Phenotyping Complex Symptoms in Adults with Multiple Sclerosis

by

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Dissertation submitted in partial fulfillment of
the requirements for the degree of Doctor
of Philosophy in the Department of
Nursing in the Graduate School
of Duke University

2021

ABSTRACT

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Abstract

Multiple Sclerosis (MS) is an incurable chronic neurodegenerative autoimmune disease of the central nervous system with a complex symptom profile. An estimated 2.5 million people in the world have MS, and it is the most common cause of non-traumatic disability in young adults. A better understanding of symptoms for adults with MS may assist in the assessment, treatment, management, and prevention of impairment to improve quality of life and maintain desired functionality.

The purpose of this dissertation is to provide the foundation for my program of research on the symptom experiences of people with Multiple Sclerosis (Duke Health IRB Pro00073408). This work will explore MS symptom phenotypes, including clusters of early MS-specific symptoms and pervasive symptom trajectory typologies. The resulting symptom clusters and trajectories will describe MS symptom experiences and inform my future research regarding symptom management and prevention of adverse symptoms in adults with MS.

This dissertation is organized into five chapters. Chapter one introduces the research problem, background, and theoretical framework/underpinning. Chapter two provides a literature review exploring the symptom-informed diagnosis experience of people with MS. Chapter three explores which early MS symptoms occur together using an exploratory factor analysis to cluster MS-specific symptoms from the first MS attack according to possible latent factors.

Chapter four examines trends in longitudinal pervasive symptom trajectory typologies classified by latent class growth analysis. Chapter five is the synthesis of the findings from each chapter and implications for practice and future research.

This better understanding of symptom clusters and trajectories for MS will aid in the development of a more detailed understanding of symptoms, with the potential to incorporate additional data like genomics, imaging, and other biomarkers to aid in the diagnosis and treatment of MS and its associated symptoms, as well as to better understanding the biological underpinning of symptoms.

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Dedication

To Catherine St. John and members of the Multiple Sclerosis community who helped to inspire this work. To the many people seeking diagnosis for unexplained symptoms, and those seeking to live well with chronic symptoms.

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CHAPTER 1. Introduction

Multiple Sclerosis

Multiple Sclerosis (MS) is an incurable chronic neurodegenerative autoimmune disease of the central nervous system with a complex symptom profile (J. R. Miller, 2004; Multiple Sclerosis International Federation, 2013; National Multiple Sclerosis Society, 2020d; World Health Organization, 2008). An estimated 2.5 million people in the world have MS (National Multiple Sclerosis Society, 2020f). As of 2017 it is estimated nearly one million adults have a diagnosis of MS in the United States (Culpepper et al., 2019; National Multiple Sclerosis Society, 2019, 2020d; Nelson et al., 2019; Wallin et al., 2019), with 200 people diagnosed weekly (Multiple Sclerosis Discovery Forum, 2013). This is nearly double the number of previously reported MS cases (National Multiple Sclerosis Society, 2019). MS is the most common cause of non-traumatic disability in young adults (Dobson & Giovannoni, 2019; World Health Organization, 2008), with 80% of people with MS developing their initial symptoms between the ages of 16 and 45 (Rocky Mountain MS Center, 2018), and with a mean age at diagnosis of 29.2 (World Health Organization, 2008, p. 16).

The cause of MS is unknown (Dobson & Giovannoni, 2019), yet it is believed to involve both genetic and environmental factors (Howard et al., 2016). The term “multiple sclerosis” refers to the formation of plaques or lesions in the central nervous system, which occurs with inflammation, demyelination, axonal

injury, and axonal loss which interferes with the transmission of nerve impulses (Howard et al., 2016; Huang et al., 2017). This injury to the central nervous system results in a wide variety of symptoms, including motor, sensory, and cognitive symptoms (Howard et al., 2016). Though there is no cure for MS, early identification allows for use of immunomodulatory agents (J. R. Miller, 2004; Tur & Thompson, 2015), and aids in managing relapses and symptoms (National Multiple Sclerosis Society, 2020b) to delay neurodegeneration and disability progression as much as possible (J. R. Miller, 2004).

Types of Multiple Sclerosis

MS is divided into types based on the patterns of symptoms and disability (Howard et al., 2016). According to this categorization, the three most common types of MS are 1) relapsing-remitting MS (RRMS), 2) secondary-progressive MS (SPMS) (Bogosian et al., 2019), and 3) primary-progressive MS (PPMS) (Howard et al., 2016) (Figure 1). The majority (85%) of people are initially diagnosed with RRMS (Howard et al., 2016). In RRMS, individuals experience episodes of symptom relapses (also called exacerbations, flares, or attacks) with new or worsening symptoms that usually last for days to months, followed by periods of symptom stability, with complete or partial improvement in symptoms, or the absence of symptoms (Howard et al., 2016; Multiple Sclerosis Association of American, 2020). Half of those with RRMS will develop SPMS (Howard et al., 2016); SPMS has a slow, steady progression of symptoms and disability (Bogosian et al., 2019; Multiple Sclerosis Association of American, 2020), and is

associated with more severe cognitive deficits (Denney et al., 2005; Papathanasiou et al., 2014), neurological symptoms, fatigue, and more hospitalizations (Bogosian et al., 2019). Initially in SPMS, there may be episodes of relapse and partial remission (Multiple Sclerosis Association of American, 2020). PPMS is seen in 10% of the MS population, where individuals experience a steady worsening of symptoms, without distinct episodes of relapses and remissions (Multiple Sclerosis Association of American, 2020). Some other less common types of MS include: progressive relapsing MS, fulminate or malignant MS, and inactive or benign MS (Multiple Sclerosis Association of American, 2020). Additionally, while awaiting an official diagnosis of MS, individuals may be diagnosed with a condition often associated with the development of MS including clinically isolated syndrome (CIS), and neuromyelitis optica (NMO), among other things.

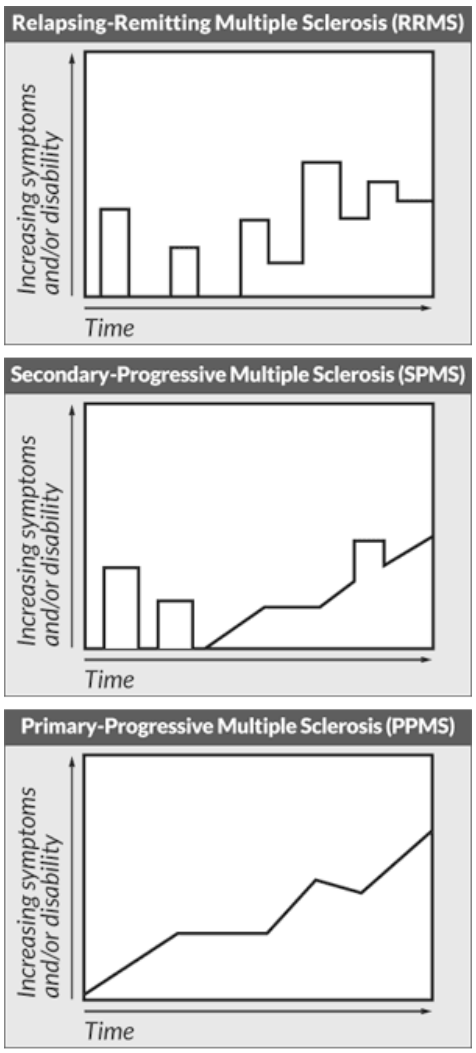

Figure 1: Three Most Common Types of MS (Holland et al., 2010)

MS Diagnostic Criteria

To diagnose MS, healthcare providers must eliminate other diagnoses, including but not limited to: lupus erythematosus, Sjogren's syndrome, vitamin and mineral deficiencies, infections, and hereditary diseases (National Multiple Sclerosis Society, 2017). There is no single finding, symptom, or laboratory test to diagnose MS (National Multiple Sclerosis Society, 2017). The 2017 McDonald

Criteria outlines additional criteria used to aid in the diagnosis of MS (Mantero et al., 2018; A. J. Thompson et al., 2018). The number of attacks is considered, along with the number of lesions, objective clinical evidence (abnormal neurological exam or imaging [MRI]), when and where attacks and lesions are occurring, as well as results from imaging and testing of the cerebrospinal fluid (CSF) (National Multiple Sclerosis Society, 2017). The 2017 McDonald Criteria shares five scenarios where an individual may be diagnosed with MS. These five scenarios are:

1) Greater than or equal to two symptomatic MS attacks with ≥ two lesions (seen on MRI of brain and spinal cord, with and without contrast) with objective clinical evidence.

2) Greater than or equal to two attacks with one lesion with objective evidence and history suggestive of a prior lesion.

3) Greater than or equal to two attacks with one lesion with objective evidence and no history suggestive of a prior lesion, with dissemination in space shown on MRI.

- Dissemination in space is shown by ≥ one T2 hyperintense lesions that are ≥ three mm (symptomatic or asymptomatic), and located in either the: 1) periventricular region of the brain (≥ one lesion, unless > 50 years old [higher number of lesions]), 2) cortical or juxtacortical region (≥ one lesion), 3) infratentorial region (≥ one lesion), or in the 4) spinal cord (≥ one lesion)

(Figure 2). Lesions on the optic nerve (optic neuritis) are not used for these criteria.

4) One attack (clinically isolated syndrome [CIS]), with ≥ two lesions with objective evidence, and with dissemination in time on MRI or by cerebrospinal fluid (CSF) specific oligoclonal bands.

- Dissemination in time is shown by a new T2-hyperintense or gadolinium-enhancing lesion (vs. a previous MRI), or simultaneous presence of gadolinium-enhancing lesion(s) and non-enhancing T2 hyperintense lesion(s) on MRI.

5) One clinical attack (CIS), with one lesion with objective evidence, and with dissemination in space and in time on MRI, or CSF-specific oligoclonal bands. (Jordan & Sharma, 2021; National Multiple Sclerosis Society, 2017; A. J. Thompson et al., 2018)

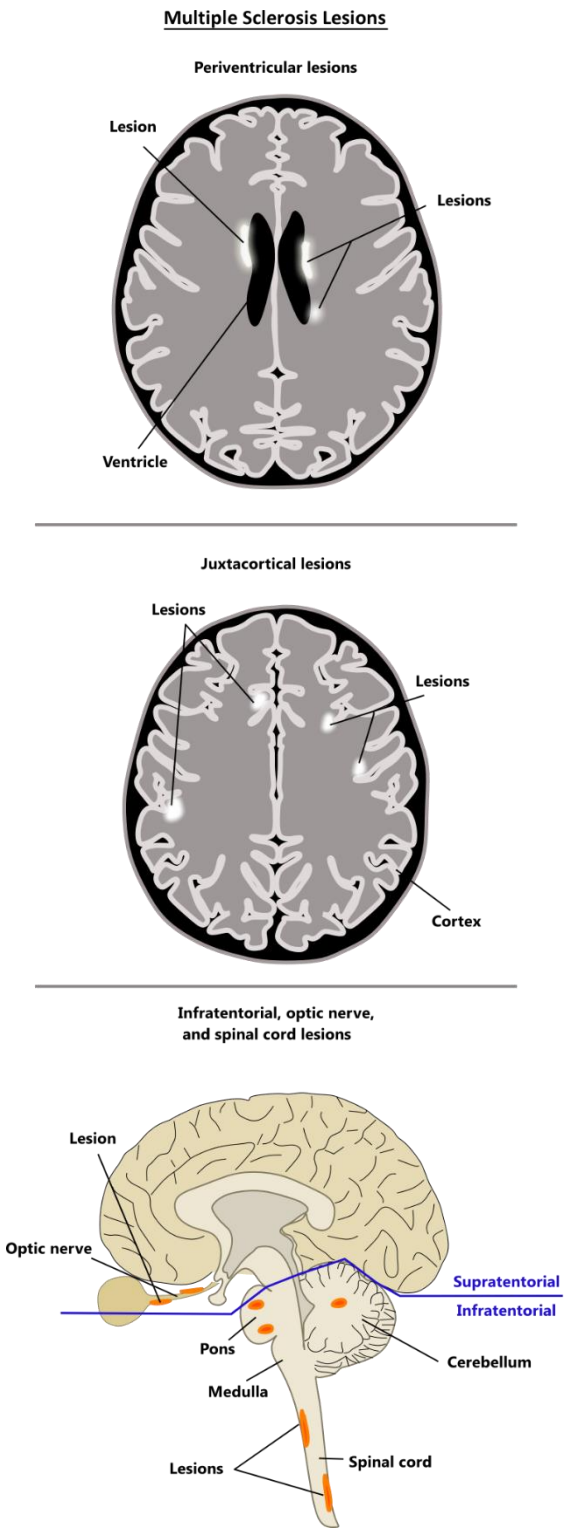

Figure 2: MS Lesion Locations (Straight Healthcare, 2021)

Clinically isolated syndrome (CIS) is a first episode of neurological symptoms lasting for at least 24 hours, and is often one of the first signs of MS (Multiple Sclerosis Trust, 2020b). Historically a definitive diagnosis of MS required a second episode of neurological symptoms, however the new 2017 McDonald diagnostic criteria indicate that if there is evidence of a previous attack (shown on MRI, oligoclonal bands in CSF, and/or abnormal neurological exam) a person with CIS can be diagnosed with MS (Jordan & Sharma, 2021; Multiple Sclerosis Trust, 2020b; National Multiple Sclerosis Society, 2017; A. J. Thompson et al., 2018). With this criteria observable/objective measures and disease progression is required for a definitive diagnosis of MS. Of note, there are some limitations with imaging and MS diagnosis, false negatives may occur (especially in early MS) (Wilson, 2019), as well as an inconsistent concordance between lesion location and symptom type and severity.

