, it has been structurally shown in other medical conditions that simply trying to implement these evidence-based management strategies in a complex African setting are set-up for failure. Hence, a third important gap in the existing body of knowledge lies with the management of MS in the African (resource-limited) context. For example, a better understanding of physician awareness and patient referral schemes, availability of disease-modifying therapies, (low-cost yet effective) rehabilitation models, and more insight into the specific symptom "burden" of pwMS in various sub-Saharan African contexts would be beneficial to health care practitioners dealing with pwMS in order to optimize care.

2.4.1 Limitations

There were certain limitations to this scoping review. First, the limited academic capacity, and awareness of MS in many sub-Saharan African countries, may lead to an underestimation of MS epidemiology. It can be questioned to what extent local research from sub-Saharan African countries find its way into established, English, peer-reviewed journals. Second, we excluded case-studies from this review that may contribute slightly that skewed picture. However, the number of case-studies was limited: three from Ethiopia, Senegal and Cameroon with single accounts of pwMS.

2.4.2 Conclusions

Research on MS originating from sub-Saharan Africa has largely been focussed on aetiology and epidemiological studies. No studies were found describing the symptom experiences and management of pwMS. Moving forward, in the light of increase awareness and resources to diagnose MS, it is recommended to shift focus to the patient symptom experience and management while in parallel create a better understanding on the epidemiology of MS across ethnicities.

CHAPTER 3

A Cross-sectional online Study on the characteristics, comorbidities and symptoms experienced by individuals with Multiple Sclerosis in South Africa

Abstract

Background: The prevalence of Multiple Sclerosis (MS) in South Africa (SA) is low (4/5 per 100 000) and there is limited research on MS beyond the level of basic epidemiology. The profile of patients with MS (pwMS) in the northern hemisphere is well documented, and factors contributing to the health state of pwMS such as fatigue, depression, sleep issues, cognitive and motor function problems are well documented. However, it can be hypothesized that the relative contribution of these factors might be context specific.

Objective and Methods: the objective of this study is to develop a profile of MS in SA, with the aims to gain insights into the various lifestyle factors that impact South African pwMS. A cross-sectional survey was sent out through the MS Society of South Africa to 1048 pwMS across the eleven provinces of SA in April 2017. The participants were asked to complete the survey within 24 hours from start to finish with no longer than a hour break between stopping for breaks. The participants were reminded to do the survey after two weeks and after four weeks if they had not completed it already. Outcomes were included across all domains of the International Classification of Functioning model (Health condition, Body Function, Activity, Participation, Environmental- and Personal factors).

Results: 122 of 1048(11.6%) completed the survey (Age=47±10 yr, Male(%)=14, disease duration=11±9 yr). PwMS were generally moderately disabled (30.2%) according to the Patient Determined Disease Steps. Comorbidity was frequent, with 39.3% of pwMS reporting three or more comorbidities. Detrimental lifestyle behaviour was prevalent with 64% of pwMS being inactive and 66% reported having smoked at some time in their lives. In contrast, fatigue assessed using the PROMIS fatigue short form was relatively low (30% severe fatigue).

Conclusion: The characteristics and symptoms experience of pwMS in in SA was much in line with those for developing countries. A triad of poor lifestyle behaviour, low levels of physical activity, and high burden of comorbidity warrant future research.

3.1 Introduction

The prevalence of Multiple Sclerosis (MS) in South Africa (SA) is low (4 to 5 per 100.000) relative to the worldwide prevalence which is 33 per 100.000.(13,14) However, it has also been reported that the incidence of MS in SA is increasing.(13) Yet, due to the low prevalence of MS in SA, there is a lack of research on MS beyond the level of basic epidemiology. A scoping review on original research originating from Sub-Saharan Africa in patients with Multiple Sclerosis(pwMS) identified thirty-three studies; with the predominant portion of these studies investigating the aetiology of MS, while only a handful studies (n=5) addressed a more clinical orientated topic (e.g. perceptions of pwMS, neuroimaging, neuropsychology). (See Chapter 2 of this thesis)

The clinical characteristics, signs and symptoms of pwMS in the northern hemisphere is relatively well documented, and factors contributing to the health status of pwMS such as fatigue, depression, sleep issues, cognitive and motor function problems have been well studied. However, it can be hypothesized that the relative contribution of these factors might to some extent be context specific. In other words, the characteristics, symptoms and health state of pwMS could be dissimilar on a micro level (e.g. rural versus urban setting), macro level (e.g. latitude, exposure to vitamin D), as well as country-specific (e.g. medical insurance which gives patients access to private medical care vs the public health care system). Hence the objective of this study is to describe the characteristics and symptoms of pwMS in SA, with the aim to gain insight into these country-specific characteristics and symptoms experiences of pwMS living in SA, and in particular those that would warrant future research to optimize the health care and well-being of South African pwMS.

3.2 Methods

3.2.1 Study Design

A cross-sectional online survey conducted through the MS Society of South Africa (MSSA) (Appendix C). This study was approved by the Health Research Ethics Committee, Stellenbosch University (N17/02/017) (Appendix B). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Appendix F) were used in reporting this cross-sectional study.(64)

There are currently 1050 pwMS affiliated to MSSA. A digital survey, using the REDCap (Research Electronic Data Capture, University of Stellenbosch, Cape Town, South Africa) data collection platform,(65) was sent out to all MSSA registered pwMS across the eleven provinces of South Africa in April 2017. The aim was to recruit all known pwMS in SA according to the MSSA. The study sample would be determined by the responses received. PwMS received a link to complete the survey directly from the MSSA to ensure anonymity. PwMS were provided with standardised information and instructions before beginning the survey, and on accepting the information, provided digital informed consent. Reminders were sent out at two weeks and four weeks after the initial email, to encourage participation in the study if they had not done so already. The survey was estimated to take one hour to complete and the respondents were able to stop and save to complete the survey later but were

encouraged to complete the entire survey in a single day. The demographic characteristics of the pwMS that were assessed included: age (years); sex (male/female); ethnicity and 1st and 2nd line family background (due to the genetic component in the incidence of MS);(2) self-reported body weight (kg) and height (cm); which are used to derive the body mass index (BMI) and classified as underweight (<18.5); normal weight (18.5-24.9); overweight (25.0-29.9); obese (≥30.0).(66)

3.2.2 Outcomes

The descriptive measures were selected based on their reported relevance for pwMS and aligned with the International Classification of Functioning (ICF) model (see Figure 3.1).(67) The ICF model identifies three core components of functioning, namely body functions and structures, activities and participation. These components subsequently interact with a persons' health condition as well as contextual factors (both environmental and personal). The respective outcome measures were chosen on pragmatic choice due to time to complete, the reported use in a SA context and together a comprehensive scope of the characteristics and experiences/perceptions of MS in SA.

3.2.2.1 Health Condition

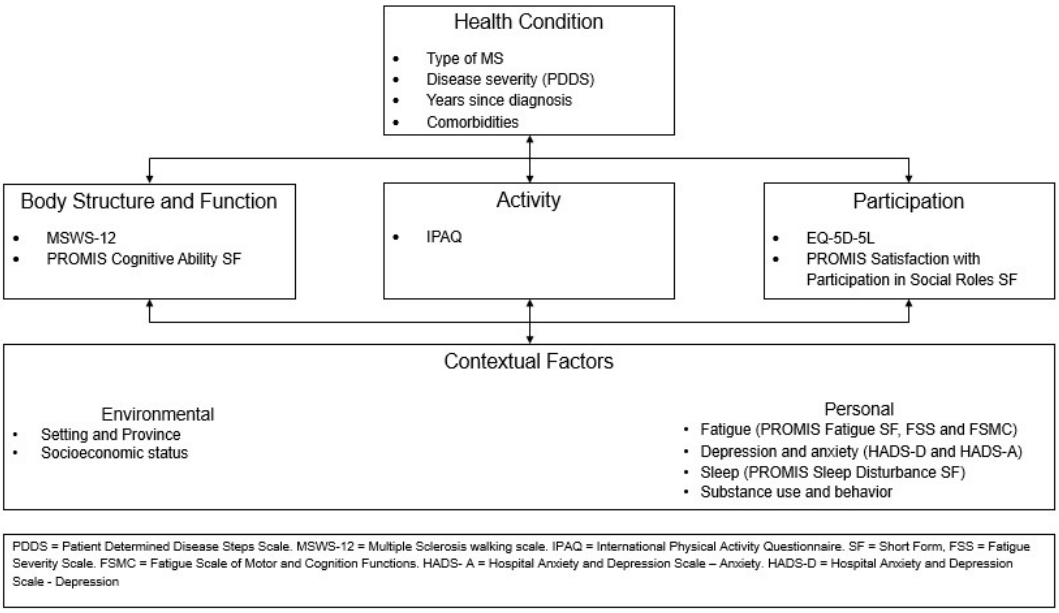
The following outcomes were included under "Health condition": type of MS, disease severity, time since diagnosis, and comorbidity profile. To determine self-report type of MS, the respondents were given a short lay-term description of each MS phenotype (e.g. relapsing – remitting, primary progressive). To determine the participant's disability level, the Patient-Determined Disease Steps (PDDS) was used.(68) The PDDS has nine ordinal levels ranging between 0 (Normal) and 8 (Bedridden) and can be categorized as mild (0-2), moderate (3-5), or severe (6-8) disability.(68) A validated self-report questionnaire for comorbidity developed for MS was used including 37 secondary health conditions.(69) HIV/AIDS and Tuberculosis were added to this list due to their specific relevance for the South African setting.

3.2.2.2 Body structure and function

Body structure and function focuses on the physiological functions of the body's systems (including psychological functions) and the anatomical parts of the body such as organs, limbs and their components.(67) To assess mobility and gait function, the MS Walking Scale-12 (MSWS-12) was used; a 12-item self-report questionnaire where the outcome is a score between 0 – 100. Higher scores indicate greater impact of MS on walking. Strong associations have been reported between the MSWS-12 and other MS-related disability outcome measures (Expanded Disability Status Scale and Multiple Sclerosis Impact Scale – 29).(70,71)

Cognitive function was assessed using the PROMIS Cognitive Ability Short Form (SF).(72) This 8-item short form uses a 5-point Likert scale (Never-Always) to assess patient-perceived functional abilities with regards to cognitive tasks. To calculate all the PROMIS scores, the guidelines from the PROMIS assessment centre's scoring manual were used.(73) A higher PROMIS T-score represents more (e.g. more cognitive ability) of the specific concept that is measured.

Figure 3.1 ICF model for the characteristics of MS©



3.2.2.3 Activity

Activity, according to the ICF model, focuses on the execution of a task or action by an individual and the difficulties an individual may have in executing activities. Physical activity over the past 7-days was assessed using the International Physical Activity Questionnaire (IPAQ). The IPAQ comprises of 22 questions over 5 different domains: work-related, transportation, housework, recreation and sitting. The responses to these 22-items are subsequently translated into metabolic equivalents (METs; i.e. energy expenditure) and MET minutes, and the sum of METs can be classified into three different levels of physical activity (inactive, minimally active and health enhancing active). These classifications have been reported to correspond well with objectively assessed step count.(74)

3.2.2.4 Participation

Participation evaluates the participant's involvement in life situations and the problems an individual may experience in certain life situations. The ability to participate socially was assessed using the validated PROMIS Satisfaction with Participation in Social Roles Short Form (SF), which is a 8-item measure.(75) The ability to engage in social activities (e.g. "I have trouble doing all of the family activities that I want to do") is rated on a 5-point Likert scale (Never to Always).(75) The response scores from the items are totalled and analysed in similar fashion as the PROMIS Cognitive Ability SF. A higher outcome (i.e. T-score) means a better perceived social participation.

The EQ-5D-5L is widely accepted as a valid, responsive and short (5 items) tool to assess the general health-related quality of life relative to the general population.(76) The descriptive system has five dimensions: Mobility, Self-care, Usual activities, Pain/discomfort and Anxiety/depression each rated on a 5-point Likert scale (No problems – Extreme problems). The responses for each of these dimensions

are then aggregated into a weighted health index using a reference value set.(77,78) The descriptive dimensions are complemented by a single general health question using a 0 (worst health) to 100 (Best health) visual analogue scale.

3.2.2.5 Contextual Factors

Environmental factors included: sociodemographic context (i.e. rural / peri-urban / urban setting); and socioeconomic status (i.e., net household income expressed using Purchasing Power Parity (PPP; International dollar).(79)

Personal factors included respondents' experience of fatigue, anxiety, depression, sleep disturbances and health related behaviour (i.e. smoking and alcohol consumption). Fatigue, is one of the more highly frequent (>80%) reported disabling symptom experienced by pwMS.(80) The self-reported questionnaires used to assess fatigue are: the PROMIS Fatigue Short Form (SF); the Fatigue Severity Scale (FSS) and the Fatigue Scale of Motor and Cognition (FSMC). The PROMIS Fatigue SF is 8 items and the responses are rated on a 5-point scale ranging from 'Never' to 'Always' and are summed and transformed to a T-score metric. Higher scores indicate more fatigue.(81) The response scores from the items are totalled and analysed in similar fashion as the PROMIS Cognitive Ability SF. The FSS is 9 items and has been known to assess the impact of fatigue on daily functioning;(82) The scale is a 7-point Likert Scale where 1= Strongly Disagree and 7= Strongly Agree. The Score range is 1-7 and a higher score indicates more severe fatigue. To determine a score a mean score is calculated. Scores ≥ 4 indicates severe fatigue.(83) The FSMC has 20 items, with separate domains for motor and cognitive aspects of fatigue.(84) The item responses are rated on a 5-point Likert Scale ranging from, "Does not apply at all" to "Applies completely". The score range is from 20-100 for an overall sum fatigue score. There is a score for cognitive fatigue and physical fatigue. The cut-off values for the summed score is ≥ 63 Severe fatigue, ≥ 53 Moderate fatigue and ≥ 43 Mild fatigue; the Cognitive Score is ≥ 34 Severe fatigue, ≥ 28 Moderate fatigue and ≥ 22 Mild fatigue; and Physical Score is ≥ 32 Severe fatigue, ≥ 27 Moderate fatigue and ≥ 22 Mild fatigue.(84) These measures, validated in patients with MS, combined, provide a comprehensive assessment (severity, impact, motor, and cognitive) of one of the most debilitating symptoms of patients with MS. Due to fatigue's subjective nature and the lack of consensus regarding definition, including multiple complementary measures to assess fatigue is recommended.(85) The Hospital Anxiety (HADS-A; 7 items) and Depression (HADS-D; 7 items) scale was used to assess the presence of anxiety and depressive symptoms respectively.(86) Each item is scored 0 to 3, and a summed score of 0 to 7 is defined as 'Normal', 8 to 10 defined as a 'Mild', 11 to 14 as a 'Moderate' and 15 to 21 as a 'Severe' case of anxiety or depression respectively.(87) Finally, sleep disturbances were assessed using the PROMIS Sleep Disturbance Short Form (SF) which is an 8-item measure, and analysed in line with the other PROMIS measures.

Smoking status was assessed using three items from the Behavioural Risk Factor Surveillance Survey.(88) A smoker was defined as having smoked ≥100 cigarettes in his/her lifetime. Alcohol intake was assessed with the AUDIT-C.(89) A score of ≥4 (men) or ≥3 (women) was considered positive for an increased risk for hazardous drinking, active alcohol abuse, or alcohol dependence.(90)

3.2.3 Data-analysis

A Shapiro-Wilk's test ($p>0.05$) and visual inspection of their histograms, normal Q-Q plots and box plots with skewedness and kurtosis were used to analyse if the data were normally distributed.(91) For data that were normally distributed, mean and 95% confidence level (95%CI) are reported. For data that were not normally distributed median and interquartile range (IQR) are presented. Descriptive statistics were used to characterise the cohort of pwMS with respect to all the outcomes presented in the survey. All analyses were conducted using IBM SPSS® version 25 software (IBM SPSS Statistics, IBM Corporation, Armonk, New York). A p-value >0.05 was considered statistically significant.

3.3 Results

3.3.1 Demographics

The survey was sent out to 1050 pwMS across all eleven provinces of South Africa. The survey was not delivered to two email addresses therefore, 1048 pwMS received the survey. There were 122 pwMS (11.6%) that responded to the survey of which 84 completed all the questions in the survey. Therefore, the sample size was 122 which was determined by the number of respondents to the survey. The demographic findings are summarised in Table 3.1, outcomes on the three domains of functioning in Table 3.2, and contextual factors in Table 3.3. The majority of the respondents were Caucasian (95%), and female (ratio of 6:1) with a mean age of 47 years (95%CI 46 to 49), and a median BMI of 28.9 (IQR 17.8-56.8). Out of the 122 respondents, 70% were classified as either overweight or obese according to the defined weight categories. The percentage of pwMS presenting with relapsing remitting MS was 68.1%, followed by secondary progressive MS (20.7%), and primary progressive MS (11.2%). The median PDDS score was 2 (IQR 1 to 3), and subsequently 30.2% of the respondents could be classified as moderately disabled. The percentage of respondents reporting no physical comorbidities was 31.1%, while 21.3% reported one, 8.2% reported two and 39.3% reported three or more comorbidities. The most frequent comorbidities reported were depression (36.1%), high blood pressure and high cholesterol (20.5%) respectively, migraines (15.6%) and anxiety disorders (13.9%). See Appendix D for a full description of the comorbidities assessed and reported.