MS Symptom Experience and Quality of Life

Symptom science seeks to understand symptoms beyond diagnosis or illness, to understand the symptom experience (National Institute of Nursing Research, 2020). Barriers in translating discoveries related to the understanding of MS into the clinical setting suggest that we may benefit from considering MS from a different perspective. Considering MS in its present diagnostic categories (RRMS, SPMS, PPMS, etc.) may be preventing the observation of meaningful differences within and between groups of people with MS. MS is quite heterogeneous in its presentation and symptom course, suggesting variation

within the group. A more detailed view at early symptoms and groups of symptoms experienced by people with MS, as well as how symptoms change over time, may help to identify subgroups of different MS experiences that go beyond the present diagnostic categories. Within these new subgroups, biomarkers may be explored and identified to see if similarities and differences exist within and between the groups, shedding light on possible differing underlying mechanisms related to the manifested symptoms. Understanding the underlying mechanisms of symptoms allows for a personalized medicine approach to care, allowing for a new way to assess and treat complex chronic conditions like MS (Whitcomb, 2012). Assessing MS from a symptom perspective may allow for this new and different perspective to identify underlying biological and behavioral underpinnings, as well as innovative and targeted treatment and prevention options.

MS is well suited to this approach to assessment as it is a chronic, incurable disease, presenting in early adulthood to middle age (Leray et al., 2016; Rolak, 2003; World Health Organization, 2008). The lifespan of a person with MS is reduced by only six to seven years (Leray et al., 2016; Rolak, 2003; World Health Organization, 2008), such that patients live many years with varying degrees of impairment that may impact their personal, academic, and professional aspects of their lives. With regards to mobility, after 15 years half of people with MS will need at least a cane to walk (Aguilera, 2008; Kister et al., 2013). People with MS experience a high disease burden due to the financial

impact of high direct and indirect costs (ex. medications, imaging, lost wages, unemployment, assistive equipment, and home modifications) (Zwibel & Smrtka, 2011). Fifteen years after diagnosis 80% of people with MS are unemployed (Koziarska et al., 2018). Even with health insurance and Medicare, the economic burden of living with MS in the U.S. is considerable (Owens, 2016), second only to congestive heart failure in direct medical costs for chronic conditions (Adelman et al., 2013) and with a total lifetime cost per patient estimated at over four million dollars (Owens et al., 2013).

People with chronic conditions like MS may experience multiple co-occurring symptoms which are often underreported, underdiagnosed, and undertreated, negatively impacting an individual's quality of life and activities of daily living (Miaskowski et al., 2017). Reducing symptom burden in people with MS may help to improve an individual's overall well-being, reduce healthcare utilization and costs, and improve outcomes (Miaskowski et al., 2017). In particular, investigating co-occurring symptoms has proven to be particularly beneficial, allowing for innovative symptom management interventions (Miaskowski et al., 2017). Being able to better address the needs of this group of people may help to reduce suffering in a meaningful way for people with MS and has the potential to also be applied to the understanding of symptoms in other disease processes with overlapping symptoms.

Specific and Pervasive Symptoms

For people with MS, symptoms include MS-specific symptoms, like vision impairment and abnormal sensations (Higginson et al., 2006), as well as more general—or pervasive symptoms, like anxiety, fatigue, and pain (National Institute of Nursing Research, 2011).

MS-Specific Symptoms

MS impacts motor function, cognition, and sensation (Zwibel & Smrtka, 2011). MS-specific symptoms are attributed to brain and spinal cord damage resulting from the disease process, including (but not limited to): fatigue, difficulty walking, vision loss, tremor, numbness, tingling, muscle spasms, stiffness, weakness, depression, anxiety, impaired cognition, sexual problems, problems swallowing, and bowel and bladder problems (Evlice et al., 2016; National Health Service, 2018; National Multiple Sclerosis Society, 2020c; Wang et al., 2016; Wicks et al., 2012).

Pervasive Symptoms

Pervasive symptoms, including depression, anxiety, fatigue, sleep disturbances, cognitive changes, anger, and pain, may be triggered by challenges experienced as a result of having MS or as a result of other known comorbidities or unknown pathologies (Deloire et al., 2006; Gunzler et al., 2015; National Institute of Nursing Research, 2011). The presence and severity of specific and pervasive symptoms contribute to an overall physiologic and psychologic load placed on an individual, leading to adverse outcomes with

behavioral, economic, vocational, and societal consequences (Gapstur, 2007). Reducing this physiologic and psychologic load is critical to preventing adverse outcomes for people with MS. However, little empirical evidence exists to identify those most at risk for adverse outcomes using both specific and pervasive symptoms.

Symptom Complexity

Symptoms and symptom severity may be highly heterogeneous both between and within individuals in the type and severity of symptoms, with the potential for symptoms to change quickly, some in a matter of minutes, hours, or days (National Multiple Sclerosis Society, 2020c; Rolak, 2003). Symptoms may change rapidly for an individual throughout the day, and a wide variety of symptoms are experienced between individuals (Isaksson & Ahlström, 2006; National Multiple Sclerosis Society, 2020c).

MS symptoms are often unobservable, making them difficult to assess, and dependent upon subjective patient self-report (Isaksson & Ahlström, 2006). The newly diagnosed person may be unfamiliar with their disease, and potentially overwhelmed by new information and unfamiliar words used by healthcare providers; even those who are highly educated may not be able to comprehend health information (Partida, 2007). Self-report of symptoms itself often presents challenges as individuals often lack the confidence or skills to describe the symptoms they are experiencing to providers. Patients need time to “learn the language” of their disease and build rapport with their healthcare team, to reach

a common place of mutual understanding of the symptom experience between the patient and provider. Some people with MS may even be reluctant, fearful, or embarrassed to share the symptoms they are experiencing with providers as they may be difficult to describe, or for fear of being labeled as hypochondriacs, malingerers, or “worried well” (Masterson, 2019). Patients may even be dismissive of symptoms if they are not painful or attribute symptoms to other aspects of their life like stress, being tired, sitting too long, “sleeping wrong,” etc. The largely subjective nature of many symptoms makes the patient report the “gold standard,” but this subjectivity presents challenges to providers as well in determining the impact of a symptom on the life of an individual, where at times a reported symptom may be unintentionally dismissed or undermanaged, leading to a potential cycle of symptom underreporting by patients who then think their symptom is not important or significant since it was not addressed in their healthcare encounter. Individuals may be trying and failing to cope with symptoms that have a potential treatment to diminish the impact of the symptom on their daily life.

The MS diagnosis experience is often a long and difficult one, at times taking years to be diagnosed (Ford et al., 2012; Squires et al., 2019; Strickland et al., 2017), and is often associated with anxiety, depression, increasing symptom severity (Moore, 2018), and can be frustrating and traumatizing (Fabian, 2019; Frost et al., 2017; Wijnands et al., 2017). Patients have multiple encounters with many different types of healthcare providers, but may feel their concerns and

symptoms are dismissed by providers as being psychosomatic and left unaddressed, undermining the patient's experience and eroding trust with healthcare providers (Frost et al., 2017; Newland et al., 2016). Those who are eventually diagnosed with MS have often experienced many moments of self-doubt and invalidation from providers who have been dismissive of their symptoms in the past, such that they may not feel comfortable sharing seemingly benign or embarrassing symptoms with providers. Thus, providers may have an incomplete perspective of the symptoms experienced by people with MS, and potential impact those symptoms are having on an individual's quality of life and may even potentially be limited in their ability to offer methods of symptom management due to this reluctance from patients. Additionally, providers may be dismissive of unexplained or seemingly benign symptoms, further contributing to the distance between patients and providers with regards to trust and effective symptom management. Unmanaged symptoms increase physiologic and psychologic distress for people with MS, potentially resulting in new or worsening symptoms, and impair their ability to fulfill roles at home and in the workplace (Compston & Coles, 2008; Glanz et al., 2012; Institute of Medicine (U.S.) Committee on Multiple Sclerosis, 2001; Madell, 2019; Stuifbergen et al., 2006).

Difficulty with diagnosis results in delayed treatment, as well as challenges in management related to communication, integration/coordination of care, and the treatment and management of symptoms associated with MS (Al-Sharman et al., 2018; Carnero Contentti et al., 2020; Dennison et al., 2018; Pearce & Meyer,

2020). Delayed treatment is particularly troublesome as it is repeatedly demonstrated that starting disease modifying drugs (DMDs), also known as disease modifying therapies (DMTs), helps to delay disease progression for a significant number of people with MS (Beiki et al., 2019; van Capelle et al., 2017; van der Vuurst de Vries et al., 2018). At times while waiting for an official diagnosis, symptoms may continue to progress leading to irreversible impairments (Al-Sharman et al., 2018).

A better understanding of early symptoms, symptom clusters, symptom trajectories, and their relationship with disability may aid in identifying at risk sub-populations among those with MS to tailor interventions to best meet their needs. For my program of research, characterizing early symptoms in MS will allow for the future exploration of biomarkers, adding an objective marker to an otherwise subjective symptom experience, and has the potential to be applied to the management of other illnesses with similar neurological symptoms, like lupus, rheumatoid arthritis, and diabetes (Cikes et al., 2008; Eilertsen et al., 2015; Kurne et al., 2008; Picascia et al., 2015; Sand, 2015)

Problems Walking

Prevailing research assessing outcomes and quality of life in people with MS focuses on problems walking as a primary indicator of disability (Meyer-Moock et al., 2014; Rudick et al., 1996). This is closely mirrored in clinical practice. Though problems walking is an independent predictor of adverse outcomes in MS (Weinshenker et al., 1989), it may be a late predictor and other

less observable symptoms often precede walking problems (Deloire et al., 2006; Healy et al., 2013; Meyer-Moock et al., 2014). This critical barrier to progress in the management of symptoms in MS is problematic for three reasons. First, MS is recognized as a disease with fluctuating symptoms, especially earlier in the disease process (Rolak, 2003). A person may need a cane or wheelchair one day, and not need it the next. For ‘problems walking’ to serve as a reliable marker of symptom phenotypes, it requires the disease to progress to a point of permanent disability, where they are unable to walk on their own at any time. ‘Problems walking’ is a late symptom and does not allow for proactive prevention to occur. To prevent disease progression, we must understand the impact of symptoms before permanent ambulatory dysfunction occurs. The second reason a focus on ‘problems walking’ is a barrier to patient care is that other symptoms may be more challenging than ‘problems walking.’ For example, numbness in the hands may make it difficult to do things like use electronic devices, type, and write, which could be detrimental to a career that requires these skills. Though ‘problems walking’ provides an observable measure of one aspect of disease progression, for many, depending upon their age and family context, there may be symptoms with greater negative impact on their quality of life. Improved understanding of the impact of other types of symptoms will assist in earlier recognition of risk for poor outcomes. The third reason a focus on ‘problems walking’ is a barrier to care, is that, given the early age of onset and key developmental tasks associated with this age cohort (ex. career establishment,

romantic relationships), a range of other symptoms may negatively impact their lives either before diagnosis, or in early disease stages. For example, a person having trouble concentrating may be seen as neglectful by their spouse. Provider recognition of symptoms that cause challenges early in the disease process may help increase self-management capacity for individuals with MS, and prevent symptom progression. The possible impact of other MS symptoms (beyond problems walking) on disease progression and disability are unknown, leaving a gap in knowledge resulting in disparities in symptom management and prevention for those who do not yet have problems walking. To address this critical barrier, I am seeking to understand symptom phenotypes incorporating more than just 'problems walking,' including early MS-specific symptoms, subsequent pervasive symptom trajectories, and individual characteristics.

A description of MS symptom phenotypes and their association with risk factors for adverse outcomes may lead to more personalized health goals and improve self-management capacity for people with MS. For providers, insight into a patient's risk for adverse outcomes will allow for more aggressive symptom management with high-risk individuals to prevent or delay symptom severity progression, referral to resources, and guidance regarding future expectations. For people with MS and their families, the future holds a great deal of uncertainty. A more definitive understanding of risk for future adverse outcomes will aid in ensuring people with MS have the resources, knowledge, and support

needed to better manage symptoms and maintain abilities to function in day-to-day life.

MS Impact on Quality of Life

Symptom management

For those with a chronic, incurable condition like MS, symptom prevention and management is essential to maintain quality of life and prevent disability (National Institute of Nursing Research, 2011). However, neurological symptoms occurring with chronic illnesses like MS may go untreated or be inadequately managed for years. The symptoms experienced by a person with MS are particularly challenging due to the often insidious onset of MS, with seemingly benign episodes of inexplicable symptoms that resolve and later reappear, as well as the difficulty for clinical assessment of subjective symptom experiences (Isaksson & Ahlström, 2006; Rolak, 2003). The complexity of MS symptoms places most symptom management responsibilities on the individual with MS and their caregivers. To improve self-management and prevention of symptom progression, patients and providers must collaborate to improve the identification and monitoring of symptoms, assessment of challenges brought on by symptoms, and planning and implementation of effective interventions.

Progress in symptom science for people with MS is also stymied by methodological issues such as small sample sizes (McCabe et al., 2015; Motl et al., 2008; Shahrbanian et al., 2015), lack of a common measurement tool, lack of data linked to individual characteristics, and lack of longitudinal symptom data.

These issues lead to the current state of research which is characterized by contradiction in findings between studies (Shahrbanian et al., 2015). Ineffective early symptom management places individuals at risk for a cycle of escalating symptom presence and severity leading to permanent dysfunctional states where people with MS are more dependent on the healthcare system. Aggressive management of earlier, seemingly benign symptoms may allow for effective symptom management and prevent symptom escalation. The challenge now for MS symptom management is to identify those most at risk for adverse outcomes early in the disease process to be able to intervene by improving self-management capacity before symptoms worsen and negatively impact day-to-day functions such as employment. Understanding the relationship between early MS-specific symptoms, longitudinal pervasive symptoms, and individual characteristics (age, sex, employment status, etc.) may assist in identifying those at increased risk for adverse outcomes, allowing for the development of personalized preventive interventions.

MURDOCK MS Dataset

The MURDOCK Study Community Registry and Biorepository Multiple Sclerosis Cohort, a longitudinal health study that collected data on 970 people with MS to explore genetic explanations for response to treatment, disease progression, and biomarker validation NCT01723709 [Duke IRB Pro00023791], will be used to address the aims of this dissertation (Duke University, 2017). Data from MURDOCK MS are intended to provide information for large-scale

epidemiologic and clinical translational research, and to identify specific phenotypes and outcomes to improve medicine (Duke University, 2017). The MURDOCK MS cohort is part of the larger MURDOCK Study Community Registry and Biorepository (NCT01708408 [Duke IRB Pro00011196] (Duke University, 2017, 2019). To enroll in the larger primary (Duke University, 2017, 2019). To enroll in the larger MURDOCK study participants provided contact information, responded to memory and cognitive questionnaires, agreed to an annual follow-up (direct contact with update to health status and medical events), release of medical information (demographics, problem list, medications, social and family history, laboratory results, etc. from paper and electronic health records), provided blood and urine for storage for future research, and agreed to be contacted up to four times a year to consider participation in additional studies (Bhattacharya et al., 2012). Enrollment goals for the larger MURDOCK study were 50,000 (reaching over 12,400 by Jan 2021 (Duke Clinical & Translational Science Institute Translational Population Health Research, 2021)), and data collection began in February 2009 (Bhattacharya et al., 2012). Data for the MURDOCK MS cohort were collected from June 2010 to May 2017. Participants were 18 and older, enrolled in the MURDOCK study, and diagnosed with MS. The MS cohort completed a one-time questionnaire (four pages) regarding their MS at enrollment administered with a study coordinator, and as part of the larger MURDOCK study completed an enrollment questionnaire and an annual questionnaire; these questionnaires included symptom and demographic data

(Duke University, 2017). The MURDOCK MS study was sponsored by Duke University, enrollment occurred at five study locations in North Carolina, USA (Concord, Davidson, Durham, Kannapolis, and Raleigh) (Duke University, 2017), though participants for the MURDOCK MS cohort were not required to be residents of Cabarrus County and/or Kannapolis, NC as required for the MURDOCK study (Bhattacharya et al., 2012; Duke University, 2017). These existing data provide an opportunity to explore the MS symptom experience over time. This will be the first study to use symptom data from the MURDOCK MS dataset, providing a unique opportunity to utilize a rich, untapped resource.

Information collected by the MURDOCK MS dataset includes a 30-item checklist of symptoms of the first MS attack (MS-Specific Symptoms) (Table 1), as well as six pervasive symptoms collected at enrollment in the larger MURDOCK study and annually (anxiety, depression, pain, fatigue, sleep disturbance, and anger). The timeline and schedule of data collection events are shown in Figure 3 and Table 2. Symptom data from this study will provide fundamental knowledge needed to characterize MS symptom phenotypes to better understand variables associated with adverse outcomes, informing future research. The use of these data also holds the potential to incorporate genetics/genomics, and other biomarkers, including imaging, in future projects.

Table 1: 30-Item MS-Specific Symptom Checklist from MURDOCK-MS (Yes/No) (MURDOCK, n.d.)

Loss of balance	Vision loss (usually affects one eye at a time)
Muscle spasms	Facial pain
Numbness/abnormal sensation in any area	Painful muscle spasms
Problems moving arms or legs	Tingling, crawling, or burning feeling in the arms and legs
Problems walking	Decreased attention span, poor judgment, and memory loss
Problems with coordination and making small movements	Difficulty reasoning and solving problems
Tremor in one or more arms/legs	Depression or feelings of sadness
Constipation and stool leakage	Dizziness and balance problems
Frequent need to urinate	Hearing loss
Strong urge to urinate	Problems with erections
Urine leakage (incontinence)	Problems with vaginal lubrication
Double vision	Slurred or difficult-to-understand speech
Eye discomfort	Trouble chewing and swallowing
Uncontrollable rapid eye movements	Fatigue

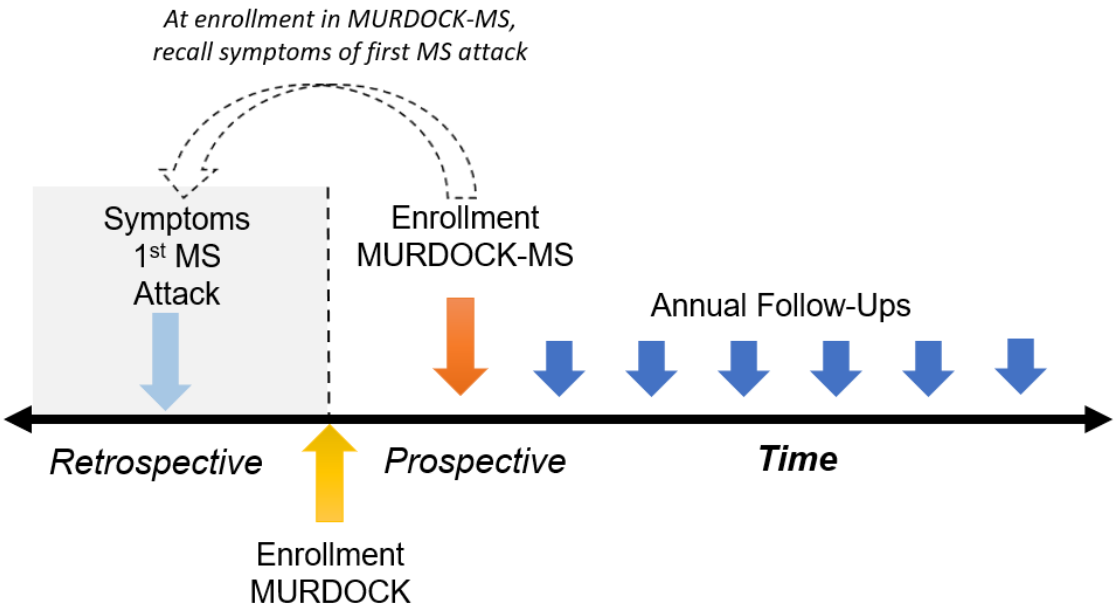

Figure 3: MURDOCK MS Timeline

Table 2: Schedule of Data Collection Events

Event	Enrollment, MURDOCK	Enrollment, MURDOCK MS	Follow-Up Year						
			1	2	3	4	5	6	…
MS-Specific Symptoms (30)*		X							
Pervasive Symptoms Anxiety, depression, pain, fatigue, sleep disturbance, anger	X		X	X	X	X	X	X	X
Enrollment Demographics Age, sex, ethnicity, race, language, marital status, education, employment status, housing, household composition, diet	X								
Ongoing Demographics Location, height, weight, health problems, medical procedures, alcohol, smoking, activities of daily living, hospitalizations, medications	X		X	X	X	X	X	X	X
MS Questionnaire Ambulation, assistive devices, lumbar puncture, MRI, family history, autoimmune history, infectious disease history, MS medication		X							
*Symptoms from first MS attack, reported at enrollment into MURDOCK MS (recall)									

Table 3: Data Concepts, Variables, Operational Definitions, Level of Measurement, and Data Source

Concept	Variable	Operational Definition	Level of Measure	Time Collected
Individual Characteristics	Age	Years [18 to 83]	Continuous	Enrollment
	Sex	Male [0], Female [1]	Categorical	Enrollment
	Race/ Ethnicity	White [0], Black [1], Hispanic [2], Other [3]	Categorical	Enrollment
	Ethnicity	Hispanic		
	Marital Status	Married [0], Divorced [1], Widowed [2], Single [3]	Categorical	Enrollment
	Level of Education	Less than high school [0], High school/GED [1], Some college/Associates [2], Bachelors [3], Masters/Higher [4]	Categorical	Enrollment
	Household Income	<$10,000 [0], 10-29,999 [1], 30-49,999 [2], 50-69,999 [3], 70-89,999 [4], >/= 90,000 [5]	Continuous	Enrollment
	Employment Status	Full-time [0], Part-time [1], Disabled [2], Unemployed [3], Other [4]	Categorical	Enrollment
	Comorbidities	Health problems (No [0] or Yes [1]): Heart [0-5], Cancer [0-9], Metabolic [0-5], Respiratory [0-2], Bone and Joint [0-5], Neurological [0-5], Gastrointestinal and Renal [0-3], Other Autoimmune [0-19] <u>Continuous Score</u>: Add total number of health problems. Scores range from 0 to 53.	Continuous	Enrollment, Annual Follow-Up
	Months Since Diagnosis	What month/year were you told by a doctor you have MS? [recode to number of months since diagnosis]	Continuous	Enrollment
	Time Since First MS Attack	What month/year did you have your first attack of MS? [recode to number of months since diagnosis]	Continuous	Enrollment
	Views About Health: (1) General health (2) Activities of daily living	3 parts: General health, activities of daily living, and satisfaction with daily routine and leisure activities, 13 questions scored w/5-point Likert scale. Scores range from [0 to 52].	Continuous	Enrollment, Annual Follow-Up

Concept	Variable	Operational Definition	Level of Measure	Time Collected
	▪ Health limit ▪ Able to (3) Satisfaction with daily routine and leisure activities	(1) General health: 1 question, Excellent [0], Very good [1], Good [2], Fair [3], Poor [4]. General health sub-score from [0 to 4].	Continuous	Enrollment, Annual Follow-Up
		Questions: (1) In general, you would say your health is: [0-4]		
		(2) Activities of daily living sub-score ("Health limit" and "Able to" combined) range from [0 to 40].	Continuous	Enrollment, Annual Follow-Up
		(2a) Activities of daily living "Health limit": 5 questions. Not at all [0], Very little [1], Somewhat [2], Quite a lot [3], Cannot do [4]. Activities of daily living "Health limit" sub-score from [0 to 20].	Continuous	Enrollment, Annual Follow-Up
		Questions: (1) Does your health now limit you in climbing one flight of stairs? [0-4], (2) Does your health now limit you in walking more than a mile? [0-4], (3) Does your health not limit you in lifting or carrying groceries? [0-4], (4) Does your health now limit you in bending, kneeling, or stooping? [0-4], (5) Does your health now limit you in doing vigorous activities, such as running, lifting heavy objects, participating in strenuous sports? [0-4]		
		(2b) Activities of daily living "Able to": 5 questions. Without any difficulty [0], With a little difficulty [1], With some difficulty [2], With much difficulty [3], Unable to do [4]. Activities of daily living "Able to" sub-score from [0 to 20].	Continuous	Enrollment, Annual Follow-Up
		Questions: (1) Are you able to do chores such as vacuuming or yard work? [0-4], (2) Are you able to dress yourself, including tying shoelaces and doing buttons? [0-4], (3) Are you able to wash and dry your body? [0-4], (4) Are you able to get on and off the toilet? [0-4], (5) Are you able to run five miles? [0-4]		
		(3) Satisfaction with daily routine and leisure activities: 2 questions, Not at all [4], A little bit [3], Somewhat [2], Quite a bit [1], Very much [0]. Satisfaction sub-score range from [0 to 8].	Continuous	Enrollment, Annual Follow-Up

Concept	Variable	Operational Definition	Level of Measure	Time Collected
		Questions: (1) I am satisfied with my ability to perform my daily routines [0-4], (2) I am satisfied with my ability to do leisure activities [0-4]		
Symptoms (MS-Specific and Pervasive)	MS-Specific Symptoms from First MS Attack*	Neurological symptoms from first MS attack (30 symptoms, No [0] or Yes [1] for each). Scores range from [0 to 30].	Continuous	Enrollment
		MS-Specific Symptoms: (1) Loss of balance, (2) Muscle Spasms, (3) Numbness/abnormal sensation, (4) Problems moving arms/legs, (5) Problems walking, (6) Problems w/coordination and making small movements, (7) Tremor in arms/legs, (8) weakness in arms/legs, (9) Constipation/stool leakage, (10) Difficulty beginning to urinate, (11) Frequent urination, (12) Strong urge to urinate, (13) Urine leakage/incontinence, (14) Double vision, (15) Eye discomfort, (16) Uncontrollable rapid eye movements, (17) Vision loss, (18) Facial pain, (19) Painful muscle spasms, (20) Tingling, crawling, burning feeling in arms/legs, (21) Decreased attention span, poor judgement, memory loss, (22) Difficulty reasoning/solving problems, (23) Depression/feelings of sadness, (24) Dizziness/balance problems, (25) Hearing loss, (26) Problems w/erections, (27) Problems w/vaginal lubrication, (28) Fatigue, (29) Slurred/difficult-to-understand speech, (30) Trouble chewing/swallowing		
	Pervasive Symptoms: (1) Anxiety (2) Depression (3) Fatigue (4) Pain (5) Sleep Disturbance (6) Anger	6 pervasive symptoms occurring over the past week. Questions for each pervasive symptom domain scored w/5-point Likert scale. Pervasive Symptom score is made up of pervasive symptom sub-scores. Range from [0 to 64].	Continuous	Enrollment, Annual Follow-Up
		(1) Anxiety: 4 questions, Never [0], Rarely [1], Sometimes [2], Often [3], Always [4]. Anxiety sub-score range from [0 to 16].	Continuous	Enrollment, Annual Follow-Up
		Questions: (1) I felt fearful [0-4], (2) I found it hard to focus on anything other than my anxiety [0-4], (3) My worries overwhelmed me [0-4], (4) I felt uneasy [0-4]		
		(2) Depression: 4 questions, Never [0], Rarely [1], Sometimes [2], Often [3], Always [4]).	Continuous	Enrollment, Annual Follow-Up