3.3.2 The three domains of functioning (Body structure and function, activity and participation)

The median score of the MSWS-12 was 50 (IQR 0-100) reflecting a wide array of walking ability within the sample. The majority of the respondents (87.2%) fell within normal limits of cognitive abilities, as indicated by a median score of 44 (IQR 27 to 65) on the PROMIS Cognitive Abilities Scale and respective classification. The median total MET minutes was 594 (IQR 0-14.385) with 63.7% of the respondents categorised as inactive and 5.5% were engaging in health enhancing activity. The mean

score for the PROMIS Satisfaction with Participation in Social Roles scale was 55 (95%CI 53 to 57), and 49.4% of the respondents fell within normal limits of social participation while 6.7% struggled severely with social participation. The median index value for the EuroQol EQ-5D-5L was 0.6 (IQR -0.2 to 1.0). The mean EQ VAS score for general health was 57.5 (95CI 52.4 to 62.6).

3.3.3 Contextual Factors:

3.3.3.1 Environmental

Geographically, most respondents were living in either the Western Cape Province (38.5%), Gauteng (26.5%) or Free State (15.6%). Half of respondents are residing in an urban (50.4%) area, 39.5% in a peri-urban, and 10.1% in a rural context. With respect to socio-economic profile, 13.4% of the respondents received a monthly household income within the upper middle and higher bracket. In contrast, 2.5% of the respondents received a household income within the lowest bracket. The emerging middle to lower middle-income bracket had the highest pwMS at 37%.

3.3.3.2 Personal factors

The PROMIS Fatigue SF median score was 59 (IQR 33 to 78). Additionally, based on established cut-off values, 41.1% of the respondents were classified as moderately fatigued while 30% of the respondents classified as severely fatigued. The FSS median score was 5.17 (IQR 1-7) with 73.9% of the respondents graded as severely fatigued. The FSMC median scores were 39 (IQR 10-50) for the cognitive domain, 41 (IQR 13-50) for the physical domain, and 78.5 (IQR 23-100) for the sum score. The cut off values for FSMC Cognitive, classified 68.9% of the respondents with severe cognitive fatigue, 82.2% with severe physical fatigue and 78.9% with an overall severe fatigue. The mean HADS score was 17.6 (95%CI 16.2 to 19.1). The mean anxiety score was 8.8 (95% confidence level 7.9-9.8). The mean depression score was 8.8 (95%CI 8.2 to 9.5). The PROMIS Sleep Disturbance mean score was 53 (95%CI 50 to 55) and 27.2% have moderate to severe sleep disturbances while 52.3% reported to have minimal sleep disturbances. With respect to alcohol use, 32.3% of the respondents scored positive on the Alcohol Use Disorders Identification Test (AUDIT-C). With respect to smoking, 65% of the respondents were considered smokers.

Table 2.1: Demographic Variables and Clinical Characteristics of Persons with Multiple Sclerosis in South Africa

Demographic Characteristics	
Age (yrs) (n=122)	47 (46-49)#
Height (cm) (n=100)	166.8 (165.2-168.3)#
Weight (kg) (n=100)	80.4 (76.8-83.9)#
BMI (n=100)	28.9 (17.8-56.8)*
Categorical Variables	**N (%)**
Sex (n = 122)	
- Female	105 (86.1)
- Male	17 (13.9)
Ethnicity (n = 122)	
- White	116 (95.1)
- Mixed ancestry	3 (2.5)
- Asian/Indian	2 (1.6)
- Black African	1 (0.8)
Marital Status (n=119)	
- Living with a partner	84 (70.6)
- Single	21 (17.6)
- Divorced	10 (8.4)
- Widowed	4 (3.4)
BMI (n=100)	
- Underweight	4 (4)
- Normal	26 (26)
- Overweight	28 (28)
- Obese	42 (42)
Continuous Health Condition Variable	
Time since diagnosis (yrs) (n=116)	7 (1-38)*
PDDS (n=116)	2 (1-3)*
Categorical Variables	**N (%)**
Type of MS (n=116)	
- RRMS	79 (68.1)
- SPMS	24 (20.7)
- PPMS	13 (11.2)
PDDS (n=116)	
- Mild	55 (47.4)
- Moderate	35 (30.2)
- Severe	26 (22.4)
Number of comorbidities (n=122)	
- None	38 (31.1)
- One comorbidity	26 (21.3)
- Two comorbidities	10 (8.2)
- Three or more comorbidities	48 (39.3)

= mean (95%CI = 95% confidence interval). * = median (IQR = Interquartile range). BMI = Body Mass Index. RRMS = relapsing-remitting multiple sclerosis. SPMS = secondary-progressive multiple sclerosis. PPMS = primary-progressive multiple sclerosis. PDDS = Patient Determined Disease Steps scale

Table 3.2: The Body Structure, Activity, Social Participation and Environmental Outcomes in Persons with Multiple Sclerosis in South Africa

Body Structure Variables	
MSWS-12 (n=84)	50 (0-100)*
PROMIS cognitive abilities scale (n=94)	44 (27-65)*
Activity Variable	
IPAQ Total Met minutes (n=91)	594 (0-14385)*
Participation Variables	
EQ-5D-5L Index value (n=90)	0.6 (-0,2-1,0)*
EQ VAS score (n=90)	57.5 (52,4-62,6)#
PROMIS Social (n=90)	55 (53-57)#
Categorical Variables	**N (%)**
PROMIS cognitive categories (n=94)	
- Within normal limits	82 (87.2)
- Mild	6 (6.4)
- Moderate	6 (6.4)
- Severe	0
IPAQ (n=91)	
- Inactive	58 (63.7)
- Minimally active	28 (23)
- Health enhancing active	5 (5.5)
PROMIS Social* (n=89)	
- Within normal limits	44 (49.4)
- Mild	22 (24.7)
- Moderate	17 (19.1)
- Severe	6(6.7)
Environmental Variables	**N (%)**
- Setting (n=119)	
- Urban	60 (50.4)
- Peri-urban	47 39.5)
- Rural	12 (10.1)
Income Level (PPP) (n=119)	
- Upper middle and higher ($23.990->$113.433)	16 (13.4)
- Emerging middle to lower middle ($10679-$23990)	44 (37)
- Low emerging middle ($5774-$10679)	13 (10.9)
- Second lowest ($4030-$5774)	9 (7.6)
- Lowest (<$2672)	3 (2.5)
- Didn't want to disclose	34 (28.6)

= Mean (95%CI = 95% confidence interval). * = Median (IQR = Interquartile range). MSWS-12 = Multiple Sclerosis walking scale. IPAQ = International Physical Activity Questionnaire. EQ-5D-5L = EuroEqol EQ-5D-5L. EQ VAS=EuroQol Visual Analogue Scale. PROMIS Social = PROMIS Satisfaction with Participation in Social Roles. PPP = Purchasing Power Parity

Table 3.3: The Fatigue, Social Participation, Sleep and Substance Abuse Outcomes of the Persons with Multiple Sclerosis in South Africa

Personal Variable	
PROMIS fatigue (n=90)	59 (33-78)*
FSS (n=88)	5.17 (1-7)*
FSMC Cognitive (n=90)	39 (10-50)*
Motor (n=90)	41 (13-50)*
Sum Total (n=90)	79 (23-100)*
HADS-D (n=90)	8.8 (8.2-9.5)#
HADS-A (n=90)	8.8 (7.9-9.8)#
HADS Total (n=90)	17.6 (16.2-19.1)#
PROMIS Sleep (n=88)	53 (50-55)#
Categorical Variables	**N (%)**
PROMIS fatigue (n=90)	
- Within normal limits	15 (16.7)
- Mild	11 (12.2)
- Moderate	37 (41.1)
- Severe	27 (30)
FSS (n=88)	
- Score <4	23 (26.1)
- Score >4	65 (73.9)
FSMC Cognitive (n= 90)	
- Within normal limits**	11 (12.2)
- Mild	6 (6.7)
- Moderate	11 (12.2)
- Severe	62 (68.9)
FSMC Motor (n=90)	
- Within normal limits**	6 (6.7)
- Mild	4 (4.4)
- Moderate	6 (6.7)
- Severe	74 (82.2)
FSMC Sum Total (n=90)	
- Within normal limits**	8 (8.9)
- Mild	6 (6.7)
- Moderate	5 (5.6)
- Severe	71 (78.9)
HADS-D (n-90)	
- Within normal limits	31 (34.4)
- Mild	29 (32.2)
- Moderate	28 (31.1)
- Severe	2 (2.2)
HADS-A (n=90)	
- Within normal limits	40 (44.4)
- Mild	17 (18.9)
- Moderate	23 (25.6)

- Severe	10 (11.1)
Categorical Variables continued	**N (%)**
PROMIS Sleep (n=88)	
- Within normal limits	46 (52.3)
- Mild	18 (20.5)
- Moderate	20 (22.7)
- Severe	4 (4.5)
Substance use	
Alcohol (n=99)	
- Female ≥3	30 (30.3)
- Male ≥ 4	2 (2)
Smoking (n=100)	
- Smoker	63 (63)
- Non-smoker	37 (37)

= mean (95%CI = 95% confidence interval). * = median (IQR = Interquartile range). HADS-D = Hospital Anxiety and Depression scale – Depression. HADS-A = Hospital Anxiety and Depression Scale – Anxiety. ** = FSMC does not have "within normal limits" as part of its cut offs so to make it easier for comparison with PROMIS Fatigue SF, "within normal limits" were added to scores that fell below the cut off set for mild fatigue.

3.4 Discussion

This study is the first cross-sectional study in SA to focus on various clinical features and outcomes, structured according to the ICF model. The survey response rate was low which means that there is uncertainty as to whether the results are able to be generalised to the South African MS population of to the global MS population. The results do give a good indication as to symptoms and characteristics experienced by pwMS in SA and further investigations into these aspects need to be considered.

Two findings that show discrepancy between this sample and the global population of MS is the female to male ratio and the mean age of pwMS. The female to male ratio in this study was found to be 6:1 whereas the global ratio of female to male is 2:1.(17) The mean age of pwMS globally is 30 years, (17) the mean age in this study was 47 years. The large difference in the female to male for pwMS in SA is not fully understood as there could be a number of reasons such as there are more females with MS in SA, or more females responded to the survey but as to whether this finding can be applied to the general population of MS in SA is uncertain and further studies are needed to confirm the true number of females to males with MS in SA. The older mean age of pwMS in comparison to the global mean age of 30 years is also an interesting finding but may be due to lack of understanding of MS and diagnosis may have been delayed. This too would need to be investigated further.

The results indicate a high presence of comorbidity (~40% reported three or more) with the most frequent comorbidities reported: depression (36.1%), high blood pressure and high cholesterol (20.5%), migraines (15.6%) and anxiety disorders (13.9%) respectively. In addition, there was a high presence of adverse lifestyle behavioural factors including smoking, alcohol use, and physical inactivity. Only 5% of pwMS in this study were able to report a level of physical activity that can be considered health-

enhancing. Despite the high prevalence of these risk factors, levels of satisfaction with social participation were relatively high.

Adverse lifestyle behaviour and comorbidity

The comorbidity profile described in this study was in line with previous reports on pwMS,(92,93) which also showed depression, high blood pressure and high cholesterol concentrations as the leading reported comorbidities or risk factors. Mental comorbidities have a higher prevalence among pwMS than the general population,(94) with depression being recognized as the most common mental comorbidity in MS with a lifetime prevalence as high as 50%.(95) Unfortunately, mental comorbidities in MS often remain underdiagnosed and undertreated especially in lower socioeconomic status (SES) pwMS.(96) This is an important consideration for the SA context as 55.5% of the general population of SA have a low SES.(97) Ataguba et al. found there is a strong and persistent negative relationship between levels of socioeconomic status and psychological distress among the general SA population.(98) In this study only 2.5% of the respondents reported having a low SES. This may mean that this sample isn't a true representation of the socioeconomic groups within SA and that there may be a lot more South Africans with MS that the MSSA are not aware of as the pwMS may not have access to the internet or the pwMS are not aware of organisations such as the MSSA. Or there are less pwMS in low SES due to the high ethnicity driven and vast inequality in SA, as well as the higher risk for MS is in Caucasian people who in majority do not have a low SES. More research is needed to assess pwMS in lower SES in SA as they are probably dealing with high levels of psychological distress.

This high prevalence of comorbid disease in pwMS is a growing concern for health care professionals due to the adverse impact that is associated with comorbidities.(99) Marrie et al. has found an association between the presence of (physical) comorbidities and time between MS symptom onset and diagnosis.(100) In addition, these patients were more likely to have severe disability at diagnosis, even after accounting for diagnostic delays, and subsequently increased health-care utilization.(100,101) Comorbidities are also associated with higher mortality rates in MS.(102) Marrie suggests two important considerations for dealing with comorbidities in pwMS, which would be useful in the SA context; firstly health care professionals should be encouraged to timely recognise these conditions when they first become noticeable so that initiating effective treatment of these conditions would prevent the adverse effects of these conditions on MS.(99)

And secondly, probably one of the best ways to address comorbidity in MS may be to prevent it altogether especially the modifiable health behaviours such as smoking, risky alcohol use, physical inactivity, and obesity.(99) These risky health behaviours are negative factors for several common comorbidities in MS, including hypertension, diabetes, hyperlipidemia, ischemic heart disease, cancers and chronic lung disease.(92,93,103) PwMS that have hypertension and hypercholesterolemia, were associated with more rapid self-reported disability progression and often needed assisted walking devices sooner than those without these conditions.(104)

This study shows a high prevalence of adverse, modifiable, risk factors specifically, in South African pwMS. Smoking is associated with an increased risk of chronic diseases such as stroke, cancer, and osteoporosis and is a possible risk factor for MS.(105) In the general SA population, 28.8% smoke,(106) where as in this study 63% of the pwMS smoke. Excessive alcohol intake has been found to be inversely associated with progression of disability in relapsing-onset MS.(107) Only 11% of the general SA population have an alcohol disorder,(106) where as 32% of the pwMS reported an alcohol disorder. This risky behaviour does raise concerns of the potential consequences of smoking and alcohol use disorders in pwMS and these concerns need to be addressed. The fact that the prevalence of smoking and alcohol disorders are higher in the pwMS compared to their healthy counterparts is even more reason for these risky behaviours to be addressed.

As to the reasons why the pwMS have a higher prevalence of risky behaviour than the general population, this may be due to coping mechanisms to try to deal with their illness but no matter the reason, pwMS need to be advised on the risks and long term effects of smoking and alcohol abuse on the progression of MS. Only 5% of the respondents reported doing any health enhancing physical activity. This means that more than 86% of the respondents were doing very little or no physical activity. In comparison; it has been found that 47.1% of the general SA population are inactive.(108) In pwMS, physical inactivity is associated with increased risks of overweight and obesity, reduced aerobic capacity, loss of muscle strength, diabetes, colon cancer, hypertension, and premature death from cardiovascular disease.(109) Educating and making pwMS aware of the outcomes of these risky behaviours needs to be a focus for pwMS living in SA.

Fatigue and Cognitive function

It was interesting to note that 87.5% of the respondents of this survey placed within the normal limits for the PROMIS Cognitive Abilities Scale. This is in contrast to previous studies that have shown that ~50% of pwMS report cognitive dysfunction already early-on in the disease course.(112,113) It has to be noted that, despite validation work of the PROMIS cognitive abilities scale done on pwMS,(72) the PROMIS cognitive abilities scale has not been widely used in pwMS. Studies that have reported higher levels of cognitive dysfunction generally used the Minimal Assessment of Cognitive Function in MS (MACFIMS),(111) or the Rao Brief Repeatable Neuropsychological Battery (BRNB).(112) Hence, it is important to consider that the PROMIS cognitive abilities scale is less sensitive to, the often subtle, cognitive dysfunction compared to other validated tools. A particular drawback of the PROMIS Cognitive Abilities scale is that cut-off values are based on the general population of the United States of America which may lack external validity to other, in particular non-Western, study populations.

Fatigue is one of the most common and often most debilitating symptom of MS, affecting as much as 70 - 80% of pwMS.(80,113) In this study only 30% of the respondents showed they had severe fatigue and 53.3% were mild to moderately fatigued on the PROMIS Fatigue SF. The PROMIS Fatigue SF is considered a more unidimensional fatigue scale compared to its counterparts (e.g. FSMC).(114) The FSMC categorised 78.9% of the pwMS as severely fatigued and the FSS had 73.9% as severely

fatigued. There is a discrepancy in the categorising of pwMS that are severely fatigued between the PROMIS Fatigue SF and the FSMC and FSS. The FSMC and FSS had similar percentages in categorising severely fatigues pwMS. The PROMIS Fatigue SF showed the largest difference. Such discrepancies may hamper diagnosis of disabling fatigue in both a clinical and research context. Heine and de Groot, question the available research on assessing severe fatigue in pwMS and then using that assessment in intervention studies.(115) They suggest that the evidence is not strong enough to support the treatment of fatigue. This poor research may be using questionnaires which are not classifying pwMS correctly for severe fatigue. There is a need for research that looks into the cut-off points for severe fatigue so that if a pwMS scores severely fatigued on one questionnaire then they are also likely to be categorised as severely fatigued on another. We have attempted to answer this question in Chapter 4 of this thesis.