Concept	Variable	Operational Definition	Level of Measure	Time Collected
		Depression sub-score range from [0 to 16].		
		Questions: (1) I felt worthless [0-4], (2) I felt unhappy [0-4], (3) I felt depressed. [0-4], (4) I felt hopeless [0-4]		
		(3) Fatigue: 3 questions, Not at all [0], A little bit [1], Somewhat [2], Quite a bit [3], Very much [4]. Fatigue sub-score range from [0 to 12].	Continuous	Enrollment, Annual Follow-Up
		Questions: (1) How fatigued were you on average [0-4] (2) How run-down did you feel on average [0-4], (3) How tired did you feel on average [0-4]		
		(4) Pain: 3 questions, Not at all [0], A little bit [1], Somewhat [2], Quite a bit [3], Very much [4]). Pain sub-score range from [0 to 12].	Continuous	Enrollment, Annual Follow-Up
		Questions: (1) How much did pain interfere with your day-to-day activities [0-4], (2) How much did pain interfere with your ability to participate in social activities [0-4], (3) How much did pain interfere with your enjoyment of life [0-4]		
		(5) Sleep Disturbance: 1 question, Not at all [0], A little bit [1], Somewhat [2], Quite a bit [3], Very much [4]. Sleep disturbance sub-score range from [0 to 4].	Continuous	Enrollment, Annual Follow-Up
		Question: (1) I was satisfied with my sleep [0-4]		
		(6) Anger: 1 question, Never [0], Rarely [1], Sometimes [2], Often [3], Always [4]. Anger sub-score range from [0 to 4].	Continuous	Enrollment, Annual Follow-Up
		Questions: (1) I felt angry [0-4]		
*Symptoms from first MS attack, reported at enrollment (recall)				

Conceptual Models

NIH Symptom Science Model

My program of research is guided by the National Institutes of Health Symptom Science Model (NIH-SSM) (Cashion & Grady, 2015). The NIH-SSM

provides an investigative sequence for the development of knowledge in symptom science that will result in symptom reduction and improvement (Cashion & Grady, 2015). The investigative sequence outlined by the model is: 1) the study of a symptom or cluster of symptoms, 2) phenotypic characterization of symptoms, 3) biomarker discovery, and 4) testing of clinical applications (Figure 4) (Cashion & Grady, 2015). For my dissertation, I will focus on phenotypic characterization of symptoms experienced in people with MS.

Symptom phenotypes developed in this dissertation will inform the next stages of my research—biomarker discovery—to identify biomarkers that will further characterize symptom phenotypes and improve the monitoring of symptoms in people with MS. This will lead the way to future research to determine the clinical application of these monitored symptoms in people with MS. The NIH-SSM will strategically guide my work seeking to improve self-management and prevention of symptom progression for people with MS.

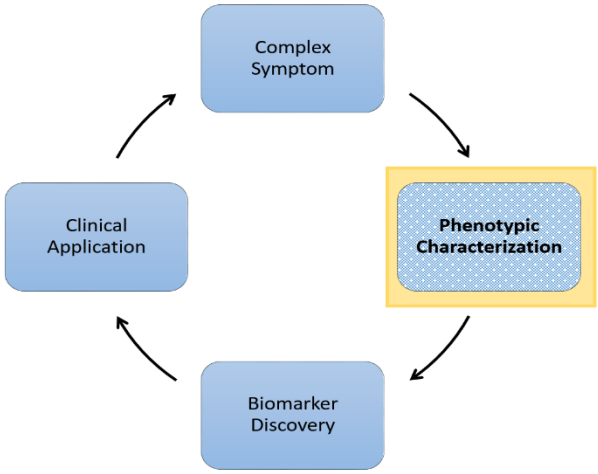

Figure 4: NIH Sympom Science Model (Cashion & Grady, 2015)

Symptom Phenotype Trajectory Model

The Symptom Phenotype Trajectory Model (Wainwright, 2016), designed for the purposes of this dissertation, will serve as the conceptual framework for the studies that will be conducted. This framework captures the interrelated concepts of specific and pervasive symptoms, that vary in severity across the disease trajectory, and their relationship to different possible outcomes. The synthesis of specific and pervasive creates unique symptom phenotype trajectory typologies that lead to a range of possible outcomes.

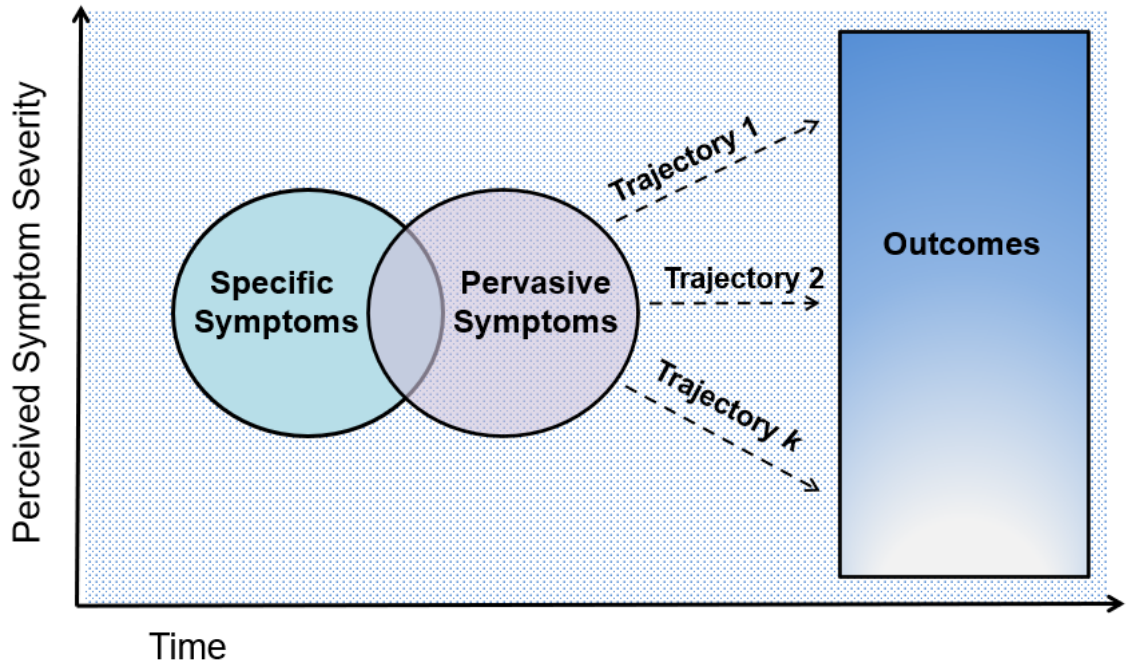

Figure 5: Symptom Phenotype Trajectory Model[1]

Purpose of Dissertation

The purpose of this dissertation is to provide the foundation for my program of research on the symptom experiences of people with Multiple Sclerosis. This work will identify MS symptom phenotypes, incorporating both early MS-specific and subsequent pervasive symptom trajectories. The resulting symptom phenotypes will describe MS symptom experiences and inform my future research regarding symptom self-management and prevention of adverse symptoms in adults with MS. An outline of the chapters are as follows:

[1] Figure and model created by Kristin J. Wainwright, 2016

- Chapter 1: The aim of this chapter is to introduce the research problem, background, and theoretical framework/underpinning.
- Chapter 2: The aim of this chapter is to conduct a literature review exploring the diagnosis experience of people with MS and identifying themes.
- Chapter 3: The aim of this chapter is to conduct an Exploratory Factor Analysis to cluster the 30 MS-specific symptoms from the first MS attack according to possible latent factors.
- Chapter 4: The aim of this chapter is to conduct a Latent Class Growth Analysis to classify longitudinal pervasive symptom trajectory typologies.
- Chapter 5: The aim of this chapter is to synthesize the findings from each chapter, discuss the limitations of the study, and provide implications for practice and future research.

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CHAPTER 2: A Literature Review of the Symptom Experience in Adults with Multiple Sclerosis

Introduction

Over 2.5 million people worldwide are believed to have multiple sclerosis, an incurable neurodegenerative disease (Browne et al., 2014; National Multiple Sclerosis Society, 2020f). People with multiple sclerosis (MS) may experience symptoms for years before diagnosis (Lublin et al., 2014; Ramagopalan et al., 2010; Wijnands et al., 2017), facing a diagnostic journey that requires disease progression before definitive diagnosis may occur. The opportunity to advance the timing of MS diagnoses to earlier in the disease trajectory, (Giovannoni, 2017; Rush et al., 2015; Wijnands et al., 2017), possibly even before symptoms present, holds with it the potential to improve long-term disease outcomes by preventing onset or progression, and better managing symptoms as they arise.

MS has a clinically heterogenous phenotype; patient presentation, symptom occurrence, severity, and trajectories may vary greatly between individuals (Rush et al., 2015; Ziemssen et al., 2016). This complexity is such that time from first symptoms to MS diagnosis may take years (Fernández et al., 2010), contributing to a delay in treatment. This delay is particularly discouraging for people with MS as it is believed that an early diagnosis is beneficial for long-term outcomes as it allows for earlier use of disease modifying drugs, improved symptom management, decreased disease burden, and better health-related quality of life (Brownlee et al., 2015; Filippini et al., 2013; Freedman et al., 2014;

Keegan, 2013; Noyes & Weinstock-Guttman, 2013). However, current diagnostic and imaging limitations (Daams et al., 2013; Kister et al., 2013; McNamara et al., 2017; Rolak, 2003) are such that the definitive diagnosis of MS requires disease progression, where patients must get worse before they can be diagnosed. This limitation in diagnostic capabilities holds with it potentially permanent physiological (Kennedy, 2013; Marrie et al., 2009; Waubant, 2012) and psychological consequences (Coenen et al., 2016). The disease burden for people with MS in the US is tremendous, with up to $70,000 annually for prescription drugs (Hartung, 2017), limited earning capabilities (Messmer Uccelli et al., 2009; Rumrill et al., 2015), decreased quality of life (Bishop et al., 2015; A. Miller & Dishon, 2006), the onset of disability (Beiki et al., 2019), strain on family and care providers (Petrikis et al., 2019), and decreased life expectancy (Lunde et al., 2017). Earlier identification of symptoms, symptom clusters and symptom trajectories indicative of MS, will likely shorten the time from initial symptom presentation to initiation of treatment, and improve symptom management. As healthcare providers and consumers seek a more proactive, preventative approach to care, a better understanding of the pre-diagnosis experience for people with MS is crucial.

Purpose

The purpose of this literature review is to identify themes from the literature regarding the pre-diagnosis and early diagnosis experience for people with multiple sclerosis.

Methods

This literature review was done in two parts, the first in April of 2017, and the second in December of 2020. The online databases PubMed, CINAHL, Scopus, and PsychINFO were searched using the terms “multiple sclerosis,” “experience,” and “diagnosis” from 2012-2017, with an updated search using the same search terms from 2017-2020 (search criteria are shown in Table 4). Inclusion criteria were: 1) diagnosis of multiple sclerosis of clinically isolated syndrome suggestive of MS, 2) component related to diagnosis experience (pre- and early diagnosis), 3) ≥18 years of age. Duplicates were removed, titles and abstracts screened, and full text articles reviewed and matrixed. Using an inductive approach, findings were analyzed and grouped into themes.

Table 4: Database, Search Terms, and Results

Date	Database	Search Terms	Results
April 2017	PubMed	(("diagnosis"[Subheading] OR "diagnosis"[All Fields] OR "diagnosis"[MeSH Terms]) AND experience [All Fields] AND ("multiple sclerosis"[MeSH Terms] OR ("multiple"[All Fields] AND "sclerosis"[All Fields]) OR "multiple sclerosis"[All Fields])) AND ("2012/04/29"[PDat] : "2017/04/27"[PDat] AND English[lang] AND "adult"[MeSH Terms])	146
April 2017	CINAHL	“multiple sclerosis” AND diagnosis AND experience AND adult Limiters: English, Published date April 2012 to April 2017	28
April 2017	Scopus	“multiple sclerosis” AND diagnosis AND experience AND adult Limit to English, and 2012, 2013, 2014, 2015, 2016, 2017	72
April 2017	PsycINFO	“multiple sclerosis” AND diagnosis AND experience AND adult Limiters: English, Published date April 2012 to April 2017	18
Dec 2020	PubMed	(("diagnosis"[Subheading] OR "diagnosis"[All Fields] OR "diagnosis"[MeSH Terms]) AND	143

Date	Database	Search Terms	Results
		experience [All Fields] AND ("multiple sclerosis"[MeSH Terms] OR ("multiple"[All Fields] AND "sclerosis"[All Fields]) OR "multiple sclerosis"[All Fields])) AND ("2017/04/01"[PDat] : "2021/04/01"[PDat] AND English[lang] AND "adult"[MeSH Terms])	
Dec 2020	CINAHL	“multiple sclerosis” AND diagnosis AND experience AND adult Limiters: English Language; Published Date: 20170401-	28
Dec 2020	Scopus	TITLE-ABS-KEY ("multiple sclerosis" AND diagnosis AND experience AND adult) AND (LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019) OR LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2017)) AND (LIMIT-TO (LANGUAGE , "English"))	93
Dec 2020	PsycINFO	“multiple sclerosis” AND diagnosis AND experience AND adult Limiters - Published Date: 20170401-; English	7

Results

For the 2012 to 2017 search (April 2017) 264 articles were identified, 46 duplicates removed, 218 abstracts were screened, 49 full text assessed, and 13 met the inclusion criteria. For the 2017 to 2020 search (December 2020), 271 articles were identified, 73 duplicates were removed, 198 abstracts were screened, 98 full text assessed, and 30 met the inclusion criteria (Figure 6). Combining the two searches, a total of 43 articles met the inclusion criteria and were condensed into a matrix.

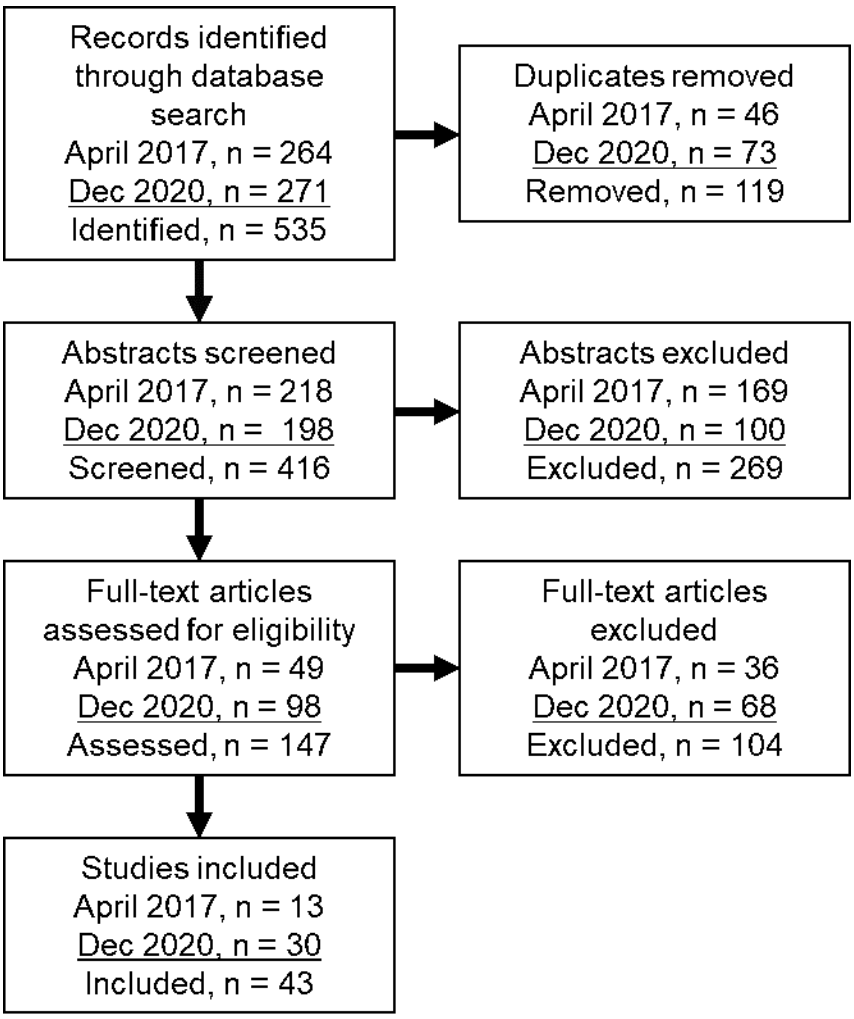


Figure 6: Flow Chart

Table 5: Literature Review Matrix of Articles, Diagnosis Experience in Multiple Sclerosis

Author (Year)	Sample Relevant to Review	Location	Data/Tools
Abd El Latif *et al.* (2020)	71 MS	Egypt	Retrospective chart review
	Results Relevant Diagnosis Experience	MS may present with eye inflammation (redness, pain, blurred vision, vision loss, "floaters," light sensitivity)	
Al-Sharman *et al.* (2018)	16 MS	Jordan	Focus groups
	Results Relevant Diagnosis Experience	Difficult to get diagnosis (delays), poor communication with providers, lack of awareness about MS. Diagnosis a difficult experience (depression, stress), wide range of symptoms, impairments due to delays	
Annunziata *et al.* (2019)	12 MS	Italy	Retrospective chart review
	Results Relevant Diagnosis Experience	People with MS may present with acute transverse myelitis	
Beiki *et al.* (2019)	7,331 MS	Sweden	Retrospective chart review
	Results Relevant Diagnosis Experience	Symptoms of 1st attack: motor, optic neuritis, easier to diagnose with newer criteria (added MRI), better prognosis with recent diagnosis (earlier treatment, better medications, identifying more benign cases)	
Bogosian *et al.* (2019)	21 MS	United Kingdom	Interviews
	Results Relevant Diagnosis Experience	How felt with first diagnosed: Depressed, needed help but none offered	
Bookwalter *et al.* (2020)	151 MS, 120,421 controls	United States	Longitudinal cohort study (Millennium Cohort Study, Military Health System Data Repository)
	Results Relevant Diagnosis Experience	History of PTSD associated with increased risk for MS over 5 years, higher in women, did not differ according to types of prior trauma and healthy behaviors not significant	
Carnero Contentti *et al. (*2020)	301 MS	Argentina	Cross-sectional online survey (PIMS Study Questionnaire, prognosis communication experiences, attitudes and preferences, MSIS-29, COPE-28, Fatigue Severity Scale, EDSS)
	Results Relevant Diagnosis Experience	72% want more information about long-term prognosis at diagnosis, 22% have never had discussed their long-term prognosis with neurologist, 47% lacked clarity about their prognosis	
	10 MS	Netherlands	Interview

Author (Year)	Sample Relevant to Review	Location	Data/Tools
Ceuninck van Capelle *et al.* (2017)	**Results Relevant Diagnosis Experience**	Decisions regarding disease modifying drugs (DMDs), 4 themes: 1) Constant confrontation with the disease (surprised by advice to start DMD right away, lifelong medication, side effects), 2) Managing inevitable decline (chance to delay progression with DMD, not all taking DMD), 3) Hope of delaying the progression of the disease (30% effective, despair with relapse, support to pay for expensive medicine, not alone), & 4) Importance of social support (choice to take DMD a social experience, family, MS nurse, drug manufacturer).	
Ciurleo *et al.* (2020)	1 MS	Italy	Case report
	Results Relevant Diagnosis Experience	Changes/distortions in sense of smell can be an early MS symptom	
Dennison *et al.* (2018)	3,175 MS	United Kingdom	Online survey (prognosis communication, attitudes, preferences, coping, tendencies to seek or avoid information in threatening situations, risk perceptions), retrospective review of registry (quality of life, anxiety and depression symptoms, and MS impact)
	Results Relevant Diagnosis Experience	Regarding discussing their long-term prognosis (LTP): 53% never discussed with provider, 54% lacked clarity, 69% wanted information at diagnosis, 79% in the future, 19% did not want to know at diagnosis, 13% did not want to know in the future, 71% felt LTP would help with decisions making about treatment, 78% finances, and 78% end-of-life care	
Dibley *et al.* (2017)	41 MS	United Kingdom	Interviews, focus groups
	Results Relevant Diagnosis Experience	Constipation may be an early MS symptom, want bowel issues discussed more, started with providers soon after MS diagnosis and at follow-up visits	
Fallahi-Khoshknab *et al.* (2014)	25 MS	Iran	Interviews
	Results Relevant Diagnosis Experience	4 themes (11 subthemes) related to facing MS diagnosis: 1) Knowledge deficit (information seeking, false perceptions), 2) Concealing the disease (disgust at others' pity & rejection, fear of job termination or unemployment), 3) Religiosity (Faith in God, resort to prayer), 4) Emotional reactions (Denial, anger, fear & anxiety, consternation & confusion, being demoralized)	
Ford *et al.* (2012)	7,279 MS	United Kingdom	Registry, feasibility of web-portal
	Results Relevant Diagnosis Experience	Registry was feasible. Early MS symptoms (n=5,969): 67% difficulty walking, 65% numbness, 59% vision problems, 25% all three. Different diagnosis experiences, 79% MRI, 29% lumbar	

Author (Year)	Sample Relevant to Review	Location	Data/Tools
		puncture, 4% neither (diagnosed with clinical findings only). 79% diagnosed by consultant neurologist, 19% by consultant physician, <2% general practitioner.	
Forn *et al.* (2013)	18 CIS* suggestive of MS, 15 age matched controls	Spain	fMRI version of SDMT, T2 lesion load, brain atrophy, Neuropsychological Tests (BRB-N, SRT, SDMT, PASAT 3s, WLG), IQ using Matrix Subtest in Weschler Adult Intelligence Scale III battery, BDI
	Results Relevant Diagnosis Experience	All within 3 months of first clinical episode. No difference between CIS and controls for demographics, brain atrophy, or neuropsychological tests. For CIS, no correlation with SDMT and MRI. CIS had enhanced pattern of brain deactivation during cognitive performance vs controls. May be an early compensatory mechanism.	
Frost *et al.* (2017)	14 PPMS**	United Kingdom	Interviews
	Results Relevant Diagnosis Experience	Diagnosis & self-management: Gender differences in diagnosis-seeking (males-sense of loss and anger with diagnosis). Lost sense of self. More difficult for women to get diagnosed, women more willing to use assistive devices, etc. to maintain roles. Men feel shame with being seen as drunk (unsteady gait, slurred speech). Symptom specific self-management strategies, planning. Left job. Importance of social networks, fear for the future, death only certainty. Validation with diagnosis, access to resources.	
Horwitz *et al.* (2014)	643 with optic neuritis (at least 388 with MS)	Denmark	National Registry, Danish MS Register, Danish MS Treatment Register
	Results Relevant Diagnosis Experience	Optic neuritis may be an early MS symptom	
Joyce *et al.* (2020)	45 autoimmune diseases (at least one MS)	United States	45 interviews
	Results Relevant Diagnosis Experience	Diagnosis experience is different for everybody, man told he did not have MS because he was male (got a second opinion), people do their own research, refer to their own experiences of others with MS, priority at diagnosis is to get their illnesses under control so that it is not a constant intrusion	
Klevan *et al.* (2014)	93 MS, 96 controls	Norway	Cross-sectional, SF-36, BDI, fatigue severity scale, Starkstein's apathy scale, neurological exam, EDSS, MS Functional Composite

Author (Year)	Sample Relevant to Review	Location	Data/Tools
	Results Relevant Diagnosis Experience	People with MS had lower health related quality of life than controls for physical health and mental health, except for bodily pain. More fatigue, depression, and apathy in people with MS than controls.	
Koffman *et al.* (2013)	43 Black Caribbean & 43 White British with MS	United Kingdom	Interviews, chart review, EDSS, Progression Index, MSSS
	Results Relevant Diagnosis Experience	Black Caribbean patients more likely to have aggressive disease, more cognitively impaired, reached functional decline more quickly, referred to feelings of extreme frustration, unresolved loss/confusion associated with rapidly advancing disease. Both groups reported a high symptom burden	
Lavorgna *et al.* (2017)	307 MS (35 LGBT)	Italy	Cross-sectional, online survey, clinical features, utilization patterns
	Results Relevant Diagnosis Experience	LGBT younger age, use less psychological services, fewer psychological consults, more likely to change MS center, higher number of visits to MS center, 85.7% of LGBT patients experienced homophobic behavior from MS center staff	
Lebrun-Frenay *et al.* (2020)	152 RRMS, 21 PPMS**	5 countries (France, Italy, Spain, Turkey, United States)	21 databases, Survival analysis, clinical data, lab results, neurological exam, MRIs, follow-up data
	Results Relevant Diagnosis Experience	451 people with Radiologically Isolated Syndrome (incidental finding of lesions, no symptoms), 152 develop MS, 21 develop PPMS. Cumulative probability of a first clinical event at 10 years was 51.2%, age, oligoclonal bands in cerebral spinal fluid, infratentorial lesions on MRI, and spinal cord lesions were predictors. 73 started MS drug before clinical episode.	
Lowden *et al.* (2014)	9 MS	Canada	Interview
	Results Relevant Diagnosis Experience	Core theme of 'redefined self' (self-image, quality of life, goals, and being a person with MS). 6 themes: 1) weighing and deciding what is important, 2) acknowledging illness as part of self, 3) playing mental game, 4) seeking credible resources, 5) evaluating symptoms and fit with quality of life, 6) managing roles and involvement of family.	
Moore (2018)	24 MS	United States	Online survey (MS-RS, HADS, Brief Cope, Illness Intrusiveness Ratings Scale)
	Results Relevant Diagnosis Experience	Dissertation. Participants with more years between symptom onset and diagnosis reported greater overall psychological distress (depression and anxiety symptoms), more symptoms of depression	