Studies have found that there is a link between poor sleep and fatigue,(116–118) but in this study sleep disturbance did not appear to be a problem for majority of the participants. This link between sleep and fatigue needs to be further investigated in future studies in the SA context. The PROMIS short forms were used to assess cognitive abilities, fatigue and sleep disturbance in this study. All three forms showed differing results to other studies using these forms and favoured pwMS in SA having fewer symptoms i.e. fatigue, sleep issues and cognitive dysfunction. This finding needs to be investigated further as the PROMIS has a unique characteristic in that the scores of PROMIS measures are reported on a T- score metric that is anchored to mean score levels in the healthy general population of the United States of America. This interpretation may not be suitable for the South African context and requires further investigation.

Social participation

Previous studies have highlighted the importance of optimizing societal participation in pwMS. We hypothesized that for instance limited public transport, access to rehabilitation medicine, and other factors might hamper societal participation of pwMS in SA. However, based on the findings from the PROMIS Satisfaction with Participation in Social Roles questionnaire used in this study, participants reported above average satisfaction. It is known that pwMS have very low levels of satisfaction with participation in social roles.(119) There are a potential number of reasons to explain this difference found between this study and other studies. Majority of the pwMS came from a higher SES and most affluent people in SA have at least one motor vehicle. This would make traveling and having independence to socialise more convenient than having to rely on public transport. In Europe and other first world countries, public transportation is the main means of traveling and may be rather daunting for pwMS to have to utilise them on their own. Another reason that the SA pwMS showed higher levels of satisfaction with participation in social roles may be due to the scores being reported on a T- score metric that is anchored to mean score levels in a healthy general population of the United States of America. Again, further investigations are needed.

3.4.1 Limitations

This study had some limitations, in addition to the conventional limitations for a cross-sectional survey (e.g. self-reported, no causal inference). In particular in the South African context (e.g. limited access to internet, limited awareness of a MS society), there may have been some selection bias. First, one may query the outreach of an MS society in rural and socio-economic challenging regions. In addition, there might be some under diagnosis of MS in some parts of the country. For instance, Modi et al. suggested that there are traditional myths among clinicians in SA that MS is not a “black population disease” and a black patient that presents with an apparent MS phenotype is investigated for possible alternative explanations and often left with an unclear diagnosis or idiopathic/nonspecific CNS demyelination.(19) This may contribute to the relative low prevalence of non-Caucasian participants in this study. Finally, it is unclear to what extent the digital means of surveying the pwMS reached the less privileged percentage of South African pwMS. This would be more applicable for pwMS living in a rural area as these areas are very often research and resource constraint settings. However, despite these limitations, the ethnic profile and urban to rural distribution of participants in this study was in line with previous reports.(13,28) The PROMIS cognitive ability scale is a limitation due to it not being used widely in studies on pwMS and may be less sensitive to cognitive abilities in pwMS and that the study population is the general population of the United States of America which may not be applicable to pwMS in SA or any other country until it has been validated.

3.4.2 Conclusions

To the best of our knowledge, this study is the first to extensively report the symptom experience of pwMS in SA. A triad of poor lifestyle behaviour, low levels of physical activity, and high burden of comorbidity is concerning and warrants future research. Increasing awareness amongst patients and health care professionals within the SA public and private medical setting with respect to lifestyle risk factors, comorbidity, and the impact of these on pwMS is called for. One of the symptoms that needs further investigation is pwMS that are affected by severe fatigue. Including pwMS that have severe fatigue in intervention studies will help improve the management of fatigue in pwMS. Studies have not shown clearly defined levels of fatigue or have not made it an inclusion criteria and so this may affect fatigue management programmes. Chapter 4 of this thesis attempts to address the need for cut off values for severe fatigue in the questionnaires used to assess fatigue which will then hopefully assist with including pwMS that have severe fatigue.

CHAPTER 4

Agreement between three self-report questionnaires to determine severe fatigue in Multiple Sclerosis – a cross-sectional online study

Abstract

Background: Fatigue, especially disabling fatigue, affects between 70% - 80% of patients with Multiple Sclerosis (pwMS). Fatigue is a subjective construct that is difficult and complex to assess. It has been suggested that its entirety can only be evaluated using multiple self-report measures. Some fatigue questionnaires have defined cut-off values to classify whether a person has severe fatigue, moderate fatigue or fatigue within normal limits. Identifying pwMS that have severe fatigue has an important role in research. Including pwMS that have severe fatigue in intervention studies will help improve the management of fatigue in pwMS. However, in the context of the suggested use of multiple fatigue measures, this raises the following questions: how well the previous reported cut-off values of various fatigue measures align, and how can researchers ensure that only patients with a specific level of fatigue are included, independent on the choice of fatigue measures?

Aim and Methods: the aim of this study is: i) to determine the agreement between the reported cut-off values for categorising severe fatigue in three commonly used fatigue questionnaires, and ii) to determine new cut off values to classify a participant as severely fatigued across all three questionnaires (e.g. 100% agreement). The data from the fatigue questionnaires from the cross-sectional survey done in chapter 3 were analysed to answer these questions. The three questionnaires used were: The Fatigue Severity Scale (FSS), The Fatigue Scale for Motor and Cognitive Functions (FSMC) and the PROMIS Fatigue Short Form (SF).

Results: 122 of 1048(11.6%) completed the survey (Age=47±10 yr, Male (%)=14, disease duration=11±9 yr). The FSS and FSMC categorised 73.9% and 78.9% respectively as severely fatigued. The PROMIS Fatigue SF categorised only 30% as severely fatigued. Using Cohen's Kappa, a significantly moderate agreement was found between FSS and FSMC, ($k = 0.563$, $p = 0.000$), and not the PROMIS Fatigue SF. Cut-off values of 5.8 out of 7 for the FSS would provide 100% certainty that the "hypothetical" patient with these values would have qualified as severely fatigued on the FSMC. Conversely, a value 88.5 out of 100 for FSMC would provide 100% certainty that this same patient would have qualified as severe fatigued on the FSS.

Conclusion: We argue for higher than the conventional cut-off values for indication of the presence of severe fatigue are used in the further study of fatigue specifically, to facilitate more accurate estimates of the effect of fatigue management programs.

4.1 Introduction

Disabling fatigue affects between 70% - 80% of patients with Multiple Sclerosis (pwMS).(80,113) Despite the high incidence of pwMS that experience disabling fatigue, treatment of the fatigue remains difficult and the overall understanding of MS fatigue is far from complete.(120) There are multiple definitions for fatigue. A commonly used definition by the Multiple Sclerosis Council for Clinical Practice Guidelines considers fatigue as a "subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities".(121) Alternatively, Mills and Young suggest that fatigue should be defined as “reversible, motor and cognitive impairment with reduced motivation and desire to rest, either appearing spontaneously or brought on by mental or physical activity, humidity, acute infection and food ingestion”.(122) Aaronson et al. proposed the following definition of fatigue; “The awareness of a decreased capacity for physical and/or mental activity due to an imbalance in the availability, utilization, and/or restoration of resources needed to perform activity”.(123) These definitions share that fatigue is a subjective feeling experienced by the pwMS and impacts “performance or capacity” over time. One may distinguish chronic from acute fatigue, where the latter follows from a temporary circumstance such as physical activity or heat sensitivity,(83,121) whereas chronic fatigue is defined as, “fatigue present for any amount of time on 50% of days for more than six weeks, which limits functional activities or quality of life”.(121)

A second distinction relates the working mechanism behind the experience of fatigue, being primary or secondary fatigue. Primary fatigue is linked to the pathological process of MS itself (e.g. muscle weakness, cognitive reserve) whilst secondary fatigue is due to the chronic effects of MS (e.g. medications, insomnia or depression).(83,121) Assessing fatigue is therefore difficult and complex due to its multifaceted and subjective construct; and it has been suggested that its entirety can only be evaluated using multiple self-report measures (e.g. Fatigue Severity Scale [FSS], Fatigue Scale for Motor and Cognitive Function [FSMC]).(8) Due to fatigue’s subjective and multidimensional character, including multiple complementary measures to assess and measure fatigue is recommended.(85)

Some fatigue questionnaires have defined cut-off values to classify whether a person has severe fatigue, moderate fatigue or fatigue within normal limits. Identifying pwMS that have severe fatigue has an important role in research. Including pwMS that have severe fatigue in intervention studies will help improve the management of fatigue in pwMS. A Cochrane review by Heine et al.(124) found that non-pharmacological interventions often have not been studied in patients with well-defined levels of fatigue, and in addition, fatigue is often not an inclusion criterion or primary outcome. This may lead to an underestimation of the true effect on fatigue of those and other fatigue management programs.(115,124) Only including patients with severe fatigue may be a means to increase the methodological quality of studies in the future. However, in the context of the suggested use of multiple fatigue measures, this raises the following questions: how well the previous reported cut-off values of various fatigue measures align, and how can researchers ensure that only patients with a specific level of fatigue are included, independent on the choice of fatigue measures?

To answer these questions, the aim of this study is: i) to determine the agreement between the reported cut-off values for categorising severe fatigue in three commonly used fatigue questionnaires, and ii) to determine new cut off values to classify a participant as severely fatigued across all three questionnaires (e.g. 100% agreement).

4.2 Methods

4.2.1 Study Design

The fatigue questionnaires data from the cross-sectional online survey through the MS Society of South Africa (MSSA) that was used in Chapter 3 were analysed to answer the questions for this chapter. This study was approved by the Health Research Ethics Committee, Stellenbosch University (N17/02/017).

A digital anonymous survey, using the REDCap (Research Electronic Data Capture, University of Stellenbosch, Cape Town, South Africa) data collection platform,(65) was sent out to all MSSA affiliated (1050) pwMS across the eleven provinces of South Africa. Participants provided digital informed consent prior to starting the survey. Reminders were sent out at two weeks and four weeks after the initial invitation. The survey was estimated to take one hour to complete, and participants were able to stop and save, but were encouraged to complete the entire survey in a single day.

A detailed description of the outcomes included in this survey is reported elsewhere (See chapter 3 of this thesis). The following descriptive characteristics of the pwMS are included: age (years), sex (male/female), ethnicity , self-report type of MS, time since diagnosis (years), time since symptom onset (years), and Patient-Determined Disease Steps (PDDS).(68) The PDDS has nine ordinal levels ranging between 0 (Normal) and 8 (Bedridden) and can be categorized as mild, moderate, or severe disability.(68)

The three fatigue questionnaires were chosen for the different aspects of fatigue they assess as well as their reported psychometric properties (e.g. validity, reliability).

The Fatigue Severity Scale (FSS):

The FSS measures the impact of fatigue on specific types of functioning, assesses the severity of fatigue symptoms and its impact on an individual's daily functioning during the past week.(125) It has been determined to be sensitive to fatigue changes over disease progression or due to treatment.(126) The FSS, due to its strong psychometric properties, sensitivity to change and being unidimensional in its measurement of fatigue plus its internal consistency and stability over time makes it a strong candidate as the gold standard of measuring fatigue especially in MS. The FSS has been shown to differentiate between subgroups of patients with MS, chronic fatigue syndrome, and primary depression.(127) The FSS has 9 items concerning respondent's fatigue, e.g., how fatigue affects motivation, exercise, physical functioning, carrying out duties, interfering with work, family, or social life and has been known to assess the impact of fatigue on daily functioning.(82,128) The scale is a 7-point

Likert Scale where 1= Strongly Disagree and 7= Strongly Agree. The Score range is 1-7 and a higher score indicates more severe fatigue. To determine a score a mean score is calculated. Scores ≥ 4 indicates severe fatigue.(83)

The Fatigue Scale for Motor and Cognitive Functions (FSMC):

The FSMC was developed to focus on the two main domains of fatigue: cognitive and physical fatigue. In addition, questions are not phrased as such they ask for a reflection over a certain time window (e.g. one week).(84) The FSMC also has good reliability, sensitivity and specificity values and the fact that it differentiates between physical and cognitive fatigue in MS are important for further understanding of the subjectivity of fatigue.(84) The FSMC has 20 items, of which the key cognitive items are concentration, decision making/executive functions, learning, occupational demands, stress and concentration, heat and thinking, thinking/motivation/drive, verbal fluency, attention/stamina and memory. The key physical items are skilfulness, stamina/resting periods, stress and physical power, social environment, muscles/strength, physical stamina, drive/motivation, speed reduction, reactivity and heat and physical energy.(84) The item responses are rated on a 5-point Likert Scale ranging from, “Does not apply at all” to “Applies completely”. The score range is from 20-100 for an overall fatigue score. There is a score for cognitive fatigue and physical fatigue. The cut-off values for the sum score is ≥ 63 Severe fatigue, ≥ 53 Moderate fatigue and ≥ 43 Mild fatigue; the Cognitive Score is ≥ 34 Severe fatigue, ≥ 28 Moderate fatigue and ≥ 22 Mild fatigue; and Physical Score is ≥ 32 Severe fatigue, ≥ 27 Moderate fatigue and ≥ 22 Mild fatigue.(84)

The Patient Reported Outcomes Measurement Information System (PROMIS) Fatigue Short Form (SF):

The PROMIS was developed to provide item banks that offer the potential for efficient (minimizes item number without compromising reliability), flexible (enables optional use of interchangeable items), and precise (has minimal error in estimate) measurement of commonly studied Patient Reported Outcomes (PROs).(129) The PROMIS Fatigue SF demonstrated reliability, precision, and construct validity based on its correlation with Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale and SF-36 Vitality Scale.(129) The PROMIS Fatigue SF is 8 items and has been developed using computer-adaptive testing.(129) Item responses are rated on a 5-point scale ranging from ‘never’ to ‘always’ and are summed and transformed to a T-score metric. Higher scores indicate more severe fatigue. Scores 2.0 Standard Deviation or worse than the mean = severe symptoms of fatigue which is a ≥65 T-score. Moderate fatigue is 55 - 65 T-score, mild fatigue is 50 - 55 T-Score and within normal limits is ≤50 T-score.(130) It assesses fatigue over the past seven days. PROMIS Fatigue SF scores have good precision across different levels of fatigue. More than 95% of the PROMIS samples were measured with a reliability greater than 0.9.(81)

4.2.2 Data-Analysis

A Shapiro-Wilk's test ($p>0.05$) and visual inspection of their histograms, normal Q-Q plots and box plots with skewedness and kurtosis were used to analyse if the data were normally distributed.(91) For data that were normally distributed, mean and 95% confidence level (95%CI) are presented. For data that were not normally distributed median and interquartile range (IQR) are presented. All analyses were conducted using IBM SPSS® version 25 software (IBM SPSS Statistics, IBM Corporation, Armonk, New York). A p-value >0.05 was considered statistically significant. To measure agreement between the three fatigue questionnaires, we calculated Cohen's kappa (κ) statistics with 95% Confidence Interval (CI), interpreting agreement as follows: slight (0–0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61– 0.80), and almost perfect (0.81–1.0). (131) Spearman's correlation coefficient (r) was used to show the strength and the direction of association between the questionnaires. Interpreting the strength of the association as follows: -1.0 to -0.5 or 1.0 to 0.5 shows a strong relationship; -0.5 to -0.3 or 0.3 to 0.5 shows a moderate relationship; -0.3 to -0.1 or 0.1 to 0.3 shows a weak relationship and -0.1 to 0.1 show no or a very weak relationship.(132)

Subsequently, sensitivity, specificity, positive and negative predictive value for each respective questionnaire with the two other questionnaires were calculated (e.g. FSS compared to FSMC sum score and PROMIS Fatigue SF). Receiver Operating Characteristics (ROC) curves were used to show the graphical representation of sensitivity and specificity for each possible cut-off of the three questionnaires and the area under the curve (AUC) helps estimate how high the discriminative power of a test is (See Appendix E).(133) AUC and diagnostic accuracy is determined as follows: <0.5 test not useful; 0.5-0.6 bad; 0.6-0.7 sufficient; 0.7-0.8 good; 0.8-0.9 very good; 0.9-1.0 excellent.(133) In order to discern new cut-off values, that would allow for a 100% certainty that patients classified as severe fatigue on questionnaire A would also classify as severely fatigued on questionnaire B, 100% specificity was cross-tabulated between all included fatigue questionnaires.(24)

4.3 Results

There were 122 pwMS (11.6%) who responded to the survey of which 84 completed the complete survey. The patient characteristics are summarised in Table 4.1. The majority of the respondents were Caucasian (95%), and female (ratio of 6:1) with a mean age of 47 years (95%CI 46 to 49). The percentage of pwMS presenting with relapsing remitting MS was 68.1%, 20.7% with secondary progressive MS, and 11.2% with primary progressive MS. The median PDDS score was 2 (IQR 1 to 3), and subsequently 30.2% of the respondents could be classified as moderately disabled. The median years since diagnosis was 7 years (IQR 1-38) and the median years since disease onset was 12 years (IQR 1-54).

The results for the three questionnaires are presented in Table 4.2. The FSS median score was 5.17 (IQR 1-7) with 73.9% of the respondents classified as severely fatigued. The FSMC median scores were 39 (IQR 10-50) for the cognitive domain, 41 (IQR 13-50) for the physical domain, and 78.5 (IQR 23-100) for the summed score. The cut off values for FSMC Cognitive, classified 68.9% of the

respondents with severe cognitive fatigue, 82.2% with severe physical fatigue and 78.9% with an overall severe fatigue. The PROMIS Fatigue SF median score was 59.4 (IQR 33.1 to 78.8). Additionally, based on population-norm based cut-off values, 41.1% of the respondents were classified as moderately fatigued while 30% of the respondents classified as severely fatigued.