Author (Year)	Sample Relevant to Review	Location	Data/Tools
		or anxiety, and fewer, but more severe MS symptoms	
Mortenssen & Rasmussen (2017)	40 MS	Denmark	Focus groups
	Results Relevant Diagnosis Experience	Unmet need for information and support, especially at time of diagnosis. Diagnosis followed by 2-3 years of distress/worries about the future, most experienced recurring emotional oversensitivity, depression, anxiety, and anger	
Newland *et al.* (2016)	1 MS	United States	Interview
	Results Relevant Diagnosis Experience	Presentation: extreme fatigue, numbness, problems walking, falls, balance problems, weakness and heavy feeling in legs, symptoms worsen with heat, fatigue interferes with daily activities and goal, impacted independence and quality of life	
Ozakbas *et al.* (2019)	1,389 MS	Turkey	Retrospective chart review
	Results Relevant Diagnosis Experience	Change in MS patient profile over 20 years (1996 to 2016). In 2016 time to diagnosis shorter in 2016, fewer CIS & SPMS, more with low EDSS, less wheelchair dependency. No difference in sex, ages, similar disease duration, no change in proportion of PPMS patients. Fewer visits in 2016 than 1996 (fewer attacks? increased workload of clinic?). Changes in diagnostic criteria (2001 McDonald criteria added MRI [shortened time to diagnosis?], starting DMDs earlier, decrease in transition from RRMS to SPMS (effectiveness of DMDs).	
Pandey *et al.* (2018)	7 MS	India	Prospective, MRI, laboratory results, lumbar puncture, visual evoked potential, IV methylprednisolone, six-month follow-up, Barthel activities of daily living index
	Results Relevant Diagnosis Experience	People with MS may present with acute transverse myelopathy. Those who developed MS were more likely to have brain lesions on MRI (juxtacortical lesions in U-fibers, Dawson's finger lesions). Early-age onset of symptoms associated with conversion to MS. IV Methylprednisolone early in the course of the disease improved disability.	
Pandit *et al.* (2012)	29 MS	India	Registry
	Results Relevant Diagnosis Experience	Optic neuritis may be an early MS symptom.	
Parton *et al.* (2019)	20 MS	Australia	Interviews
	Results Relevant Diagnosis Experience	Mother's sense of self with MS, 3 themes identified: 1) The Failing Mother (biographical disruption), 2) Fear of Judgement and Burdening Others (social interactions), and 3) The Normal Mother (adopting strategies to manage limitations).	
	16 MS	Canada	Interviews

Author (Year)	Sample Relevant to Review	Location	Data/Tools
Pearce *et al.* (2020)	**Results Relevant Diagnosis Experience**	Managing uncertainty. Heightened uncertainty & denial in initial MS diagnosis, communication with providers did not help much with uncertainty. Participants saw their provider as a guide to reputable online sources	
Persson *et al.* (2019)	8,695 MS, 86,934 matched non-MS (US military) 6,932 MS & 68,526 matched non-MS (United Kingdom)	United States & United Kingdom	Retrospective review of two electronic databases
	Results Relevant Diagnosis Experience	Identified those diagnosed with MS at least 1 year after being in database. Most female, diagnosed before age 60, those with MS had more psychiatric conditions (depression), epilepsy, fractures, infections, neurological symptoms before MS diagnosis. Results consistent between databases.	
Peters *et al.* (2013)	1,157 MS	United Kingdom	Cross-sectional questionnaire
	Results Relevant Diagnosis Experience	Delays with diagnosis, 37% of people with MS report time from GP to specialist consult > 6 months, 43% time from 1st GP consult to diagnosis >1 yr, 58% communicated diagnosis sympathetically & professionally, 44% offered follow-up appointment, 70% given all info, 28% of those taking meds given info about side effects, 46% feel meds reviewed adequately	
Russell *et al.* (2019)	11 MS	Australia	Interview
	Results Relevant Diagnosis Experience	Dietary response to MS diagnosis. 3 themes: 1) perceived incompatibility or lack of dietary advice at time of diagnosis, 2) research & information seeking with difficulty judging credibility, & 3) self-experimentation with diet to try to control MS symptoms or cure MS.	
Sennou *et al.* (2014)	1 MS	Morocco	Interview, chart review
	Results Relevant Diagnosis Experience	Initial MS symptoms may also include symptoms that appear to be psychiatric disorders	
Soltys *et al.* (2017)	3 MS	United States	Case series, chart review, MRI, optical coherence tomography, T cell gene expression analysis (mRNA profiling)
	Results Relevant Diagnosis Experience	mRNA levels of IL-10 and LIF significantly increased in T cells of people with benign MS (diagnosis is primarily retrospective, heavily weighted towards motor progression, EDSS ≤ 3 after 10-15 years of disease onset without disease modifying drug). However, they do experience non-motor symptoms (cognitive dysfunction, pain, depression)	
Soundy *et al.* (2012)	11 MS	United Kingdom	12-week MS rehabilitation program, interviews

Author (Year)	Sample Relevant to Review	Location	Data/Tools
	Results Relevant Diagnosis Experience	Understanding hope and MS. 3 main themes related to the paradox of chronic illness: 1) defiance (hope in taking action), 2) accepting diagnosis & prognosis (turmoil with insight into future), 3) accepting deterioration (last time doing things).	
Squires *et al.* (2019)	14 MS	United Kingdom	Focus groups
	Results Relevant Diagnosis Experience	Accepting assistive technology (AT), 3 themes, create a chronological narrative of before, during, & after use of AT: 1) critical MS events (developing symptoms & disability, delayed diagnosis & coping, public reaction, progression to AT), 2) matching AT for continued use (accept MS & use of AT), 3) impact of AT (promote or lose independence, stigma, embarrassment).	
Stoppe *et al.* (2017)	108 CIS/MS	Germany	Prospective (1 yr), clinical, treatment, & outcome data
	Results Relevant Diagnosis Experience	Outcomes with MS medications. For CIS (1st MS attack) (n=31), 15 had visual symptoms (48%), 7 sensory (23%), 6 brainstem (19%), 5 motor (16%), 3 cerebellum (10%), 1 cognitive (3%), 0 ambulatory, 0 bowel & bladder, 4 involved >1 one functional system. Outcome of CIS after IV methylprednisolone: 10 (32%) full remission, 15 (48%) partial, 3 (10%) no change, 3 (10%) worse after primary treatment.	
Strickland *et al.* (2017)	10 MS	United Kingdom	Interview
	Results Relevant Diagnosis Experience	Explore MS diagnosis experience. Core theme: Impact on self (diagnosis a “threshold moment”); 3 themes: 1) road to diagnosis (story, a journey, detailed leading up to diagnosis), 2) liminal self (disrupted sense of self, losing their ‘taken for granted’ self, their biography/narrative is challenged, try to maintain specific roles [ex. Mother]), 3) learning to live with MS, uncertain future (daily life impacted, re-assess lifestyle, on-going, never stable, never know how severe symptoms will be, take things as they come).	
Tehranineshat et al. (2020)	18 MS carers	Iran	Interview
	Results Relevant Diagnosis Experience	Carers describe diagnosis experience with MS patient. Stigma, financial strain for treatment, people treat you differently (avoid), negative view of MS, fear, do not know much about MS when diagnosed, feel did not get enough information at diagnosis, thought would be paralyzed & die within a few months.	
van der Vuurst de Vries *et al.* (2018)	229 CIS*	Netherlands	Retrospective & prospective (1, 3, & 5 yrs), McDonald 2010 & 2017 criteria, MRIs, CSF (oligoclonal bands), DMDs

Author (Year)	Sample Relevant to Review	Location	Data/Tools
	Results Relevant Diagnosis Experience	Comparing McDonald diagnostic criteria (2010 to 2017): 113 (49%) CIS diagnosed with clinically definite MS (CDMS), median time to CDMS 23.4 months, 55 (24%) treated with a DMD before CDMS. 2017 criteria more sensitive by less specific for a 2nd MS attack. More MS diagnosed at baseline. Higher number of MS diagnoses, with less active disease course.	
Weisfeld-Adams (2016)	1 MS	United States & United Kingdom	Personal experience
	Results Relevant Diagnosis Experience	Pre-diagnosis symptoms: suddenly could not write (tremor), heaviness, asymmetrical pupils, uneasiness, panic. Uncertainty & relief with diagnosis. Fear for the future (provide for family, disability).	
Wijnands *et al.* (2019)	2,058 MS, 9,837 controls	Canada	Retrospective chart review, physician encounters in 5 yrs before MS symptom onset
	Results Relevant Diagnosis Experience	No difference in total number of encounters for PPMS vs. RRMS, PPMS had more nervous system related encounters and fewer encounters with dermatologists	
*CIS = Clinically isolated syndrome **PPMS = Primary-progressive multiple sclerosis			

For the 43 articles included in the final matrix, they included research conducted in 20 different countries, ranging from the author sharing their personal story and case studies to large studies (thousands of participants) with controls (tens of thousands of participants) (Table 5). Methods of data collection included but were not limited to interviews (the most popular method), retrospective chart reviews, cross sectional studies, online surveys, focus groups, registries, and databases (Table 5).

Synthesis of Results

Using an inductive approach, findings were analyzed and grouped into themes. The six themes identified related to the pre-diagnosis experience for

people with MS were: (1) change in self-image and role, (2) different reactions to diagnosis, (3) different readiness for learning about diagnosis, (4) need for support at many levels, (5) heterogeneity and complexity of symptom experience, and (6) difficulty with diagnosis and symptom management.

Theme 1. Change in Self-Image and Role

Fifteen of the 43 articles describe people experiencing a change in their self-image and role leading up to diagnosis, during, and after diagnosis (Fallahi-Khoshknab et al., 2014; Ford et al., 2012; Frost et al., 2017; Klevan et al., 2014; Koffman et al., 2013; Lowden et al., 2014; Mortensen & Rasmussen, 2017; Newland et al., 2016; Parton et al., 2019; Soundy et al., 2012; Squires et al., 2019; Strickland et al., 2017; Tehranineshat et al., 2020; van Capelle et al., 2017; Weisfeld-Adams, 2016). Individuals experiencing symptoms leading up to an MS diagnosis may question their own abilities, even their own sanity (Frost et al., 2017). Strange and difficult-to-explain symptoms may lead to feelings of panic, uneasiness, vulnerability, guilt, and shame (Frost et al., 2017; Lowden et al., 2014; Mortensen & Rasmussen, 2017; Weisfeld-Adams, 2016). Changes in abilities and being unable to meet their own expectations may lead to a sense of moral failing at work and at home, where people feel they are unable to trust the person they thought they were (Fallahi-Khoshknab et al., 2014; Ford et al., 2012; Frost et al., 2017; Klevan et al., 2014; Koffman et al., 2013; Lowden et al., 2014; Mortensen & Rasmussen, 2017; Newland et al., 2016; Parton et al., 2019; Soundy et al., 2012; Squires et al., 2019; Strickland et al., 2017; Tehranineshat

et al., 2020; van Capelle et al., 2017; Weisfeld-Adams, 2016). There may grieve the loss of their old self, experiencing ‘ambiguity death,’ where they are still there, but the person they used to be is gone (Koffman et al., 2013, p. 4). Expecting to get worse, they may change their expectations for the future, including dating, marriage, leisure activities, pursuing higher education, or seeking certain types of employment (Lowden et al., 2014; Mortensen & Rasmussen, 2017; Soundy et al., 2012). This includes concerns about parenting (Mortensen & Rasmussen, 2017; Parton et al., 2019; Strickland et al., 2017; Weisfeld-Adams, 2016) when faced with potential physical and financial constraints that may limit their ability to care for a child, the impact of medications on pregnancy, fear of symptom worsening or exacerbation with pregnancy and childbirth, as well as the potential of passing MS to their children.

The majority report their diagnosis of MS is a major life event, a change in life course and identity, and a disrupted biography and life plan (Koffman et al., 2013; Lowden et al., 2014, 2014; Mortensen & Rasmussen, 2017; Squires et al., 2019). Acknowledging having an MS diagnosis can be a struggle, going from being healthy and able to sick and impaired (Frost et al., 2017; Lowden et al., 2014; Mortensen & Rasmussen, 2017; Squires et al., 2019). Having MS is seen as negative and stigmatizing, a threat to independence (Frost et al., 2017; Newland et al., 2016; Squires et al., 2019; van Capelle et al., 2017), and may be thought to be a death sentence (Fallahi-Khoshknab et al., 2014; Tehranineshat et al., 2020). People fear becoming a burden to others, and may question their

ability to maintain their various roles (financial, household, etc.), fearing they will not be able to fulfil their responsibilities or feel excluded, invalidated, and lonely, like they no longer belong in these settings (Fallahi-Khoshknab et al., 2014; Ford et al., 2012; Frost et al., 2017; Koffman et al., 2013; Mortensen & Rasmussen, 2017; Newland et al., 2016; Soundy et al., 2012; Squires et al., 2019; Strickland et al., 2017; van Capelle et al., 2017; Weisfeld-Adams, 2016). They may even hide their diagnosis for fear of being avoided, pitied, or fired from their job (Fallahi-Khoshknab et al., 2014; Frost et al., 2017; Lowden et al., 2014).

There can be much uncertainty and fear with an MS diagnosis, challenging what the individual imagined their life would be (Squires et al., 2019; Strickland et al., 2017), and potentially impacting their development and future planning when faced with incorporating the diagnosis of a chronic condition into their perception of themselves (Frost et al., 2017; Orenstein & Lewis, 2020). One person described being “reduced to living in the present” (Frost et al., 2017, p. 329). Some try to carry on as normal, to be present and engaged, living one day at a time (Newland et al., 2016; Soundy et al., 2012; Weisfeld-Adams, 2016). But, if symptoms progress they become a significant source of stress (Newland et al., 2016). This attempt at normalcy while living with uncertainty was well described by James D. Weisfeld-Adams (2016) (a physician diagnosed with MS):

> Life is short and unpredictable: we all endure the challenges of uncertainty, with an unknowable timeline stretching into an invisible future. Having a chronic, fluctuating, neurodegenerative illness amplifies and

> refocuses that sense of the abyss yawning beneath our feet. To establish a balance there — to go on living life as though the ground between us and the abyss were actually solid — is the tough part, the daily struggle. (p. 715)

Despite the large number of people who report the huge impact MS has had on their life, there are some who report they do not feel their illness has a huge impact on their life, that having MS doesn't define who they are (Lowden et al., 2014). That MS is just something they have and take medication for, like friends and family members who have to take medications for other types of chronic conditions (Lowden et al., 2014).

Theme 2. Different Reactions to Diagnosis

Seventeen of the 43 articles describe the different reactions to an MS diagnosis (Al-Sharman et al., 2018; Bogosian et al., 2019; Fallahi-Khoshknab et al., 2014; Frost et al., 2017; Koffman et al., 2013; Lowden et al., 2014; Mortensen & Rasmussen, 2017; Newland et al., 2016; Parton et al., 2019; Pearce & Meyer, 2020; Russell et al., 2019; Soundy et al., 2012; Squires et al., 2019; Strickland et al., 2017; Tehranineshat et al., 2020; van Capelle et al., 2017; Weisfeld-Adams, 2016). The most often reported reactions to diagnosis were relief, acceptance, hope, increased spirituality, denial, defiance, overwhelm, fear, anger, frustration, depression, hopelessness, guilt, and grief, that could occur in isolation, or in various combinations. All reactions are normal, and these initial response may

continue for some time (weeks, months, even years) (Fallahi-Khoshknab et al., 2014).

Relief

People described feeling a “perverse relief” with their diagnosis of MS (Weisfeld-Adams, 2016, p. 715), an external validation and legitimization of their symptom experience (they were worried it was all in their head) (Frost et al., 2017; Strickland et al., 2017). They felt relieved to have a name and a reason for their symptoms (Lowden et al., 2014), while also recognizing their uncertain future and potential decline in their health and well-being (Frost et al., 2017; Strickland et al., 2017; Weisfeld-Adams, 2016). With an official diagnosis also came hope that having a diagnosis would facilitate access to resources and assistance, but this wasn’t always the case (Frost et al., 2017).

Acceptance

Some accept and acknowledge their diagnosis more readily than others, reporting they must accept it as they have no other choice (Koffman et al., 2013; Soundy et al., 2012). Those who accept their diagnosis were more able to choose treatment options and lifestyle changes, like the use of an assistive (Frost et al., 2017; Lowden et al., 2014; Squires et al., 2019), though this acceptance process may take time (Fallahi-Khoshknab et al., 2014; Lowden et al., 2014; Mortensen & Rasmussen, 2017). Acceptance may seem to be the most desired state, however, even acceptance had with it a sense of loss, an acceptance of possible deterioration (Mortensen & Rasmussen, 2017; Soundy et al., 2012).

Acceptance of uncertainty can be distressing and may be seen as a sort of self-objectification, a less emotional view of what is happening that allows them to move forward with more certainty (Soundy et al., 2012, p. 346).

Hope

Paradoxically, people may both accept their MS diagnosis and potential decline, while also defying their illness by hoping to restore their pre-MS identity; hoping for a cure while also believing there will not be a cure (Soundy et al., 2012, p. 348). People hoped to get better, while also expecting to get worse (Soundy et al., 2012). Hope was associated with taking action (ex. starting medications), but was also associated with defiance and denial (Frost et al., 2017; Russell et al., 2019; Soundy et al., 2012).

Increased Spirituality

With an MS diagnosis some became more spiritual, leaning on religious values and beliefs to help them accept their diagnosis, cope with and manage symptoms, and gain a sense of purpose (Fallahi-Khoshknab et al., 2014; Soundy et al., 2012).

Denial

Denial of diagnosis was another common initial response to diagnosis (Frost et al., 2017; Koffman et al., 2013; Lowden et al., 2014; Mortensen & Rasmussen, 2017; Pearce & Meyer, 2020; Soundy et al., 2012), and some did seek a second opinion regarding their MS diagnosis (Fallahi-Khoshknab et al., 2014). Denial may be a part of the acceptance process, moving from initial denial

to acceptance (Squires et al., 2019). With denial there may be delays in effective coping and resistance to changing abilities and roles that may negatively impact the individual, their job, and their relationships (Frost et al., 2017; Pearce & Meyer, 2020; Squires et al., 2019). Denial may also be associated with avoiding needed care (Pearce & Meyer, 2020), and refusal or delays in treatment (Fallahi-Khoshknab et al., 2014; Lowden et al., 2014).

Defiance

A defiant reaction to an MS diagnosis may manifest as refusal of care, medications, and use of an assistive device (Fallahi-Khoshknab et al., 2014; Soundy et al., 2012; van Capelle et al., 2017). Acceptance of impairment was described as “giving in” to their MS (Fallahi-Khoshknab et al., 2014; Soundy et al., 2012; van Capelle et al., 2017). By being defiant against MS they are fiercely seeking to maintain their independence and carry on; to them accepting an MS diagnosis is accepting decline (Soundy et al., 2012). Some even take pride in doing what they can to defy their diagnosis, like running a marathon or walking for miles despite their MS symptoms (Newland et al., 2016).

Overwhelm

Receiving an MS diagnosis may be incredibly overwhelming, leaving individuals struggling to understanding and adjust to having this diagnosis (Fallahi-Khoshknab et al., 2014; Lowden et al., 2014; Parton et al., 2019; Pearce & Meyer, 2020; Squires et al., 2019). One individual reported being in a state of

shock, wandering aimlessly for hours after they were told they have MS (Fallahi-Khoshknab et al., 2014).

Fear, Anger, and Frustration

Lack of knowledge about MS, societal misperceptions, and stigma have led to feeling afraid when diagnosed. They may believe they have been given a death sentence, expecting to quickly decline to being paralyzed and die within a few months (Fallahi-Khoshknab et al., 2014; Frost et al., 2017; Lowden et al., 2014; Weisfeld-Adams, 2016). Fear may manifest in other ways, fears around finances, job loss, insurance, disability support, and medical bills (Fallahi-Khoshknab et al., 2014; Weisfeld-Adams, 2016). As well as fear of being treated differently or pitied (Fallahi-Khoshknab et al., 2014), and even fear of traveling away from established healthcare providers (van Capelle et al., 2017). People may fear what their future will be like, and fear of seeing others with MS who are impaired (Lowden et al., 2014). Some respond to their diagnosis with anger and frustration (Fallahi-Khoshknab et al., 2014; Lowden et al., 2014), and may even lash out (Fallahi-Khoshknab et al., 2014).

Low Mood

Sadness, despair, depression, hopelessness, and helplessness were other initial responses to an MS diagnosis (Al-Sharman et al., 2018; Bogosian et al., 2019; Fallahi-Khoshknab et al., 2014; Mortensen & Rasmussen, 2017; Soundy et al., 2012). Participants reported ruminating on death and disability, crying every day, and wanting to be alone (Fallahi-Khoshknab et al., 2014).

Some feel guilt, that they caused this to happen to themselves, self-hate, and feelings of failure (Fallahi-Khoshknab et al., 2014). People may need time to make sense of what it means to live with an MS diagnosis, and may mourn the losses they feel (Fallahi-Khoshknab et al., 2014; Koffman et al., 2013; Lowden et al., 2014).

Theme 3: Different Readiness for Learning About MS

Thirteen of the 43 articles describe different readiness for learning about their MS diagnosis. People with MS exhibited different degrees of readiness for learning related to all aspects of their diagnosis based on their experiences, knowledge, and mindset (Carnero Contentti et al., 2020; Dennison et al., 2018; Dibley et al., 2017; Fallahi-Khoshknab et al., 2014; Koffman et al., 2013; Lowden et al., 2014; Newland et al., 2016; Pearce & Meyer, 2020; Russell et al., 2019; Soundy et al., 2012; Squires et al., 2019; Tehranineshat et al., 2020; van Capelle et al., 2017). Preferences regarding when and what to learn are specific to the individual (Carnero Contentti et al., 2020; Dennison et al., 2018; Dibley et al., 2017; Lowden et al., 2014; Newland et al., 2016; Russell et al., 2019; van Capelle et al., 2017).

Less May Be Better

Though some report being ready for and wanting a great deal of information about MS at the time of diagnosis (Fallahi-Khoshknab et al., 2014; Lowden et al., 2014; Pearce & Meyer, 2020; Soundy et al., 2012; Squires et al., 2019; Tehranineshat et al., 2020), there appears to be contradictory information

in the literature. Even within the articles discussing a need for more information at diagnosis, participants stated being overwhelmed by too much information, preferring less information, and to be given time and space to adjust to having just been diagnosed with a chronic health condition (Dennison et al., 2018; Koffman et al., 2013; Pearce & Meyer, 2020).

Emotional Needs Greater than MS Knowledge

A few participants expressed an unmet need for information and referrals related to adjusting emotionally to receiving a life changing diagnosis, instead of information specific to MS (Pearce & Meyer, 2020). The articles reviewed highlighted that treatment decisions in particular may be difficult for a newly diagnosed person, where patients feel overwhelmed by the treatment options shared with them and underqualified to make these types of decisions (Lowden et al., 2014). Determining the initial medication approach can feel overwhelming to patients due to the number of choices available, side effects, risks/benefits, methods of administration (including by mouth, intramuscular, and intravenous), and cost (Peters et al., 2013; van Capelle et al., 2017). If this period of feeling overwhelmed and indecisive becomes prolonged such that it delays the use of disease modifying drugs for months or years, it may become harmful to long term patient outcomes.

Theme 4: Need for Support at Many Levels

Sixteen of the 43 articles express the importance of support for people with MS at many levels, from family, friends, healthcare providers, spiritual

affiliations, social groups, the workplace, and the general public (Bogosian et al., 2019; Fallahi-Khoshknab et al., 2014; Frost et al., 2017; Koffman et al., 2013; Lavorgna et al., 2017; Lowden et al., 2014; Newland et al., 2016; Pearce & Meyer, 2020; Peters et al., 2013; Russell et al., 2019; Soundy et al., 2012; Squires et al., 2019; Strickland et al., 2017; Tehranineshat et al., 2020; van Capelle et al., 2017; Weisfeld-Adams, 2016).

Healthcare Providers

Support from healthcare providers specializing in MS is particularly important for a newly diagnosed person. They are seen as a reliable source of information and referral to reputable sources, and as subject matter expert can clarify information and misperceptions about MS (Lowden et al., 2014; Pearce & Meyer, 2020; Peters et al., 2013; Russell et al., 2019; Soundy et al., 2012; Squires et al., 2019; Strickland et al., 2017; Tehranineshat et al., 2020). Despite the reliance on providers as a reputable source, it may take time for providers to build trust with the newly diagnosed patient, especially if their symptoms have been dismissed as psychosomatic in previous interactions with healthcare professionals (Frost et al., 2017). Support from care providers is important with regards to beginning a disease modifying drug (van Capelle et al., 2017), as early treatment improves long term outcomes (Pearce & Meyer, 2020). Medication selection is often a team decision among healthcare providers, family, and peers, especially when considering an injectable or IV medications (van Capelle et al., 2017). Care needs may go beyond those of MS specialists. For

instance, support for the psychological impact of an MS diagnosis (Bogosian et al., 2019), nonpharmacological symptom management, and palliative care options (Newland et al., 2016). Considerations must be made as well for minority and disenfranchised groups. For instance, people of color (Koffman et al., 2013) and members of the LBGTQ community (Lavorgna et al., 2017) may be at increased risk for poor outcomes and may experience discrimination in the healthcare setting that is damaging to the patient-provider relationship.

Peers with MS

Other people with MS are seen as a highly trusted source of information and support for the newly-diagnosed as they can share their own experiences, helping to education, validate, reassure, and give insight into what the future may be like (Lowden et al., 2014; Pearce & Meyer, 2020; Soundy et al., 2012). Though this interaction with peers may also be challenging, seeing people with MS whose symptoms are severe or have progressed to a level of impairment (Soundy et al., 2012).

Spiritual Support

People newly diagnosed with MS also receive support from a religious/spiritual community, from religious leaders, and through prayer (Fallahi-Khoshknab et al., 2014; Soundy et al., 2012).

Family and Friends

Depending on the dynamics of the relationships, family and friends may be an essential source of support for the newly diagnosed. Though fear of being

a burden, as well as misperceptions about MS and it's symptoms may present a challenge (Fallahi-Khoshknab et al., 2014; Mortensen & Rasmussen, 2017; Newland et al., 2016; Squires et al., 2019). Families and friends may be highly involved with the diagnosis process, even encouraging loved ones to initially seek care for their symptoms (Frost et al., 2017). When family and friends do not understand what it means for a person to have MS the newly diagnosed may feel invalidated by those around them, like "no one gets it" (Koffman et al., 2013; Newland et al., 2016, p. 393). There may be feelings of frustration if family and friends may treat people differently after they are diagnosed with MS (Mortensen & Rasmussen, 2017; Squires et al., 2019), as well as feelings of fear if family and friends call unwanted attention to decline as the person with MS worsens (Koffman et al., 2013).

The General Public

Social isolation is a risk for people with MS (Strickland et al., 2017), in part due to feeling uncomfortable in public (Squires et al., 2019). Societal misperceptions about MS and it's symptoms may leave people with MS feeling judged, criticized, mocked, avoided, and ignored (Fallahi-Khoshknab et al., 2014; Frost et al., 2017; Squires et al., 2019). Symptoms like depression, fatigue, and cognitive impairment may be misinterpreted in the workplace as being lazy or uninterested (Newland et al., 2016). Changing needs with regards to the use of assistive devices may lead to negative public and workplace encounters (Squires et al., 2019). For example, an individual may not need an assistive device one

day, but the next day need a cane or wheelchair (Squires et al., 2019). This perceived inconsistency in impairment may be interpreted negatively and judged by others.