The agreement and the association between the questionnaires are presented in Table 4.3. A significant moderate agreement (κ =0.563, p = 0.000) and a strong association (r = 0.713, p = 0.000) was found between the FSS and FSMC. The agreement between FSMC sum total and PROMIS Fatigue SF was slight (κ=0.170, p = 0.008) but a strong association (r = 0.624, p = 0.000). FSS and PROMIS fatigue SF showed a slight agreement (κ=0.194, p = 0.008) but also a strong association (r =0.650, p=0.000).
Table 4.4 shows the cut offs for both 100% Sensitivity and 100% Specificity. The cut-offs needed for 100% sensitivity for FSS would be 2.8 and 3.3 to include all pwMS that have severe fatigue on FSMC and PROMIS Fatigue SF respectively; for FSMC it would be 43 for both FSS and PROMIS Fatigue SF; and for PROMIS Fatigue SF it would be 39.75 and 46.25 T scores for FSMC and FSS respectively. Cut-offs at 100% specificity to exclude pwMS that do not have severe fatigue for FSS would be a score of 5.8 for FSMC and 6.9 for PROMIS Fatigue SF (98% specificity). For FSMC; a score of 88.5 would be required to exclude those without fatigue on the FSS and for PROMIS Fatigue SF, the FSMC score would need to be 99 but this would be at 95% specificity. The T scores required on the PROMIS Fatigue SF to exclude those with severe fatigue would be 65.85 and 66.95 on the FSMC and FSS respectively.

Table 4.1: Demographic Variables and Clinical Characteristics of Persons with Multiple Sclerosis in South Africa

Demographic Characteristics	**Mean**	**95% CI**	**N**	**Continuous Health Condition Variable**	**Median**	**IQR**	**N**
Age (yrs)	47	46-49	122	Disease diagnosis(yrs)	7	1-38	116
				Disease onset (yrs)	12	1-54	115
				PDDS	2	1-3	116
Categorical Variables	**N**	**%**	**N**	**Categorical Variables**	**N**	**%**	**N**
Gender			122	Type of MS			116
Female	105	86.1		RRMS	79	68.1	
Male	17	13.9		SPMS	24	20.7	
				PPMS	13	11.2	
Ethnicity			122				
White	116	95.1		PDDS			116
Mixed Ancestry	3	2.5		Mild	55	47.4	
Asian/Indian	2	1.6		Moderate	35	30.2	
Black African	1	0.8		Severe	26	22.4	

95%CI = 95% confidence interval. IQR = Interquartile range. p value = 0.05. RRMS = relapsing-remitting multiple sclerosis. SPMS = secondary-progressive multiple sclerosis. PPMS = primary-progressive multiple sclerosis. PDDS = Patient Determined Disease Steps scale.

Table 4.2: The Fatigue Severity Scale, the Fatigue Scale for Motor and Physical Functions and the PROMIS Fatigue Short Form Questionnaires Median, Interquartile and Categorical Data for the Persons with Multiple Sclerosis in South Africa.

	Median	**IQR**	**N**
FSS	5.17	1-7	88
FSMC Cognitive	39.00	10-50	90
Motor	41.00	13-50	90
Sum Total	78.50	23-100	90
PROMIS Fatigue SF	59.40	33.1-77.8	90
Categorical Variables	**N**	**%**	**N**
FSS			88
Score <4	23	26.1	
Score >4	65	73.9	
FSMC Cognitive			90
Within normal limits*	11	12.2	
Mild	6	6.7	
Moderate	11	12.2	
Severe	62	68.9	
FSMC Motor			90
Within normal limits*	6	6.7	
Mild	4	4.4	
Moderate	6	6.7	
Severe	74	82.2	
FSMC Sum Total			90
Within normal limits*	8	8.9	
Mild	6	6.7	
Moderate	5	5.6	
Severe	71	78.9	
PROMIS Fatigue SF			90
Within normal limits	15	16.7	
Mild	11	12.2	
Moderate	37	41.1	
Severe	27	30.0	

IQR = Interquartile range. FSS = Fatigue Severity Scale. FSMC = The Fatigue Scale for Motor and Cognitive Functions. PROMIS Fatigue SF = PROMIS Fatigue Short Form. * = FSMC does not have “within normal limits” as part of its cut offs so to make it easier for comparison with PROMIS Fatigue SF, “within normal limits” were added to scores that fell below the cut off set for mild fatigue.

Table 4.3: Cohen's Kappa for agreement and Spearman's correlation for associations between the Fatigue Severity Scale, the Fatigue Scale for Motor and Physical Functions and the PROMIS Fatigue Short Form Questionnaires.

	N	κ (95% CI)	r; p
FSMC/FSS	88	0.563 (0.341-0.745)	0.713, p=0.000
FSMC/PROMIS	90	0.170(0.064-0.276)	0.624, p=0.000
FSS/PROMIS	88	0.194 (0.069-0.319)	0.650, p=0.000

FSS = Fatigue Severity Scale. FSMC = The Fatigue Scale for Motor and Cognitive Functions. PROMIS = PROMIS Fatigue Short Form. κ = Cohen's Kappa. 95% CI = 95% Confidence Interval. r = Spearman's correlation coefficient. Probability (p) = 0.005.

Table 4.4: Optimal cut off values, sensitivity, and specificity, area under the curve, sensitivity 100% and specificity 100% for the Fatigue Severity Scale, the Fatigue Scale for Motor and Physical Functions and the PROMIS Fatigue Short Form Questionnaires

	N	Sensitivity	Specificity	PPV	NPV	Score	AUC (95%CI)	Sensitivity (100%)	Specificity (100%)
FSMC/FSS	88	0.86	0.84	0.95	0.62	4.3	0.90 (0.82-0.99)	2.8	5.8
PROMIS/FSS	88	0.67	0.85	0.67	0.85	5.9	0.82(0.72-0.91)	3.3	6.9*
FSS/FSMC	88	0.82	0.83	0.93	0.61	72.5	0.87 (0.79-0.96)	43	88.5
PROMIS/FSMC	90	0.78	0.59	0.45	0.86	77.5	0.73 (0.63-0.84)	43	99**
FSMC/PROMIS	90	0.82	0.84	0.95	0.55	56.1	0.89(0.80-0.98)	39.75	65.85
FSS/PROMIS	88	0.85	0.83	0.93	0.66	56.1	0.87(0.78-0.96)	46.25	66.95

PPV = Positive Predictive Value. NPV = Negative Predictive Value. Score = new optimal cut off. AUC = Area under the curve. 95% CI = 95% Confidence Interval. FSS = Fatigue Severity Scale. FSMC = the Fatigue Scale for Motor and Cognitive Functions. PROMIS = PROMIS Fatigue Short Form. * = Specificity at 98%. ** = Specificity at 95%.

4.4 Discussion

The study of fatigue in patients with Multiple Sclerosis is hampered by the complex, subjective, multidimensional character of fatigue. The present study explored the agreement between three fatigue measures to classify patients as having severe fatigue based on established cut-off values, and set out determined new cut-off values for severe fatigue across these fatigue measures to inform future research that aims to study fatigue and the management of fatigue in pwMS.

A significantly moderate agreement was found between the FSS and FSMC, but only slight agreement was found between the FSS and FSMC with the PROMIS Fatigue SF. A cut-off value of 5.8 on the FSS or cut-off value of 88.5 for the FSMC would allow for the inclusion of patients with severe mental and/or physical fatigue (FSMC) and with severe impact on daily functioning (FSS). These cut-off values are considerably higher than the original cut-off values of ≥4 for FSS and ≥ 63 for FSMC. However, it would

mean that using these higher cut-off values researchers are more likely to include patients with severe fatigue in their interventions, and inclusion of patients will be less dependent on the selection of a specific questionnaire. The suggestion of using higher cut-off values is in line with previous work. For instance, it has been suggested to adjust the FSS cut-off score to at least >5 for studies (or 5.8 according this the present study) wanting to include severely fatigued pwMS as scores between 4 and 5 can be considered borderline fatigue.(134,135)

Creating more certainty in terms of the inclusion of fatigue patients is paramount for the research into fatigue management of patients with MS. A Cochrane review by Heine et al.(124) found that non-pharmacological interventions often have not been studied in patients with well-defined levels of fatigue, and in addition, fatigue is often not an inclusion criterion or primary outcome. This may lead to an underestimation of the true effect on fatigue of those and other fatigue management programs.(115,124) Studies performed by Dalgas et al. and Hayes et al. used the FSS (> 4.0) to select pwMS that had fatigue a priory. (136,137) Despite heterogeneous findings of exercise therapy for fatigue in pwMS, these studies which included fatigued patients specifically, showed significant benefits of the studied exercise paradigm on fatigue.(136,137) However, conversely, a study by Aydin et al. (FSS) and Skjerbaek et al. (FSMC), showed no significant benefits of exercise therapy on fatigue, despite that the baseline fatigue values surpassed the reported cut-off value for the respective questionnaire used.(138)(139) The cut-off values derived in the present study, would allow for a more stringent classification of severe fatigue as an inclusion criterion, and may facilitate a better estimation of the “true” effect of management programs for fatigue in patients with MS. It reduces the bias introduced by selecting a specific fatigue questionnaire (e.g. FSS) using original cut-off values, as inclusion measure for severely fatigued patients with MS.

While there was a significant and moderate agreement between the FSS and FSMC, the agreement between these two fatigue measures and the PROMIS Fatigue SF was unsatisfying. When using the PROMIS Fatigue SF, a mere 30% of the participants could be categorised as severely fatigued and 41.1% as moderately fatigued. In contrast, 73.9% and 78.9% were classified as severely fatigued based on the FSS and FSMC respectively. A plausible explanation for the lack of agreement between the PROMIS Fatigue SF and the other fatigue measures could be that the questionnaires measure quite different domains of fatigue. The PROMIS Fatigue SF cut-off values for this study are similar to the suggested cut-off values. This study’s cut-off values are 66.95 and 65.85 and the recommended cut-off is ≥65. However, the PROMIS cut-off scores are determined by the American general population whereas our cut-offs are determined by pwMS in SA. The PROMIS initiative has developed a fatigue short form for pwMS and in validating the content of the questionnaire, they found mean scores on the two measures varied by less than one point therefore making the PROMIS Fatigue SF similar to the PROMIS Fatigue SF for pwMS making it appropriate for assessing pwMS that have fatigue.(114) However, this PROMIS Fatigue SF for pwMS still uses the general population scores to determine the cut-offs. There is a need to develop cut-off values based on pwMS as this will help determine appropriate categorisations for the different levels of fatigue.

There are many different fatigue measures in circulation, and to date there is no true golden standard. The present study gives more certainty when using FSS or FSMC for the inclusion of patients with severe fatigue and severe impact of fatigue; yet we are unsure how that corresponds with questionnaires that allegedly assess other “aspects” of this complex construct. It has been suggested that there is a significantly strong association between the FSS and MFIS even though they measure different constructs of fatigue.(82,140) Penner et al. eluded to a significant and strong association between FSMC and the MFIS and the FSS.(84) This study is a first step in using multiple questionnaires to increase certainty of including severely fatigued pwMS and therefore encourage more studies on multiple fatigue questionnaires to be utilised when investigating fatigue. This would help to increase the standard of the studies done on fatigue on pwMS. The use of PROMIS Fatigue SF is uncertain even though the correlation between the PROMIS Fatigue SF and FSS and FSMC was a strong association with a slight agreement, there needs to be further investigations into the PROMIS Fatigue SF use. These findings may only be true for the South African context but further investigations into the SF and its application to other countries is needed.

4.4.1 Limitations

The limitations of this study include the use of a cross-sectional survey to gather data which relies on self-reported data and that there is missing data from some of the fatigue questionnaires which may affect the outcomes assessed. The low response rate is a limitation in that it questions whether the data gathered from the survey and analysed, is representative of the MS population in South Africa and whether it can be applied to the global MS population. The information gathered from the survey is important as it shows the need to do further studies into the symptoms and characteristics of pwMS in South Africa. Another limitation is that none of the questionnaires for fatigue in this study have been extensively validated in a South African context which may not give a true assessment of fatigue experienced by South Africans.

4.4.2 Conclusions

The cut-off values for the FSS and FSMC derived from this study, can be used as more stringent values for the inclusion of fatigued patients with MS. It is argued that the use of these higher values may increase the precision when studying the effect of fatigue management interventions. Due to the lack of agreement with the PROMIS Fatigue SF, further research is needed to clarify the added value of the PROMIS Fatigue SF in the study of fatigue in pwMS.

CHAPTER 5
Summary and Conclusion

5.1 Introduction

The objectives of this thesis was to scope the existing literature on Multiple Sclerosis (MS) originating from sub-Saharan Africa, to evaluate the characteristics and key symptoms of persons with MS (pwMS) in South Africa (SA) through a cross-sectional study and to investigate the agreement between the reported cut-off values for categorising severe fatigue in three fatigue questionnaires and to determine new cut-off values to classify a participant as severely fatigued in the three questionnaires.

5.2 Summary: Scoping Review of MS in sub-Saharan Africa

In Chapter 2, a scoping review of the literature originating in sub-Saharan Africa focusing on MS was conducted. A total of 33 studies were included in the review from 1967 to 2018. The review highlighted that there is an increase in the reporting of MS amongst Africans across all ethnic groups. However, Africa is considered low risk for pwMS because there is very limited research on the epidemiology, aetiology and symptoms and experiences of pwMS. Studies conducted on the aetiology of MS in South Africa were important studies adding to the global research of MS. Unfortunately, due to low resources and MS not being considered a high-risk disease the studies on epidemiology were last conducted in 2008 in South Africa. The understanding of the symptoms and perceptions of pwMS is also very poorly investigated. These findings all indicate large gaps in the research and understanding of MS in sub-Saharan Africa.

5.3 Summary: Cross-Sectional Study of MS in South Africa

Chapter 3 investigated the information gathered from a cross-sectional online survey of pwMS in South Africa, contacted through the Multiple Sclerosis Society of South Africa. The outcomes were consolidated under the International Classification of Functioning (ICF) model, (Health, Body Structure and Function, Activity, Participation and Contextual Factors – Personal and Environmental). The participants who responded to the survey were 122 out of 1048 (11.6%) pwMS. The cross-sectional survey highlighted that pwMS in SA present similarly to pwMS in the Western world in terms of majority of the participants were: female (ratio 6:1) even though this ratio is higher than the global statistics for female to male ratio, there are still more females than males with MS in SA, Caucasian (95%), disease duration of 11 years ± 9 years and majority of the pwMS reported relapsing remitting MS (68.1%). The important findings from this cross-sectional survey of pwMS were:

1) Seventy percent were classified as either overweight or obese according to BMI.
2) The presence of comorbidities was high, with 39.3% of PwMS reporting three or more comorbidities. The most frequent comorbidities reported were depression (36.1%), high blood pressure and high cholesterol (20.5%) respectively, migraines (15.6%) and anxiety disorders (13.9%).
3) Detrimental lifestyle behaviour was prevalent with 64% of pwMS being inactive, 66% reported having smoked at some time in their lives and 32.3% scored positive for having an alcohol disorder.

5.4 Summary: Agreement between three self-report questionnaires to determine severe fatigue in Multiple Sclerosis – a cross-sectional study

Chapter 4 investigated three fatigue questionnaires, the Fatigue Severity Scale (FSS), the Fatigue Scale for Motor and Physical outcomes (FSMC) and the PROMIS Fatigue Short Form (SF), and the agreement between the reported cut-off values for categorising severe fatigue in the three questionnaires and to determine new cut-offs values to classify a participant as severely fatigued across all three questionnaires. The data used for this part of the thesis came from the cross-sectional study presented in Chapter 3. The main findings were:

1) The FSS and FSMC categorised 73.9% and 78.9% of the participants, respectively as severely fatigued. The PROMIS Fatigue SF categorised only 30% as severely fatigued.
2) A significantly moderate agreement was found between FSS and FSMC, ($k = 0.563$, $p = 0.000$), and not the PROMIS Fatigue SF.
3) The new cut-off value for the FSS was 5.8 out of 7 and this value would provide 100% certainty that this patient would have qualified as severely fatigued on the FSMC.
4) The new cut off value for the FSMC was 88.5 out of 100, which would provide 100% certainty that this patient would have qualified as severe fatigued on the FSS.

5.5 Summary: Clinical implications

The main clinical implications of the research presented in this thesis are as follows:

- It is important to increase awareness of MS in both the public and private sectors of healthcare with regards to the signs and symptoms of MS. Creating referral pathways to national or international experts in the cases of suspected MS to increase early detection and appropriate pharmacological and non-pharmacological management of MS would also be beneficial. This would require advocating for better awareness of MS at government level by presenting the findings of this study and other studies to the ministry of health to show the need to take more interest in this disease.
- Comorbidities, inactivity, overweight and obesity and smoking are all major concerns for people living in sub-Saharan Africa and these issues have a greater impact on pwMS. These issues cause delays in diagnosing MS and can be linked to causing MS so education and awareness of these concerns need to be made known to pwMS. The prevalence of these risk factors for disability and increased disease progression appears higher in a South African context than reported for developed countries hence may warrant additional research and awareness. Developing consensus guidelines for the diagnosing and treatment of MS in SA and Sub-Saharan Africa would be beneficial to helping to tackle these issues. Rehabilitation of MS in SA is unheard of and developing intervention studies to help assist the management of the symptoms of MS amongst pwMS would be most beneficial.

- Higher cut-off values, as reported in this thesis for the FSS and FSMC, can be used in clinical research in the future, to create a higher level of certainty in studying patients with severe fatigue in terms of both severity (FSMC) and impact (FSS).
- Country specific norms for the PROMIS short forms need to be developed to increase the value of the PROMIS initiative.

5.6 Future studies

This thesis has highlighted that there are important gaps in the research on pwMS in sub-Saharan Africa, and South Africa specifically. There is no up-to-date research on the epidemiology of MS in sub-Saharan Africa, despite the increase availability and awareness. A focus shift towards studies evaluating the symptom management of pwMS, the impact of the health care systems on their diagnosis and treatment options, and validating MS-specific questionnaires that are relevant for the sub-Saharan context are justified. Of importance in the South Africa context, is the myriad of comorbidity, and lifestyle risk behaviour that may have a negative impact on the disease course and burden. The assessment of fatigue, independent of its context, remains complex. Yet, one avenue moving forward, is using more stringent inclusion criteria for fatigue severity to obtain better effect estimates of management interventions.

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Appendices

Appendix A: PubMed Search Strategy

Appendix B: Ethics approval letter for the cross-sectional survey of comorbidity and risk factors for comorbidity in people with Multiple Sclerosis living in South Africa

Appendix C: A cross-sectional survey of comorbidity and risk factors for comorbidity in people with Multiple Sclerosis living in South Africa

Appendix D: Self-reported prevalence of comorbidities from the survey

Appendix E: ROC curves for the three fatigue questionnaires for Chapter 4

Appendix F: PRISMA-ScR and STROBE Checklists for Chapters 2-4

Appendix G: Turn It In report

Appendix A: PubMed Search Strategy (Literature Search performed: 7 September 2018)

Sub-Saharan Africa

1. (Angola[mesh] OR Benin[Mesh] OR Botswana[mesh] OR “Burkina Faso”[Mesh] OR Burundi[Mesh] OR “Cape Verde”[Mesh] OR Cameroon[Mesh] OR “Central African Republic”[Mesh] OR Chad[Mesh] OR Comoros[Mesh] OR Congo[Mesh] OR Zaire[Mesh] OR “Cote d'Ivoire”[Mesh] OR Djibouti[Mesh] OR Eritrea[Mesh] OR Ethiopia[Mesh] OR Gabon[Mesh] OR Gambia[Mesh] OR Ghana[Mesh] OR Kenya[Mesh] OR Lesotho[Mesh] OR Liberia[Mesh] OR Madagascar[Mesh] OR Malawi[Mesh] or Mali[Mesh] or Mauritius[Mesh] OR Mauritania[Mesh] or Mozambique[Mesh] or Namibia[Mesh] OR Niger[Mesh] or Nigeria[Mesh] OR “Republic of Guinea”[Mesh] or Rwanda[Mesh] OR Senegal[Mesh] or “Sierra Leone”[Mesh] or Somalia[Mesh] or Sudan[Mesh] or “South Africa”[mesh] or Swaziland[Mesh] or Tanzania[Mesh] or Togo[Mesh] or Uganda[Mesh] OR Zambia[Mesh] OR Zimbabwe[Mesh])
2. Angola[tiab] Or “Benin”[Tiab] Or Botswana[tiab] or "Burkina Faso"[Tiab] OR "Burkina Fasso"[Tiab] OR "Upper Volta"[Tiab] OR Burundi[Tiab] OR Urundi[Tiab] OR "Cabo Verde"[Tiab] OR "Cape Verde"[Tiab] OR Cameroon[Tiab] OR Cameroons[Tiab] OR Cameron[Tiab] OR "Central African Republic"[Tiab] OR Chad[Tiab] OR Comoros[Tiab] OR "Comoro Islands"[Tiab] OR Comores[Tiab] OR Mayotte[Tiab] OR Congo[Tiab] OR Zaire[Tiab] OR "Cote d'Ivoire"[Tiab] OR "Ivory Coast"[Tiab] OR Djibouti[Tiab] OR "French Somaliland"[Tiab] OR Eritrea[Tiab] OR Ethiopia[Tiab] OR Gabon[tiab] OR Gambia[Tiab] OR Ghana[Tiab] OR "Gold Coast"[Tiab] OR Kenya[Tiab] OR Lesotho[Tiab] OR Basutoland[Tiab] OR Liberia[Tiab] OR Madagascar[Tiab] OR Malawi[Tiab] or Namibia[Tiab] OR Nyasaland[Tiab] or Mali[Tiab] or Mauritius[Tiab] OR Mauritania[Tiab] or Mozambique[Tiab] or Niger[Tiab] or Nigeria[Tiab] OR “Republic of Guinea”[Tiab] or Rwanda[Tiab] or "Sao Tome"[Tiab] or Senegal[Tiab] or "Sierra Leone"[Tiab] or Somalia[Tiab] or “South Africa”[Tiab] or Sudan[Tiab] or Swaziland[Tiab] or Tanzania[Tiab] or Togo[Tiab] or "Togolese Republic"[Tiab] or Uganda[Tiab] or Yemen[Tiab] OR Zambia[Tiab] OR Zimbabwe[Tiab])
3. 2 OR 3

Multiple sclerosis

4. ("Multiple Sclerosis"[mh] OR "Encephalomyelitis"[mh] OR "Myelitis"[mh] OR multiple scleros*[tiab] OR optic neurit*[tiab] OR acute disseminated encephalomyelit*[tiab] OR myelooptic neuropath*[tiab] OR myelo optico neuropath*[tiab] OR myelit*[tiab] OR neuromyelitis optica[tiab] OR encephalomyelit*[tiab] OR clinically isolated syndrome*[tiab] OR transverse myelit*[tiab] OR devic disease*[tiab] OR devics[tiab] OR demyelinating disease*[tiab] OR demyelinating disorder*[tiab] OR adem[tiab])
5. 3 AND 4
6. Limit 5 to humans only

Appendix B: Ethics approval letter for the cross-sectional survey of comorbidity and risk factors for comorbidity in people with Multiple Sclerosis living in South Africa

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Approval Notice

Response to Modifications- (New Application)

19-Apr-2017
Heine, Martin M

Ethics Reference #: N17/02/017

Title: **A cross-sectional survey of comorbidity and risk factors for comorbidity in people with Multiple Sclerosis living in South Africa**

Dear Dr Martin Heine,

The **Response to Modifications -** ***(New Application)*** received on **27-Mar-2017**, was reviewed by members of **Health Research Ethics Committee 2** via Expedited review procedures on **19-Apr-2017** and was approved.
Please note the following information about your approved research protocol:

Protocol Approval Period: **19-Apr-2017 -18-Apr-2018**

Please remember to use your **protocol number** (**N17/02/017**) on any documents or correspondence with the HREC concerning your research protocol.

Please note that the HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

After Ethical Review:
Please note a template of the progress report is obtainable on www.sun.ac.za/rds and should be submitted to the Committee before the year has expired. The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit.
Translation of the consent document to the language applicable to the study participants should be submitted.

Federal Wide Assurance Number: 00001372
Institutional Review Board (IRB) Number: IRB0005239

The Health Research Ethics Committee complies with the SA National Health Act No.61 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 Part 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes 2004 (Department of Health).

Provincial and City of Cape Town Approval

Please note that for research at a primary or secondary healthcare facility permission must still be obtained from the relevant authorities (Western Cape Department of Health and/or City Health) to conduct the research as stated in the protocol. Contact persons are Ms Claudette Abrahams at Western Cape Department of Health (healthres@pgwc.gov.za Tel: +27 21 483 9907) and Dr Helene Visser at City Health (Helene.Visser@capetown.gov.za Tel:

+27 21 400 3981). Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics approval is required BEFORE approval can be obtained from these health authorities.

We wish you the best as you conduct your research.
For standard HREC forms and documents please visit: www.sun.ac.za/rds

If you have any questions or need further assistance, please contact the HREC office at .

Included Documents:

endorsement letter Martin Heine Dr Stellenbosch 2017.pdf
Declaration_Hanekom.pdf
Paymentform_signed.pdf
CV, Wayne Derman_used for ethics.pdf
CV_ SH_abbrev_2017.pdf
20170327 Response letter_signed.pdf
Emails_MSSA.pdf
Synopsis.pdf
Protocol document Appendix 1.pdf
Applicationform_signed.pdf
20170327 Response to Mods - ID_MH.pdf
20170327 Response to Mods - IC_27032017.pdf
Declaration_Heine.pdf
CoverLetter_Signed.pdf
20170327 Response to Mods - ICF
20170327 response to Mods - ID_WD.pdf
CV, Martin Heine_used for ethics.pdf
Declaration_Derman.pdf
20170327 Response to Mods - Protocol_MS_v4 2.pdf
20170327 response to Mods - ID_SDH.pdf

Sincerely,

Francis Masiye
HREC Coordinator
Health Research Ethics Committee 2

Investigator Responsibilities

Protection of Human Research Participants

Some of the responsibilities investigators have when conducting research involving human participants are listed below:

1.Conducting the Research. You are responsible for making sure that the research is conducted according to the HREC approved research protocol. You are also responsible for the actions of all your co-investigators and research staff involved with this research.

2.Participant Enrolment. You may not recruit or enrol participants prior to the HREC approval date or after the expiration date of HREC approval. All recruitment materials for any form of media must be approved by the HREC prior to their use. If you need to recruit more participants than was noted in your HREC approval letter, you must submit an amendment requesting an increase in the number of participants.

3.Informed Consent. You are responsible for obtaining and documenting effective informed consent using **only** the HREC-approved consent documents, and for ensuring that no human participants are involved in research prior to obtaining their informed consent. Please give all participants copies of the signed informed consent documents. Keep the originals in your secured research files for at least fifteen (15) years.

4.Continuing Review. The HREC must review and approve all HREC-approved research protocols at intervals appropriate to the degree of risk but not less than once per year. There is **no grace period.** Prior to the date on which the HREC approval of the research expires, **it is your responsibility to submit the continuing review report in a timely fashion to ensure a lapse in HREC approval does not occur.** If HREC approval of your research lapses, you must stop new participant enrolment, and contact the HREC office immediately.

5.Amendments and Changes. If you wish to amend or change any aspect of your research (such as research design, interventions or procedures, number of participants, participant population, informed consent document, instruments, surveys or recruiting material), you must submit the amendment to the HREC for review using the current Amendment Form. You **may not initiate** any amendments or changes to your research without first obtaining written HREC review and approval. The **only exception** is when it is necessary to eliminate apparent immediate hazards to participants and the HREC should be immediately informed of this necessity.

6.Adverse or Unanticipated Events. Any serious adverse events, participant complaints, and all unanticipated problems that involve risks to participants or others, as well as any research-related injuries, occurring at this institution or at other performance sites must be reported to the HREC within **five (5) days** of discovery of the incident. You must also report any instances of serious or continuing problems, or non-compliance with the HRECs requirements for protecting human research participants. The only exception to this policy is that the death of a research participant must be reported in accordance with the Stellenbosch Universtiy Health Research Ethics Committee Standard Operating Procedures www.sun025.sun.ac.za/portal /page/portal/Health_Sciences/English/Centres%20and%20Institutions/Research_Development_Support/Ethics/Application_package All reportable events should be submitted to the HREC using the Serious Adverse Event Report Form.

7.Research Record Keeping. You must keep the following research-related records, at a minimum, in a secure location for a minimum of fifteen years: the HREC approved research protocol and all amendments; all informed consent documents; recruiting materials; continuing review reports; adverse or unanticipated events; and all correspondence from the HREC

8.Reports to the MCC and Sponsor. When you submit the required annual report to the MCC or you submit required reports to your sponsor, you must provide a copy of that report to the HREC. You may submit the report at the time of continuing HREC review.

9.Provision of Emergency Medical Care. When a physician provides emergency medical care to a participant without prior HREC review and approval, to the extent permitted by law, such activities will not be recognised as research nor will the data obtained by any such activities should it be used in support of research.

10.Final reports. When you have completed (no further participant enrolment, interactions, interventions or data analysis) or stopped work on your research, you must submit a Final Report to the HREC.

11. On-Site Evaluations, MCC Inspections, or Audits. If you are notified that your research will be reviewed or audited by the MCC, the sponsor, any other external agency or any internal group, you must inform the HREC immediately of the impending audit/evaluation.

Appendix C: A cross-sectional survey of comorbidity and risk factors for comorbidity in people with Multiple Sclerosis living in South Africa

Welcome

Title of Research Project: A cross-sectional survey of comorbidity and risk factors for comorbidity in people with Multiple Sclerosis living in South Africa

We would like to invite you to take part in a research project which involves the completion of an online questionnaire. Your participation is entirely voluntary and you are free to decline to participate or to stop completing the questionnaire at any time, even if you have agreed to take part initially. However, once you have submitted your completed questionnaire online, you will no longer be able to withdraw your responses as there will be no way of linking your responses back to you.

This study aims to
- Get a better understanding of people with MS living in South Africa. In particular, how having more than one medical condition may affect the well-being of people with MS, and which factors might explain which people are likely or less-likely to develop secondary health conditions next to their Multiple Sclerosis

- This study is conducted by the Institute of Sports and Exercise Medicine, and division of Physiotherapy, of Stellenbosch University.

- All people with MS who are acquainted with "Multiple Sclerosis South Africa" will receive an invitation.

- Questions will concern your Multiple Sclerosis, secondary health conditions, use of medication, and a variety of important factors to consider including fatigue, sleep, mood, quality of life, and social participation.

Why are you being asked to participate?
- You are being asked to participate, as you are known within "Multiple Sclerosis South Africa", as an adult (over 18 years old) living with Multiple Sclerosis.

If you agree to participate you will be requested to
- Complete an online survey which will take approximately one hour to complete. The survey is completely anonymous unless you decide to disclose your personal information at the end of this survey.

The potential benefits of this research are...
- There are no direct benefits for you if you decide to participate. However, the information we gather due to this survey, may improve our understanding of people living with MS, in particular those living in South Africa where multiple sclerosis is relatively rare.

- We will randomly give away five books on health and physical activity for persons with MS. To be eligble to win one of these books, you will need to disclose your contact details at the end of this survey otherwise we will not know who to send the book to. This is entirely optional.

Are there any risks involved in your taking part in this research?
- There are no direct risks associated with participating in this study.

- All data gathered from this survey is anonymous, or will be de-identified (in case you decide to disclose your personal information at the end of the survey). All data gathered will be treated confidentially.

- The online survey is not being run from a "secure" https server of the kind typically used to handle credit card transactions, so there is a small possibility that responses could be viewed by unauthorized third parties (e.g., computer hackers).

- Do not use reply all to the invitation / reminder received from "Multiple Sclerosis South Africa".

You can email or phone the Principal Investigator of this study, Dr. Martin Heine at 21455899@sun.ac.za or 076 076 8342 if you have any questions about this study or encounter any problems.
This study has been approved by the Health Research Ethics Committee at Stellenbosch University. The study will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, and the Department of Health Ethics in Health Research: Principles, Processes and Studies (2015).

You can phone the Health Research Ethics Committee at 021 938 9677/9819 if there still is something that concerns you about how this study is being conducted, or if you have a complaint.

A copy of this consent form can be downloaded below.

By clicking SUBMIT you are confirming that you are over 18 years old and have read and understood the above explanation about the study, and that you agree to participate. You also understand that your participation in this study is strictly voluntary.

[Attachment: "Informed_consent_31012017.pdf"]

MS in South Africa survey

In this first section, we will get to know a little bit more about you, your background, and your living circumstances. Please recall that none of this information can be tracked back to you in person.

Please state your sex

◯ Male
◯ Female

What is your age (years)?

_____
(*Years)

Ethnicity

	White	Black African	Coloured	Indian/Asian	Other
You	○	○	○	○	○
Mother	○	○	○	○	○
Father	○	○	○	○	○
Mothers Mother	○	○	○	○	○
Mothers Father	○	○	○	○	○
Fathers Mother	○	○	○	○	○
Fathers Father	○	○	○	○	○

Living and household conditions

Please state your province of residence

- ◯ Northern Cape
- ◯ Western Cape
- ◯ Eastern Cape
- ◯ KwaZulu Natal
- ◯ Gauteng
- ◯ Northwest
- ◯ Free state
- ◯ Limpopo
- ◯ Mpumalanga
- ◯ I'm not a South African resident

Would you consider your home to be in a rural, suburban or urban setting?

- ◯ Urban area (e.g.larger cities, towns)
- ◯ Suburban (a residential district located on the outskirts of a city)
- ◯ Rural area or countryside (a geographic area that is located outside towns and cities).

Whats your marital status?

- ◯ Single, never married
- ◯ Married or living with common law partner
- ◯ Separated
- ◯ Divorced
- ◯ Widowed

How many adults (≥ 18 years old), excluding your partner, make up your household?

_____
(* Fill in 0 if there are none)

How many children (< 18 years old) make up your household?

_____
(* Fill in 0 if there are none)

Could you please provide an estimate of your net (after taxes), yearly, household, income? (*in ZAR)

- ◯ R71 479 and above
- ◯ R28 092 - R71 478
- ◯ R13 819 - R28 091
- ◯ R6 486 - R13 818
- ◯ Up to R6 485
- ◯ I don't want to disclose this information

Education and insurance

What is the highest level of education you have completed?

- ◯ Elementary School
- ◯ Senior certificate (Grade 12) / High school diploma
- ◯ Technical college (e.g. business management, engineering)
- ◯ Undergraduate (Bachelor)
- ◯ Graduate (Masters / Honours)
- ◯ Doctorate degree
- ◯ Other

If other, please describe: _____

Which option best describes your medical aid?

- ◯ No medical aid
- ◯ Basic medical aid
- ◯ Extensive medical aid
- ◯ Comprehensive medical aid

Health Condition

Your Multiple Sclerosis

As you might know, not every person with multiple sclerosis (MS) progresses over time in the same way. There are three basic "types" of MS. Please indicate which description best describes your MS.

Relapsing Remitting MS (RRMS): This is the most common form of MS. About 85% of people with MS are initially diagnosed with RRMS. People with RRMS have temporary periods called relapses, flare-ups or exacerbations, when new symptoms appear.

Secondary Progressive MS: SPMS, symptoms worsen more steadily over time, with or without the occurrence of relapses and remissions. Most people who are diagnosed with RRMS will transition to SPMS at some point.

Primary Progressive MS (PPMS): This type of MS is not very common, occurring in about 10% of people with MS. PPMS is characterized by slowly worsening symptoms from the beginning, with no relapses or remissions.

Please choose the described disease course that best matches your MS or perhaps your neurologist has told which type of MS you have.

◯ Relapsing-Remitting MS
◯ Secondary Progressive MS
◯ Primary Progressive MS

Please provide the year in which the first symptoms occurred: _____ (*YYYY)

Please provide the year in which the definite diagnose of MS was made: _____ (*YYYY)

Please read the choices listed below and choose the one that best describes your own situation. This scale focuses mainly on how well you walk. You might not find a description that reflects your condition exactly, but please mark the one category that describes your situation the closest.

◯ Normal: I may have some mild symptoms, mostly sensory due to MS but they do not limit my activity. If I do have an attack, I return to normal when the attack has passed.
◯ Mild Disability: I have some noticeable symptoms from my MS but they are minor and have only a small effect on my lifestyle.
◯ Moderate Disability: I don't have any limitations in my walking ability. However, I do have significant problems due to MS that limit daily activities in other ways.
◯ Gait Disability: MS does interfere with my activities, especially my walking. I can work a full day, but athletic or physically demanding activities are more difficult than they used to be. I usually don't need a cane or other assistance to walk, but I might need some assistance during an attack.
◯ Early Cane: I use a cane or a single crutch or some other form of support (such as touching a wall or leaning on someone's arm) for walking all the time or part of the time, especially when walking outside. I think I can walk 25 feet in 20 seconds without a cane or crutch. I always need some assistance (cane or crutch) if I want to walk as far as 3 blocks.
◯ Late Cane: To be able to walk 25 feet, I have to have a cane, crutch or someone to hold onto. I can get around the house or other buildings by holding onto furniture or touching the walls for support. I may use a scooter or wheelchair if I want to go greater distances.
◯ Bilateral Support: To be able to walk as far as 25 feet I must have 2 canes or crutches or a walker. I may use a scooter or wheelchair for longer distances.
◯ Wheelchair / Scooter: My main form of mobility is a wheelchair. I may be able to stand and/or take one or two steps, but I can't walk 25 feet, even with crutches or a walker.
◯ Bedridden: Unable to sit in a wheelchair for more than one hour.

Use of medication for your MS (disease-modyfing therapy).

Are you currently taking any prescription medication for your multiple sclerosis? Please indicate which:

- ☐ I'm not taking any disease-modifying medication
- ☐ Aubagio (teriflunomide)
- ☐ Avonex (interferon beta-1a)
- ☐ Betaseron (interferon beta-1b)
- ☐ Copaxone (glatiramer acetate)
- ☐ Extavia (interferon beta-1b)
- ☐ Gilenya (fingolimod)
- ☐ Glatopa (glatiramer acetate -- generic equivalent of Copaxone 20mg dose)
- ☐ Lemtrada (alemtuzumab)
- ☐ Novantrone (mitoxantrone)
- ☐ Plegridy (peginterferon beta-1a)
- ☐ Rebif (interferon beta-1a)
- ☐ Tecfidera (dimethyl fumarate)
- ☐ Tysabri (natalizumab)
- ☐ Zinbryta (daclizumab)
- ☐ Other

You have selected other; please provide the name of the prescription medication you are currently receiving.

_____

Medication-use for MS-related symptoms

Are you currently taking medication for any of the following symptoms? (mark all that apply)

- ☐ Bladder dysfunction
- ☐ Bowel dysfunction
- ☐ Depressive symptoms
- ☐ Dizziness or vertigo
- ☐ Emotional changes
- ☐ Fatigue
- ☐ Pain
- ☐ Sexual problems
- ☐ Spasticity
- ☐ Tremors
- ☐ Walking (Gait) probems

Please write down the medication(s) you take for bladder dysfunction.

_____

Please write down the medication(s) you take for bowel dysfunction.

_____

Please write down the medication(s) you take for depressive symptoms.

_____

Please write down the medication(s) you take for dizziness or vertigo.

_____

Please write down the medication(s) you take for emotional changes.

_____

Please write down the medication(s) you take for fatigue.

_____

Please write down the medication(s) you take for pain.

_____

Please write down the medication(s) you take for spasticity.

_____

Please write down the medication(s) you take for tremors (uncontrolled shaking).

_____

Please write down the medication(s) you take for walking (gait) problems.

_____

Which of the following supplements do you take? (mark all that apply)

- ☐ Alpha Lipoic Acid
- ☐ Asian Ginseng
- ☐ Bee Venom
- ☐ Biotin
- ☐ Bovine Colostrum
- ☐ Calcium
- ☐ Cannabidiol
- ☐ Cranberry
- ☐ Creatine
- ☐ Curcumin
- ☐ Echinacea
- ☐ Fish Oil
- ☐ Flaxeed Oil
- ☐ Gingko Biloba
- ☐ Glucosamine (Sulfate)
- ☐ Magnesium
- ☐ Marijuna / Cannabis
- ☐ Melatonin
- ☐ Milk Thistle
- ☐ Omega-6 Fatty Acids
- ☐ Phenylalanine
- ☐ Probiotics
- ☐ Selenium
- ☐ St. John's Wort
- ☐ Threonine
- ☐ Transfer Factor
- ☐ Turmeric
- ☐ Valerian
- ☐ Vitamin A
- ☐ Vitamin B6
- ☐ Vitamin B12
- ☐ Vitamin C
- ☐ Vitamin D
- ☐ Vitamin E
- ☐ Zinc
- ☐ Other
- ☐ I'm not taking any supplements

If other, please describe

_____

The next section is about other medical conditions you might have, next to the MS. In the context of this study, this section is very important. Hence please take a moment to go through each of the options and mark all that apply.

Has a doctor ever told you that you have any of the following conditions? (Mark all that apply)

- ☐ None
- ☐ High cholesterol (hyperlipidemia)
- ☐ High blood pressure (hypertension)
- ☐ Heart trouble (such as angina, congestive heart failure, or coronary artery disease)
- ☐ Disease of arteries in the legs (peripheral vascular disease)
- ☐ Lung trouble (asthma, emphysema, chronic bronchitis, COPD)
- ☐ Diabetes mellitus
- ☐ Cancer of the breast
- ☐ Cancer of the colon (large bowel)
- ☐ Cancer of the rectum
- ☐ Cancer of the lung
- ☐ Skin cancer
- ☐ Other cancers
- ☐ Uveitis (inflammation of the eye)
- ☐ Glaucoma
- ☐ Cataracts
- ☐ Migraine
- ☐ Thyroid disease (such as Graves' disease, Hashimoto's thyroiditis; not thyroid cancer)
- ☐ Vitamin B 12 deficiency (pernicious anemia)
- ☐ Lupus (systemic lupus erythematosus, SLE)
- ☐ Sjögren's syndrome
- ☐ Inflammatory bowel disease (Crohn's disease, ulcerative colitis)
- ☐ Rheumatoid arthritis
- ☐ Degenerative arthritis (osteoarthritis)
- ☐ Osteoporosis (bone disease causing thin bones leading to fractures of the hip, wrist, and spine)
- ☐ Hip replacement(s)
- ☐ Knee replacement(s)
- ☐ Fibromyalgia
- ☐ Anemia or other blood disease
- ☐ Kidney disease
- ☐ Open sore or ulcer in the lining of the stomach, esophagus, duodenum (peptic ulcer disease)
- ☐ Liver problems (such as cirrhosis)
- ☐ Irritable bowel syndrome
- ☐ Epilepsy (seizure disorder)
- ☐ Depression
- ☐ Anxiety disorder
- ☐ Bipolar disorder (manic depression)
- ☐ Schizophrenia
- ☐ HIV / AIDS
- ☐ Tuberculosis

Please provide the year of diagnosis for "high cholesterol (hyperlipidemia)" _____ (*YYYY)

Are you currently receiving treatment for this condition?
- ◯ Yes
- ◯ No

Please provide the year of diagnosis for "high blood pressure (hypertension)" _____ (*YYYY)

Are you currently receiving treatment for this condition?
- ◯ Yes
- ◯ No

Please provide the year of diagnosis for "Heart trouble (such as angina, congestive heart failure, or coronary artery disease)" _____ (*YYYY)

Are you currently receiving treatment for this condition? ◯ Yes ◯ No

Please provide the year of diagnosis for "Disease of arteries in the legs (peripheral vascular disease)" _____ (*YYYY)

Are you currently receiving treatment for this condition? ◯ Yes ◯ No

Please provide the year of diagnosis for "Lung trouble (asthma, emphysema, chronic bronchitis, or COPD)" _____ (*YYYY)

Are you currently receiving treatment for this condition? ◯ Yes ◯ No

Please provide the year of diagnosis for "Diabetes mellitus" _____ (*YYYY)

Are you currently receiving treatment for this condition? ◯ Yes ◯ No

Please provide the year of diagnosis for "cancer of the breast" _____ (*YYYY)

Are you currently receiving treatment for this condition? ◯ Yes ◯ No

Please provide the year of diagnosis for "cancer of the colon (large bowel)" _____ (*YYYY)

Are you currently receiving treatment for this condition? ◯ Yes ◯ No

Please provide the year of diagnosis for "cancer of the rectum" _____ (*YYYY)

Are you currently receiving treatment for this condition? ◯ Yes ◯ No

Please provide the year of diagnosis for "cancer of the lung" _____ (*YYYY)

Are you currently receiving treatment for this condition? ◯ Yes ◯ No

Please provide the year of diagnosis for "skin cancer" _____ (*YYYY)

Please describe the type of skin cancer: _____

Are you currently receiving treatment for this condition? ◯ Yes ◯ No

Please provide the year of diagnosis for "other type of cancer" _____ (*YYYY)

Please describe the other type of cancer: _____

Are you currently receiving treatment for this condition?
◯ Yes
◯ No

Please provide the year of diagnosis for "Uveitis (inflammation of the eye)"
_____ (*YYYY)

Are you currently receiving treatment for this condition?
◯ Yes
◯ No

Please provide the year of diagnosis for "Glaucoma"
_____ (*YYYY)

Are you currently receiving treatment for this condition?
◯ Yes
◯ No

Please provide the year of diagnosis for "Cataracts"
_____ (*YYYY)

Are you currently receiving treatment for this condition?
◯ Yes
◯ No

Please provide the year of diagnosis for "Migraine"
_____ (*YYYY)

Are you currently receiving treatment for this condition?
◯ Yes
◯ No

Please provide the year of diagnosis for "Thyroid disease (such as Graves' disease, Hashimoto's thyroiditis; not thyroid cancer)"
_____ (*YYYY)

Are you currently receiving treatment for this condition?
◯ Yes
◯ No

Please provide the year of diagnosis for "Vitamin B 12 deficiency (pernicious anemia)"
_____ (*YYYY)

Are you currently receiving treatment for this condition?
◯ Yes
◯ No

Please provide the year of diagnosis for "Lupus (systemic lupus erythematosus, SLE)"
_____ (*YYYY)

Are you currently receiving treatment for this condition?
◯ Yes
◯ No

Please provide the year of diagnosis for "Sjögren's syndrome"
_____ (*YYYY)

Are you currently receiving treatment for this condition?
◯ Yes
◯ No

Please provide the year of diagnosis for "Inflammatory bowel disease (Crohn's disease, ulcerative colitis)"
_____ (*YYYY)

Are you currently receiving treatment for this condition?
◯ Yes
◯ No

Please provide the year of diagnosis for "Rheumatoid arthritis"
_____ (*YYYY)

Are you currently receiving treatment for this condition?
◯ Yes
◯ No

Please provide the year of diagnosis for "Degenerative arthritis (osteoarthritis)" _____ (*YYYY)

Are you currently receiving treatment for this condition? ◯ Yes ◯ No

Please provide the year of diagnosis for "Osteoporosis (bone disease causing thin bones -leading to fractures of the hip, wrist, and spine)" _____ (*YYYY)

Are you currently receiving treatment for this condition? ◯ Yes ◯ No

Please provide the year of diagnosis for "Hip replacement(s)" _____ (*YYYY)

Are you currently receiving treatment for this condition? ◯ Yes ◯ No

Please provide the year of diagnosis for "Knee replacement(s)" _____ (*YYYY)

Are you currently receiving treatment for this condition? ◯ Yes ◯ No

Please provide the year of diagnosis for "Fibromyalgia" _____ (*YYYY)

Are you currently receiving treatment for this condition? ◯ Yes ◯ No

Please provide the year of diagnosis for "Anemia or other blood disease" _____ (*YYYY)

Are you currently receiving treatment for this condition? ◯ Yes ◯ No

Please provide the year of diagnosis for "Kidney disease" _____ (*YYYY)

Are you currently receiving treatment for this condition? ◯ Yes ◯ No

Please provide the year of diagnosis for "Open sore or ulcer in the lining of the stomach, esophagus, duodenum (peptic ulcer disease)" _____ (*YYYY)

Are you currently receiving treatment for this condition? ◯ Yes ◯ No

Please provide the year of diagnosis for "Liver problems (such as cirrhosis)" _____ (*YYYY)

Are you currently receiving treatment for this condition? ◯ Yes ◯ No

Please provide the year of diagnosis for "Irritable bowel syndrome" _____ (*YYYY)

Are you currently receiving treatment for this condition? ◯ Yes ◯ No

Please provide the year of diagnosis for "Epilepsy (seizure disorder)" _____ (*YYYY)

Are you currently receiving treatment for this condition?
◯ Yes
◯ No

Please provide the year of diagnosis for "Depression"
_____
(*YYYY)

Are you currently receiving treatment for this condition?
◯ Yes
◯ No

Please provide the year of diagnosis for "Anxiety disorder"
_____
(*YYYY)

Are you currently receiving treatment for this condition?
◯ Yes
◯ No

Please provide the year of diagnosis for "Bipolar disorder (manic depression)"
_____
(*YYYY)

Are you currently receiving treatment for this condition?
◯ Yes
◯ No

Please provide the year of diagnosis for "Schizophrenia"
_____
(*YYYY)

Are you currently receiving treatment for this condition?
◯ Yes
◯ No

Please provide the year of diagnosis for "HIV / AIDS"
_____
(*YYYY)

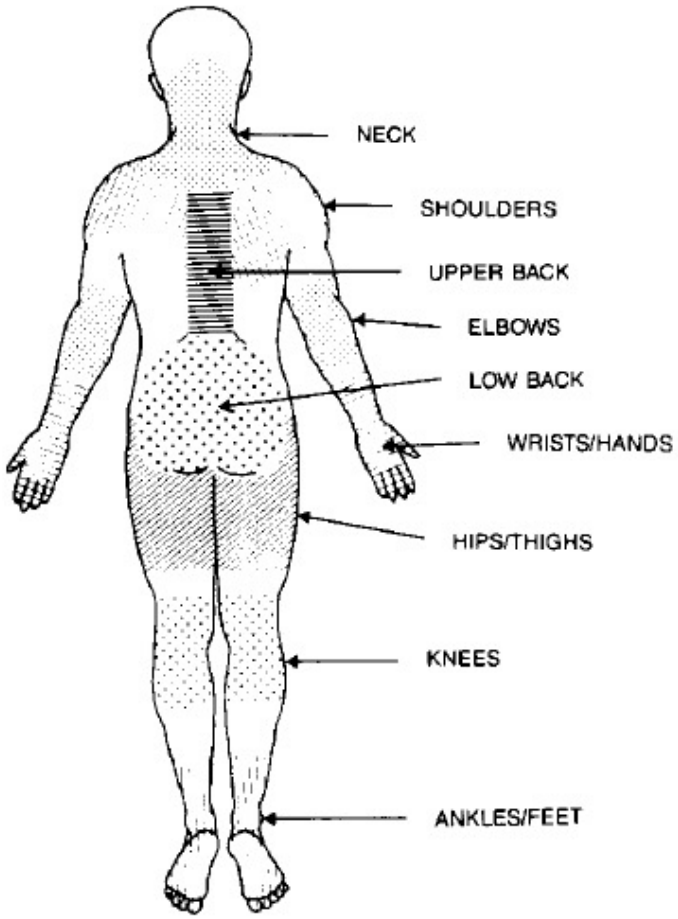
Are you currently receiving treatment for this condition?
◯ Yes
◯ No

Please provide the year of diagnosis for "Tuberculosis"
_____
(*YYYY)

Are you currently receiving treatment for this condition?
◯ Yes
◯ No

Trouble with the locomotive organs.

In the below picture you can see the approximate position of the parts of the body referred to in the next set of questions. Limits are not sharply defined and parts may overlap. You should decide for yourself in which part you had trouble (if any).



Have you add any time during the last 12 months had trouble (pain, ache, discomfort) in:

	No	Yes
Neck	◯	◯
Shoulders	◯	◯
Elbows	◯	◯
Wrists/hands	◯	◯
Upper back	◯	◯
Lower back (small of the back)	◯	◯
One of both hips/thighs	◯	◯
One or both knees	◯	◯
One of both ankles/feet	◯	◯

Regarding your neck trouble; have you had any time during the last 12 months been prevented from doing your normal work (at home or away from home) because of your neck trouble?
◯ Yes
◯ No

Have you had any neck trouble at any time during the past 7 days?
◯ Yes
◯ No

Do you consider your neck trouble a directly related to your MS? (e.g. neuropathic pain, or muscle stiffness, spasms)
◯ Yes
◯ No

Do you have shoulder trouble in:
◯ the left shoulder
◯ the right shoulder
◯ both shoulders

Regarding your shoulders; have you had any time during the last 12 months been prevented from doing your normal work (at home or away from home) because of your shoulder trouble?
◯ Yes
◯ No

Have you had any shoulder trouble at any time during the past 7 days?
◯ Yes
◯ No

Do you consider your shoulder trouble directly related to your MS? (e.g. neuropathic pain, or muscle stiffness, spasms)
◯ Yes
◯ No

Do you have elbow trouble in:
◯ the left elbow
◯ the right elbow
◯ both elbows

Regarding your elbows; have you had any time during the last 12 months been prevented from doing your normal work (at home or away from home) because of your elbow trouble?
◯ Yes
◯ No

Have you had any elbow trouble at any time during the past 7 days?
◯ Yes
◯ No

Do you consider your elbow trouble directly related to your MS? (e.g. neuropathic pain, or muscle stiffness, spasms)
◯ Yes
◯ No

Do you have hand/wrist trouble in:	◯ the left hand/wrist ◯ the right hand/wrist ◯ both hands/wrists
Regarding your hands/wrists; have you had any time during the last 12 months been prevented from doing your normal work (at home or away from home) because of your hand/wrist trouble?	◯ Yes ◯ No
Have you had any hand/wrist trouble at any time during the past 7 days?	◯ Yes ◯ No
Do you consider your hand/wrists trouble directly related to your MS? (e.g. neuropathic pain, or muscle stiffness, spasms)	◯ Yes ◯ No
Regarding your upper back; have you had any time during the last 12 months been prevented from doing your normal work (at home or away from home) because of your upper back trouble?	◯ Yes ◯ No
Have you had any upper back trouble at any time during the past 7 days?	◯ Yes ◯ No
Do you consider your upper back trouble directly related to your MS? (e.g. neuropathic pain, or muscle stiffness, spasms)	◯ Yes ◯ No
Regarding your lower back; have you had any time during the last 12 months been prevented from doing your normal work (at home or away from home) because of your lower back trouble?	◯ Yes ◯ No
Have you had any lower back trouble at any time during the past 7 days?	◯ Yes ◯ No
Do you consider your lower back trouble directly related to your MS? (e.g. neuropathic pain, or muscle stiffness, spasms)	◯ Yes ◯ No
Regarding your hips/thighs; have you had any time during the last 12 months been prevented from doing your normal work (at home or away from home) because of your hips/thighs trouble?	◯ Yes ◯ No
Have you had any hips/thighs trouble at any time during the past 7 days?	◯ Yes ◯ No
Do you consider your hip/thigh trouble directly related to your MS? (e.g. neuropathic pain, or muscle stiffness, spasms)	◯ Yes ◯ No
Regarding your knees; have you had any time during the last 12 months been prevented from doing your normal work (at home or away from home) because of your knees trouble?	◯ Yes ◯ No
Have you had any knees trouble at any time during the past 7 days?	◯ Yes ◯ No
Do you consider your knee trouble directly related to your MS? (e.g. neuropathic pain, or muscle stiffness, spasms)	◯ Yes ◯ No

Regarding your ankles/feet; have you had any time during the last 12 months been prevented from doing your normal work (at home or away from home) because of your ankles/feet trouble?
◯ Yes
◯ No

Have you had any ankles/feet trouble at any time during the past 7 days?
◯ Yes
◯ No

Do you consider your ankle/feet trouble directly related to your MS? (e.g. neuropathic pain, or muscle stiffness, spasms)
◯ Yes
◯ No

Health behaviour

Body composition

What is your current body weight in kilograms? _____

What is your current height in centimeters? _____

Smoking

When was the last time you smoked a cigarette even a single puff?

- ◯ Less than one day ago
- ◯ 1-7 days ago
- ◯ 8-30 days ago
- ◯ 31-90 days ago
- ◯ 90-180 days ago
- ◯ 180-365 days ago
- ◯ More than 1 year ago
- ◯ I have not smoked at least 100 cigarettes in my lifetime.

On average in the past 7 days, how many cigarettes have you smoked per day?

- ◯ Nothing in the past 7 days
- ◯ Less than 1 cigarette per day on average in the past 7 days
- ◯ 1-5 cigarettes per day in the past 7 days
- ◯ 6-10 cigarettes per day in the past 7 days
- ◯ 11-20 cigarettes per day in the past 7 days
- ◯ 21-40 cigarettes per day in the past 7 days
- ◯ More than 40 cigarettes per day in the past 7 days

Alcohol consumption

How often do you have a drink containing alcohol?

◯ Never
◯ Monthly or less
◯ 2-4 times a month
◯ 2-3 times a week
◯ 4 or more times a week

How many standard drinks containing alcohol do you have on a typical day?

◯ 1 or 2
◯ 3 or 4
◯ 5 or 6
◯ 7 to 9
◯ 10 or more

How often do you have six or more drinks on one occasion?

◯ Never
◯ Less than monthly
◯ Monthly
◯ Weekly
◯ Daily or almost daily

Sports and Exercise participation

During the last 12 months did you participate in any physical activities for exercise, recreation or sport?
- ◯ Yes
- ◯ No
- ◯ Don't know / unsure

How many different physical activities for exercise, recreation or sport did you participate in?
- ◯ 1
- ◯ 2
- ◯ 3,
- ◯ More than 3

Can you shortly describe the most frequent physical activity for exercise, recreation or sport you participated in? For example soccer, squash, or brisk walking.

_____

On average, how often did you participate in this physical activity for exercise, recreation or sport?
- ◯ Less than once a month
- ◯ One to three times a month
- ◯ Once a week
- ◯ Twice a week
- ◯ More than twice a week

Would you consider this particular physical activity for exercise, recreation or sport:
- ◯ Low intensity
- ◯ Moderate intensity
- ◯ High intensity

Can you shortly describe the second most frequent physical activity for exercise, recreation or sport you participated in? For example soccer, squash, or brisk walking.

_____

On average, how often did you participate in this physical activity for exercise, recreation or sport?
- ◯ Less than once a month
- ◯ One to three times a month
- ◯ Once a week
- ◯ Twice a week
- ◯ More than twice a week

Would you consider this particular physical activity for exercise, recreation or sport:
- ◯ Low intensity
- ◯ Moderate intensity
- ◯ High intensity

Can you shortly describe the third most frequent physical activity for exercise, recreation or sport you participated in? For example soccer, squash, or brisk walking.

_____

On average, how often did you participate in this physical activity for exercise, recreation or sport?
- ◯ Less than once a month
- ◯ One to three times a month
- ◯ Once a week
- ◯ Twice a week
- ◯ More than twice a week

Would you consider this particular physical activity for exercise, recreation or sport:
- ◯ Low intensity
- ◯ Moderate intensity
- ◯ High intensity

Dietary habits

How would you rate your personal dietary habits and/or food intake?

Unhealthy — Healthy

(Place a mark on the scale above)

Fatigue part 1

The following questionnaire is about problems in everyday life which are directly associated with an extreme form of tiredness (fatigue). This extreme form of tiredness refers to an overwhelming state of lethargy, exhaustion and lack of energy which comes on abruptly and is unrelated to any obvious external causes. It does not mean the sort of isolated episodes which everyone might experience in the course of the day, after exertion, or after a sleepless night.

Please read each statement carefully. Then decide to what extent each statement applies to you and your everyday life. Please try not to base your answers on the way you are feeling at the moment; instead try to give us a picture of the way you feel in normal day-to-day life. Please select the appropriate circle.

	Does not apply at all	Does not apply much	Slightly applies	Applies a lot	Applies completely
177) When I concentrate for a long time, I get exhausted sooner than other people of my age	○	○	○	○	○
178) When I am experiencing episodes of exhaustion, my movements become noticeably clumsier and less coordinated	○	○	○	○	○
179) Because of my episodes of exhaustion, I now need more frequent and/or longer rests during physical activity than I used to	○	○	○	○	○
180) When I am experiencing episodes of exhaustion, I am incapable of making decisions	○	○	○	○	○
181) When faced with stressful situations, I now find that I get physically exhausted quicker than I used to	○	○	○	○	○
182) Because of my episodes of exhaustion, I now have considerably less social contact than I used to	○	○	○	○	○
183) Because of my episodes of exhaustion, I now find it more difficult to learn new things than I used to	○	○	○	○	○
184) The demands of my work exhaust me mentally more quickly than they used to	○	○	○	○	○

185)

I feel the episodes of exhaustion particularly strongly in my muscles	○	○	○	○	○
186) I no longer have the stamina for long periods of physical activity that I used to have	○	○	○	○	○

	Does not apply at all	Does not apply much	Slightly applies	Applies a lot	Applies completely
187) My powers of concentration decrease consi- derably when I'm under stress	○	○	○	○	○
188) When I am experiencing episodes of exhaustion, I am less motivated than others to start activities that involve physical effort	○	○	○	○	○
189) My thinking gets increasingly slow when it is hot	○	○	○	○	○
190) When I am experiencing an episode of exhaustion, my movements become noticeably slower	○	○	○	○	○
191) Because of my episodes of exhaustion, I now feel less like doing things which require concentration	○	○	○	○	○
192) When an episode of exhaustion comes on, I am simply no longer able to react quickly	○	○	○	○	○
193) When I am experiencing episodes of exhaustion, certain words simply escape me	○	○	○	○	○
194) When I am experiencing episodes of exhaustion, I lose concentration considerably quicker than I used to	○	○	○	○	○
195) When it is hot, my main feeling is one of extreme physical weakness and lack of energy	○	○	○	○	○
196) During episodes of exhaustion, I am noticeably more forgetful	○	○	○	○	○

Cognitive function

197) In the past 7 days,
My thinking has been slow

- ◯ Never
- ◯ Rarely (Once)
- ◯ Sometimes (Two or three times)
- ◯ Often (About once a day)
- ◯ Very often (Several times a day)

198) In the past 7 days,
It has seemed like my brain was not working as well as usual

- ◯ Never
- ◯ Rarely (Once)
- ◯ Sometimes (Two or three times)
- ◯ Often (About once a day)
- ◯ Very often (Several times a day)

199) In the past 7 days,
I have had to work harder than usual to keep track of what I was doing

- ◯ Never
- ◯ Rarely (Once)
- ◯ Sometimes (Two or three times)
- ◯ Often (About once a day)
- ◯ Very often (Several times a day)

200) In the past 7 days,
I have had trouble shifting back and forth between different activities that require thinking

- ◯ Never
- ◯ Rarely (Once)
- ◯ Sometimes (Two or three times)
- ◯ Often (About once a day)
- ◯ Very often (Several times a day)

201) In the past 7 days,
I have had trouble concentrating

- ◯ Never
- ◯ Rarely (Once)
- ◯ Sometimes (Two or three times)
- ◯ Often (About once a day)
- ◯ Very often (Several times a day)

202) In the past 7 days,
I have had to work really hard to pay attention or I would make a mistake

- ◯ Never
- ◯ Rarely (Once)
- ◯ Sometimes (Two or three times)
- ◯ Often (About once a day)
- ◯ Very often (Several times a day)

203) In the past 7 days,
I have had trouble forming thoughts

- ◯ Never
- ◯ Rarely (Once)
- ◯ Sometimes (Two or three times)
- ◯ Often (About once a day)
- ◯ Very often (Several times a day)

204) In the past 7 days,
I have had trouble adding or subtracting numbers in my head

- ◯ Never
- ◯ Rarely (Once)
- ◯ Sometimes (Two or three times)
- ◯ Often (About once a day)
- ◯ Very often (Several times a day)

Mobility

You're about halfway now. Please feel free to take a break and continue later. However, we would really appreciate it if you could complete the questionnaire on the same day you started.

Are you able to walk, even if it is just a little bit?

◯ Yes
◯ No

In the past two weeks, how much has your MS:

	Not at all	A little	Moderately	Quit a lot	Extremely
Limited your ability to walk?	○	○	○	○	○
Limited your ability to run?	○	○	○	○	○
Limited your ability to climb up and down stairs?	○	○	○	○	○
Made standing when doing things more difficult?	○	○	○	○	○
Limited your balance when standing or walking?	○	○	○	○	○
Limited how far you are able to walk?	○	○	○	○	○
Increased the effort needed for you to walk?	○	○	○	○	○
Made it necessary for you to use support when walking indoors (eg holding on to furniture, using a stick, etc.)?	○	○	○	○	○
Made it necessary for you to use support when walking outdoors (eg using a stick, a frame, etc.)?	○	○	○	○	○
Slowed down your walking?	○	○	○	○	○
Affected how smoothly you walk?	○	○	○	○	○
Made you concentrate on your walking?	○	○	○	○	○

Physical Activity

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. Your answers will help us to understand how active we are compared with people in other countries. The questions are about the time you spent being physically active in the last 7 days. They include questions about activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport. Please answer each question even if you do not consider yourself to be an active person. In answering the following questions, vigorous physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. moderate activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal.

1a. During the last 7 days, on how many days did you do vigorous physical activities like heavy lifting, digging, aerobics, or fast bicycling?

Think about only those physical activities that you did for at least 10 minutes at a time.

- ◯ 1 day per week
- ◯ 2 days per week
- ◯ 3 days per week
- ◯ 4 days per week
- ◯ 5 days per week
- ◯ 6 days per week
- ◯ 7 days per week
- ◯ none

1b. How much time in total did you usually spend on one of those days doing vigorous physical activities?

hours _____

minutes _____

2a. Again, think only about those physical activities that you did for at least 10 minutes at a time. During the last 7 days, on how many days did you do moderate physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

- ◯ 1 day per week
- ◯ 2 days per week
- ◯ 3 days per week
- ◯ 4 days per week
- ◯ 5 days per week
- ◯ 6 days per week
- ◯ 7 days per week
- ◯ none

2b. How much time in total did you usually spend on one of those days doing moderate physical activities?

hours _____

minutes _____

3a. During the last 7 days, on how many days did you walk for at least 10 minutes at a time? This includes walking at work and at home, walking to travel from place to place, and any other walking that you did solely for recreation, sport, exercise or leisure.

- ◯ 1 day per week
- ◯ 2 days per week
- ◯ 3 days per week
- ◯ 4 days per week
- ◯ 5 days per week
- ◯ 6 days per week
- ◯ 7 days per week
- ◯ none

3b. How much time in total did you usually spend walking on one of those days?

hours _____

minutes _____

The last question is about the time you spent sitting on weekdays while at work, at home, while doing course work and during leisure time. This includes time spent sitting at a desk, visiting friends, reading traveling on a bus or sitting or lying down to watch television.

4. During the last 7 days, how much time in total did you usually spend sitting on a week day?

hours _____

minutes _____

Fatigue part 2

229) During the past 7 days:
I feel fatigued
- ◯ Not at all
- ◯ A little bit
- ◯ Somewhat
- ◯ Quite a bit
- ◯ Very much

230) In the past 7 days
How fatigued were you on average?
- ◯ Not at all
- ◯ A little bit
- ◯ Somewhat
- ◯ Quite a bit
- ◯ Very much

231) In the past 7 days
How run-down did you feel on average?
- ◯ Not at all
- ◯ A little bit
- ◯ Somewhat
- ◯ Quite a bit
- ◯ Very much

232) During the past 7 days:
I have trouble starting things because I am tired
- ◯ Not at all
- ◯ A little bit
- ◯ Somewhat
- ◯ Quite a bit
- ◯ Very much

233) In the past 7 days
How much were you bothered by your fatigue on average?
- ◯ Not at all
- ◯ A little bit
- ◯ Somewhat
- ◯ Quite a bit
- ◯ Very much

234) In the past 7 days
To what degree did your fatigue interfere with your physical functioning?
- ◯ Not at all
- ◯ A little bit
- ◯ Somewhat
- ◯ Quite a bit
- ◯ Very much

235) In the past 7 days
How often did you have to push yourself to get things done because of your fatigue?
- ◯ Never
- ◯ Rarely
- ◯ Sometimes
- ◯ Often
- ◯ Always

236) In the past 7 days
How often did you have trouble finishing things because of your fatigue?
- ◯ Never
- ◯ Rarely
- ◯ Sometimes
- ◯ Often
- ◯ Always

Health-Related Quality of Life

237) Mobility

- ◯ I have no problems walking about
- ◯ I have slight problems walking about
- ◯ I have moderate problems walking about
- ◯ I have severe problems walking about
- ◯ I am unable to walk about

238) Self-care

- ◯ I have no problems washing or dressing myself
- ◯ I have slight problems washing or dressing myself
- ◯ I have moderate problems washing or dressing myself
- ◯ I have severe problems washing or dressing myself
- ◯ I am unable to wash or dress myself

239) Usual activities (e.g. work, study, housework)

- ◯ I have no problems doing my usual activities
- ◯ I have slight problems doing my usual activities
- ◯ I have moderate problems doing my usual activities
- ◯ I have severe problems doing my usual activities
- ◯ I am unable to do my usual activities

240) Pain / Discomfort

- ◯ I have no pain or discomfort
- ◯ I have slight pain or discomfort
- ◯ I have moderate pain or discomfort
- ◯ I have severe pain or discomfort
- ◯ I have extreme pain or discomfort

241) Anxiety / Depression

- ◯ I am not anxious or depressed
- ◯ I am slightly anxious or depressed
- ◯ I am moderately anxious or depressed
- ◯ I am severely anxious or depressed
- ◯ I am extremely anxious or depressed

GENERAL HEALTH

242) 1. We would like to know how your health is today

2. This scale is marked from 0 - 100

3. 100 means the best health you can imagine, 0 means the worst health you can imagine

4. Move the slider to indicate how your health is today

The worst health you can imagine	The best health you can imagine

(Place a mark on the scale above)

Mood and anxiety

This questionnaire helps to know how you are feeling. Read every sentence. Select the button of the answer that best describes how you have been feeling during the LAST WEEK. You do not have to think too much to answer. In this questionnaire, spontaneous answers are more important.

243) I feel tense or 'wound up'
- ◯ Most of the time
- ◯ A lot of the time
- ◯ From time to time (occasionally)
- ◯ Not at all

244) I still enjoy the things I used to enjoy
- ◯ Definitely as much
- ◯ Not quite as much
- ◯ Only a little
- ◯ Hardly at all

245) I get a sort of frightened feeling as if something awful is about to happen
- ◯ Very definitely and quite badly
- ◯ Yes, but not too badly
- ◯ A little, but it doesn't worry me
- ◯ Not at all

246) I can laugh and see the funny side of things
- ◯ As much as I always could
- ◯ Not quite so much now
- ◯ Definitely not so much now
- ◯ Not at all

247) Worrying thoughts go through my mind
- ◯ A great deal of the time
- ◯ A lot of the time
- ◯ From time to time, but not often
- ◯ Only occasionally

248) I feel cheerful
- ◯ Not at all
- ◯ Not often
- ◯ Sometimes
- ◯ Most of the time

249) I can sit at ease and feel relaxed
- ◯ Definitely
- ◯ Usually
- ◯ Not often
- ◯ Not at all

250) I feel as if I am slowed down
- ◯ Nearly all the time
- ◯ Very often
- ◯ Sometimes
- ◯ Not at all

251) I get a sort of frightened feeling like "butterflies" in the stomach
- ◯ Not at all
- ◯ Occasionally
- ◯ Quite often
- ◯ Very often

252) I have lost interest in my appearance
- ◯ Definitely
- ◯ I don't take as much care as I should
- ◯ I may not take quite as much care
- ◯ I take just as much care

253) I feel restless as I have to be on the move
- ◯ Very much indeed
- ◯ Quite a lot
- ◯ Not very much
- ◯ Not at all

254) I look forward with enjoyment to things

- ◯ As much as I ever did
- ◯ Rather less than I used to
- ◯ Definitely less than I used to
- ◯ Hardly at all

255) I get sudden feelings of panic

- ◯ Very often indeed
- ◯ Quite often
- ◯ Not very often
- ◯ Not at all

256) I can enjoy a good book or radio/TV program

- ◯ Often
- ◯ Sometimes
- ◯ Not often
- ◯ Very seldom

Social participation

257) I have trouble doing all of my regular leisure activities with others
- ◯ Never
- ◯ Rarely
- ◯ Sometimes
- ◯ Usually
- ◯ Always

258) I have trouble doing all of the family activities that I want to do
- ◯ Never
- ◯ Rarely
- ◯ Sometimes
- ◯ Usually
- ◯ Always

259) I have trouble doing all of my usual work (include work at home)
- ◯ Never
- ◯ Rarely
- ◯ Sometimes
- ◯ Usually
- ◯ Always

260) I have trouble doing all of the activities with friends that I want to do
- ◯ Never
- ◯ Rarely
- ◯ Sometimes
- ◯ Usually
- ◯ Always

261) I have to limit the things I do for fun with others
- ◯ Never
- ◯ Rarely
- ◯ Sometimes
- ◯ Usually
- ◯ Always

262) I have to limit my regular activities with friends
- ◯ Never
- ◯ Rarely
- ◯ Sometimes
- ◯ Usually
- ◯ Always

263) I have to limit my regular family activities
- ◯ Never
- ◯ Rarely
- ◯ Sometimes
- ◯ Usually
- ◯ Always

264) I have trouble doing all of the work that is really important to me (include work at home)
- ◯ Never
- ◯ Rarely
- ◯ Sometimes
- ◯ Usually
- ◯ Always

Fatigue part 3

The next 9 question are about your fatigue over the past week. Please answer on a score between 1 (Disagree) to 7 (Agree)

Over the past week, I found that

	1 (Disagree)	2	3	4	5	6	7 (Agree)
265) My motivation is lower when I am fatigued	○	○	○	○	○	○	○
266) Exercise brings on my fatigue	○	○	○	○	○	○	○
267) I am easily fatigued	○	○	○	○	○	○	○
268) Fatigue interferes with my physical functioning	○	○	○	○	○	○	○
269) Fatigue causes frequent problems for me	○	○	○	○	○	○	○
270) My fatigue prevents sustained physical functioning	○	○	○	○	○	○	○
271) Fatigue interferes with carrying out certain duties and responsibilities	○	○	○	○	○	○	○
272) Fatigue is among the three most disabling symptoms	○	○	○	○	○	○	○
273) Fatigue interferes with my work, family, or social life	○	○	○	○	○	○	○

Quality of sleep

In the past 7 days
I was satisfied with my sleep.

- ◯ Not at all
- ◯ A little bit
- ◯ Somewhat
- ◯ Quite a bit
- ◯ Very much

In the past 7 days
My sleep was refreshing.

- ◯ Not at all
- ◯ A little bit
- ◯ Somewhat
- ◯ Quite a bit
- ◯ Very much

In the past 7 days
I had a problem with my sleep.

- ◯ Not at all
- ◯ A little bit
- ◯ Somewhat
- ◯ Quite a bit
- ◯ Very much

In the past 7 days
I had difficulty falling asleep.

- ◯ Not at all
- ◯ A little bit
- ◯ Somewhat
- ◯ Quite a bit
- ◯ Very much

In the past 7 days
My sleep was restless.

- ◯ Not at all
- ◯ A little bit
- ◯ Somewhat
- ◯ Quite a bit
- ◯ Very much

In the past 7 days
I tried hard to get to sleep.

- ◯ Not at all
- ◯ A little bit
- ◯ Somewhat
- ◯ Quite a bit
- ◯ Very much

In the past 7 days
I worried about not being able to fall asleep.

- ◯ Not at all
- ◯ A little bit
- ◯ Somewhat
- ◯ Quite a bit
- ◯ Very much

In the past 7 days
My sleep quality was...

- ◯ Very poor
- ◯ Poor
- ◯ Fair
- ◯ Good
- ◯ Very good

That's it! You are all done!

Thank you for your time and effort in completing this survey.

Please mark that apply.
(If you agree to either one of the two options above, you will be asked to provide your email-adress so we can contact you. However, please note when processing this survey, this information is disregarded and your results remain completely anonymous.)

☐ Would it be alright if we contact you again in one years time to repeat this survey?
☐ Would you like to be eligible for winning one of five copies of "Everyday Health and Fitness with Multiple Sclerosis, by David Lyons and Jacob Sloane", published in February 2017

Email:

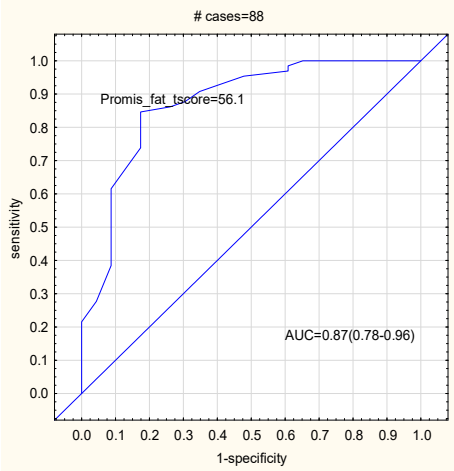
_____

Appendix D: Self-reported prevalence of comorbidities from the survey

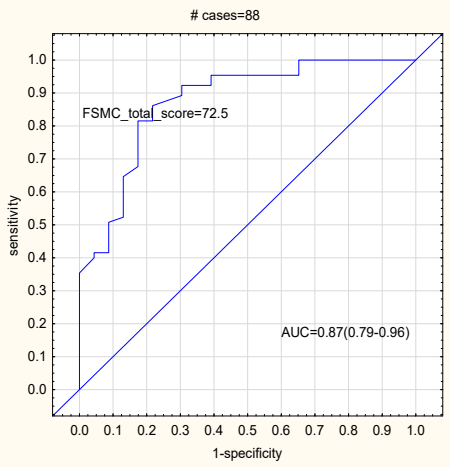
Comorbidity (122 respondents)	N (%)
Anemia or other blood disease	11 (9)
Anxiety disorder	17(13.9)
Bipolar disorder (manic depression)	3 (2.5)
Cancer of the breast	1 (0.8)
Cancer of the colon (large bowel)	1 (0.8)
Cancer of the lung	1 (0.8)
Cancer of the rectum	1 (0.8)
Cataracts	7 (5.7)
Degenerative arthritis (osteoarthritis)	6 (4.9)
Depression	44 (36.1)
Diabetes Mellitus	6 (4.9)
Disease of arteries in the legs (peripheral vascular disease)	3 (2.5)
Epilepsy (seizure disorder)	8 (6.6)
Fibromyalgia	5 (4.1)
Glaucoma	3 (2.5)
Heart trouble (such as angina, congestive heart failure, or coronary artery disease)	5 (4.1)
High blood pressure (hypertension)	25 (20.5)
High cholesterol (hyperlipidaemia)	25 (20.5)
Hip replacement(s)	1 (0.8)
HIV / AIDS	0
Inflammatory bowel disease (Crohn's disease, ulcerative colitis)	2 (1.6)
Irritable bowel syndrome	13 (10.7)
Kidney disease	3 (2.5)
Knee replacement(s)	3 (2.5)
Liver problems (such as cirrhosis)	5 (4.1)
Lung trouble (asthma, emphysema, chronic bronchitis, COPD)	16 (13.1)
Lupus (systemic lupus erythematosus, SLE)	2 (1.6)
Migraine	19 (15.6)
Open sore or ulcer in the lining of the stomach, oesophagus, duodenum (peptic ulcer disease)	6 (4.9)
Osteoporosis (bone disease causing thin bones leading to fractures of the hip, wrist, and spine)	3 (2.5)
Other cancers	2 (1.6)
Rheumatoid arthritis	2 (1.6)
Schizophrenia	0
Sjögren's syndrome	0
Skin cancer	4 (3.3)
Thyroid disease (such as Graves' disease, Hashimoto's thyroiditis; not thyroid cancer)	11 (9.0)
Tuberculosis	0
Uveitis (inflammation of the eye)	1 (0.8)
Vitamin B 12 deficiency (pernicious anaemia)	7 (5.7)

Appendix E: ROC curves for the three fatigue questionnaires for Chapter 4

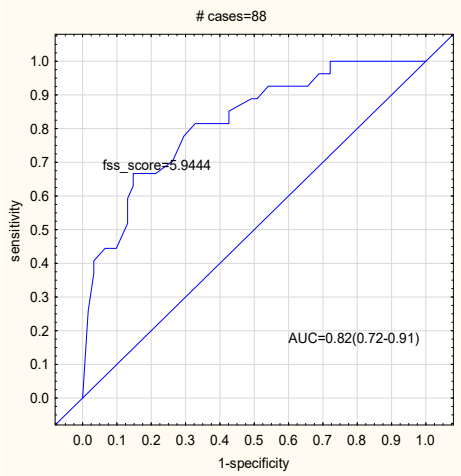
ROC curves Fatigue Severity Scale (FSS), the Fatigue Scale for Motor and Physical Functions (FSMC) and the PROMIS Fatigue Short Form Questionnaires



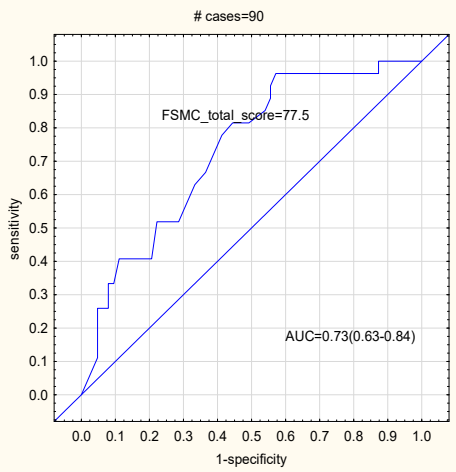
1.FSS/PROMIS



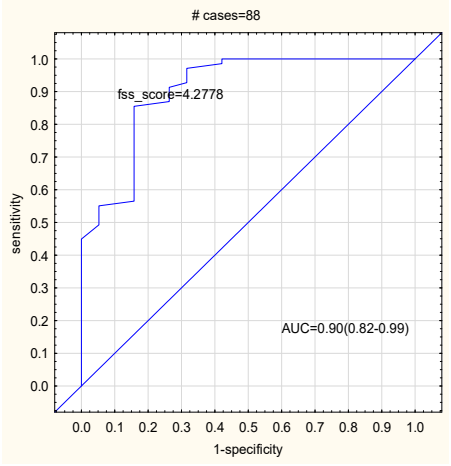
2. FSS/FSMC



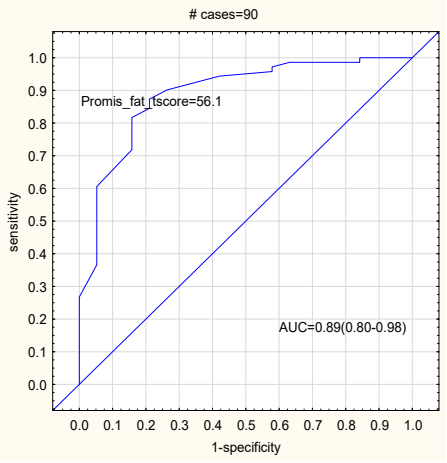
3.PROMIS/FSS



4. PROMIS/FSMC



5.FSMC/FSS



6. FSMC/PROMIS

Appendix F: PRISMA-ScR and STROBE Checklists for Chapters 2-4

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	4
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	5
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	5
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	5
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	5-6
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	5
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Appendix A
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	6
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	6
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	Click here to enter text.
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	6

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	Fig 2.1 p13
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	Table 2.1 p8
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	Click here to enter text.
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	13
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	13
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	14
Limitations	20	Discuss the limitations of the scoping review process.	15
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	15
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	NA

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.
* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.
† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).
‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.
§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med. ;169:467–473. doi: 10.7326/M18-0850

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Chapter 3 Page No	Chapter 4 Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	16	35
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	16	35
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	17	36
Objectives	3	State specific objectives, including any prespecified hypotheses	17	36
Methods				
Study design	4	Present key elements of study design early in the paper	17	37
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	17	37
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	17	37
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	18-20	37-38

Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	18-20	37-38
Bias	9	Describe any efforts to address potential sources of bias		
Study size	10	Explain how the study size was arrived at	21	39
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	21	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	21	39
		(*b*) Describe any methods used to examine subgroups and interactions		
		(*c*) Explain how missing data were addressed		
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy		
		(*e*) Describe any sensitivity analyses		

Continued on next page

Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	21	39
		(b) Give reasons for non-participation at each stage		
		(c) Consider use of a flow diagram		
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	21	39
		(b) Indicate number of participants with missing data for each variable of interest		
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)		
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time		
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—Report numbers of outcome events or summary measures		
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included		
		(*b*) Report category boundaries when continuous variables were categorized		
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses		
Discussion				
Key results	18	Summarise key results with reference to study objectives	21-25	43-45
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	33	45
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	30	43
Generalisability	21	Discuss the generalisability (external validity) of the study results	34	45
Other information				

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NA	NA

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Appendix G: Turn It In Report

MSc DM

ORIGINALITY REPORT

18%	12%	15%	%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.jove.com Internet Source	1%
2	pubmed.cn Internet Source	1%
3	Vanessa K. Noonan. "Measuring fatigue in persons with multiple sclerosis: creating a crosswalk between the Modified Fatigue Impact Scale and the PROMIS Fatigue Short Form", Quality of Life Research, 11/03/2011 Publication	1%
4	journals.sagepub.com Internet Source	1%
5	Estelle Herbert, Penelope Engel-Hills, Coenraad Hattingh, Jean-Paul Fouche et al. "Fractional anisotropy of white matter, disability and blood iron parameters in multiple sclerosis", Metabolic Brain Disease, 2018 Publication	<1%
6	Marrie, Ruth Ann, and Heather Hanwell. "General Health Issues in Multiple Sclerosis :	<1%