Theme 5. Heterogeneity and Complexity of the Symptom Experience

Twenty-eight out of 43 articles describe the heterogeneity and complexity of the MS symptom experience. Participants reported over 60 different initial or early MS symptoms. Symptoms may be subjective or objective, with differing rates of progression and degrees of severity, as well as potential differences impacted by age, sex, race, socioeconomic status, ethnicity, culture, and country of residence (Abd El Latif et al., 2020; Al-Sharman et al., 2018; Beiki et al., 2019; Bookwalter et al., 2020; Ciurleo et al., 2020; Dibley et al., 2017; Ford et al., 2012; Forn et al., 2013; Frost et al., 2017; Horwitz et al., 2014; Joyce & Jeske, 2020; Klevan et al., 2014; Koffman et al., 2013; Lebrun-Frenay et al., 2020; Moore, 2018; Mortensen & Rasmussen, 2017; Newland et al., 2016; Pandey et al., 2018; Pandit et al., 2012; Persson et al., 2019; Sennou et al., 2014; Soltys et al., 2017; Soundy et al., 2012; Squires et al., 2019; Stoppe et al., 2017; Strickland et al., 2017; Weisfeld-Adams, 2016; Wijnands et al., 2017). People with MS reported lower health related quality of life, lower physical health, lower mental health, lower functional abilities, more apathy, and more disability than those without MS (Klevan et al., 2014; Mortensen & Rasmussen, 2017; Newland et al., 2016).

Lots of Symptoms

Symptoms reported as being the most common pre-diagnosis included:

- Problems walking (Al-Sharman et al., 2018; Ford et al., 2012; Frost et al., 2017; Koffman et al., 2013; Newland et al., 2016; Squires et al., 2019).
- Sensory disturbances (including numbness) (Ford et al., 2012; Frost et al., 2017; Klevan et al., 2014; Mortensen & Rasmussen, 2017; Newland et al., 2016; Persson et al., 2019; Soltys et al., 2017; Squires et al., 2019; Stoppe et al., 2017; Strickland et al., 2017).
- Vision problems (including optic neuritis) (Abd El Latif et al., 2020; Beiki et al., 2019; Ford et al., 2012; Horwitz et al., 2014; Klevan et al., 2014; Pandit et al., 2012; Persson et al., 2019; Soltys et al., 2017; Soundy et al., 2012; Stoppe et al., 2017).
- Motor symptoms (Beiki et al., 2019; Frost et al., 2017; Pandey et al., 2018; Persson et al., 2019; Sennou et al., 2014).
- Muscle weakness (Klevan et al., 2014; Mortensen & Rasmussen, 2017; Newland et al., 2016; Persson et al., 2019; Weisfeld-Adams, 2016).
- Fatigue (Klevan et al., 2014; Koffman et al., 2013; Mortensen & Rasmussen, 2017; Newland et al., 2016; Persson et al., 2019; Strickland et al., 2017).

Less commonly reported symptoms of MS included:

- Psychiatric symptoms (depression, anxiety, psychotic episodes, delusions, etc.) (Klevan et al., 2014; Koffman et al., 2013; Moore,

2018; Newland et al., 2016; Persson et al., 2019; Sennou et al., 2014; Soundy et al., 2012).

- Changes in sense of smell (Ciurleo et al., 2020).
- Cognitive impairment (including memory loss, confusion, and forgetfulness) (Koffman et al., 2013; Mortensen & Rasmussen, 2017; Newland et al., 2016; Stoppe et al., 2017).
- Pain (Abd El Latif et al., 2020; Koffman et al., 2013; Lebrun-Frenay et al., 2020; Mortensen & Rasmussen, 2017; Persson et al., 2019; Weisfeld-Adams, 2016).
- Problems with sleep (Newland et al., 2016).
- Heat sensitivity (Frost et al., 2017; Mortensen & Rasmussen, 2017; Newland et al., 2016; Weisfeld-Adams, 2016).
- Linguistic problems (Mortensen & Rasmussen, 2017).
- Bladder dysfunction (Klevan et al., 2014; Mortensen & Rasmussen, 2017).
- Constipation (Dibley et al., 2017).

Symptoms were often times were reported as occurring together, suggesting they may be occurring in clusters (Ford et al., 2012). Note, however, that symptom frequency did not reflect symptom severity or the degree of impact or distress the symptom caused. In one study, problems walking and pain were more often rated as severe or overwhelming, and qualitative interviews identified

anxiety, depression, fatigue, pain, confusion, and memory loss as the most distressing symptoms (Koffman et al., 2013, p. 7).

Labs and Imaging

Possible laboratory changes associated with MS included increases in IL-10 and LIF (Soltys et al., 2017). MRI changes were also observed with MS diagnoses, with brain lesions in specific areas and forming anticipated patterns (Pandey et al., 2018). Interestingly, changes on fMRI showed higher functional connectivity in the brain possibly indicating enhanced connectivity as a compensatory mechanism in early MS (Forn et al., 2013). This ability to compensate cognitive differences may not be observed early in the disease process (Forn et al., 2013).

Patterns of Symptom Type and Severity

People with MS may experience different patterns in symptom type, severity, and rate of progression over time (Koffman et al., 2013; MS Society U.K., 2021; Soundy et al., 2012). Symptoms may get better, worse, resolve completely, or new symptoms may appear (Soundy et al., 2012). Weisfeld-Adams described “invisible and mysterious symptoms that come and go” (2016, p. 715). Some early mild symptoms may go unreported to healthcare providers for years and may not be recognized as MS symptoms until after diagnosis (Frost et al., 2017). There may also be a cascade effect with symptoms, where an MS related symptom leads to secondary and tertiary consequences (Newland

et al., 2016). For example, fatigue may lead to depression, to less socialization, an increase in job absenteeism, and job loss (Newland et al., 2016).

Comorbidities

Studies looking at MS vs. controls found that people with MS experienced more symptoms than people without MS (Persson et al., 2019). Prior to MS diagnosis they were more likely to have had depression (Persson et al., 2019), asthma, chronic obstructive pulmonary disease (COPD), epilepsy, other autoimmune disorders, hypertension, dyslipidemia, cardiovascular diseases, fracture (Persson et al., 2019), and post-traumatic stress disorder (PTSD) (Bookwalter et al., 2020).

Demographic Characteristics

There may be differences in symptom experience as well based on sex (Frost et al., 2017), race (Koffman et al., 2013), ethnicity, culture, country of residence, sexual orientation, gender identity (Lavorgna et al., 2017), MS type (Wijnands et al., 2017), and medications/treatments received (Stoppe et al., 2017). For instance, Black Caribbean people in the UK had more aggressive MS, more cognitive impairment, and faster functional decline than White British people (Koffman et al., 2013). For primary progressive MS (PPMS) vs. relapsing remitting MS (RRMS), those diagnosed with PPMS had more neurologically-related encounters with healthcare providers the 5 years before their diagnosis than the RRMS group (which had more dermatological visits than the PPMS group) (Wijnands et al., 2017).

Theme 6. Difficulty with diagnosis and symptom management

Twenty-eight of the 43 articles demonstrate difficulty with diagnosis and symptom management (Al-Sharman et al., 2018; Beiki et al., 2019; Bookwalter et al., 2020; Ciurleo et al., 2020; Fallahi-Khoshknab et al., 2014; Ford et al., 2012; Frost et al., 2017; Horwitz et al., 2014; Joyce & Jeske, 2020; Klevan et al., 2014; Koffman et al., 2013; Lavorgna et al., 2017; Lebrun-Frenay et al., 2020; Lowden et al., 2014; Moore, 2018; Newland et al., 2016; Ozakbas et al., 2019; Pandit et al., 2012; Persson et al., 2019; Peters et al., 2013; Sennou et al., 2014; Squires et al., 2019; Stoppe et al., 2017; Strickland et al., 2017; van Capelle et al., 2017; van der Vuurst de Vries et al., 2018; Weisfeld-Adams, 2016; Wijnands et al., 2017).

Improvement, but Still Frustrating

The time from initial symptom to diagnosis seems to be improving (van der Vuurst de Vries et al., 2018), but patients continue to express frustration with the amount of time it takes to reach their diagnosis (Al-Sharman et al., 2018; Peters et al., 2013). This may be in part due to the delayed ability to see a specialist (Peters et al., 2013). However, some research shows that recent changes in diagnostic criteria (made in 2017) have shortened the time between first symptoms and MS diagnosis, allowing for an earlier start on a disease modifying drug (Ozakbas et al., 2019; van der Vuurst de Vries et al., 2018). The 2017 McDonald Criteria was found to be more sensitive than the previous criteria, but less specific for a second MS attack such that more diagnoses of MS are being

made, but with fewer subsequent MS attacks over 5 years (Beiki et al., 2019; van der Vuurst de Vries et al., 2018). This allows people to take disease modifying drugs without having to wait for a second symptom attack (per previous diagnostic criteria) (Beiki et al., 2019; van der Vuurst de Vries et al., 2018). With the included articles, there are differences as to whether providers felt it was appropriate for a person with clinically isolated syndrome (CIS) suggestive of MS to start a disease modifying drug, or to wait until a person had a second symptom attack to start a disease modifying drug (Beiki et al., 2019; Squires et al., 2019; van der Vuurst de Vries et al., 2018; Weisfeld-Adams, 2016).

Consequences of Diagnostic Delays

The MS diagnosis experience is often a long and difficult one, at times taking years to be diagnosed (Ford et al., 2012; Squires et al., 2019; Strickland et al., 2017), and the longer it takes for a person to be diagnosed, the greater their psychological distress (anxiety and depression) and symptom severity (Moore, 2018). Unexplained and unmanaged symptoms, multiple encounters with healthcare providers, and the time it takes to get an official MS diagnosis can be frustrating and traumatizing, and may damage an individual's relationship with healthcare providers if they feel their concerns and troubling symptoms have been dismissed (Frost et al., 2017; Joyce & Jeske, 2020; Wijnands et al., 2017). Difficulty with diagnosis results in delayed treatment, delayed access to needed services like medication assistance, workplace accommodations, and protection against discrimination (Al-Sharman et al., 2018; Frost et al., 2017; Squires et al.,

2019), as well as challenges in management related to communication, integration/coordination of care, and the treatment and management of symptoms (Al-Sharman et al., 2018; Carnero Contentti et al., 2020; Dennison et al., 2018; Pearce & Meyer, 2020). Delayed treatment is particularly troublesome as it is repeatedly demonstrated that starting a disease modifying drug helps to delay disease progression for a significant number of people with MS (Beiki et al., 2019; van Capelle et al., 2017; van der Vuurst de Vries et al., 2018). At times while waiting for an official diagnosis, symptoms may continue to progress leading to irreversible impairments (Al-Sharman et al., 2018).

Different Paths to Diagnosis

The way individuals come to providers who diagnosis their MS is varied. Diagnosis most often comes from a neurologist, but has been reported as being diagnosed by general practitioners as well (Ford et al., 2012). Some of the included articles describe people becoming diagnosed with MS after seeing providers for problems like optic neuritis optic neuritis (Horwitz et al., 2014; Pandit et al., 2012; Soltys et al., 2017), psychiatric conditions (Persson et al., 2019; Sennou et al., 2014), eye problems (Abd El Latif et al., 2020), acute transverse myelopathy (Pandey et al., 2018), skin problems (Wijnands et al., 2017), post-traumatic stress disorder (PTSD) (Bookwalter et al., 2020), and changes in sense of smell (Ciurleo et al., 2020). For instance, with radiologically isolated syndrome (an incidental finding of lesions on MRI but no symptoms), about half go on to develop MS symptoms (Lebrun-Frenay et al., 2020).

Subjective, Invisible Symptoms

Many of the early symptoms associated with MS cannot be observed objectively, which some refer to as subjective or ‘invisible’’ symptoms (Newland et al., 2016). This includes, but is not limited to headaches, fatigue, anxiety, depression, pain, and sensory disturbances (Newland et al., 2016). Sensory disturbances may be ‘positive’ (present) versus ‘negative’ (absent). For example, positive symptoms include paresthesia (pins and needles, itching, burning, feelings of vibration or warmth), and hypersensitivity to pain (Newland et al., 2016). Negative symptoms include sensory loss like numbness, problems feeling temperature, problems with proprioception (Newland et al., 2016). These invisible symptoms may be underrecognized and undertreated, though their impact on the individual may be significant (Newland et al., 2016).

Difficult to Describe

The nature of neurological symptoms may make them difficult or embarrassing to describe. Often times layman terms or metaphors are used to describe symptoms, like ‘weak’ for ‘fatigue,’ or “running out of steam” (Koffman et al., 2013). Some symptoms also carry stigma with them such that people deny them despite having them, like depression (sadness, feeling low) or suicidal ideation (Koffman et al., 2013). Cognitive problems are also underreported (e.g., confusion, memory loss, forgetting) (Koffman et al., 2013).

Diagnostic Bias

It appears there may be challenges with regards to diagnostic bias in the realm of MS, in particular with regards to sex. Data show that more women than men have MS, yet it is reported that a diagnosis was more difficult to obtain for women, with many of them stating they felt their symptoms were ignored by providers for many years (Frost et al., 2017). However, in contrast to this, one man stated that a provider did not think he had MS because he was male (Joyce & Jeske, 2020). Though MS diagnosis may occur most often in white women in their 30s, this idea of the 'typical person' with MS may be particularly damaging as men and minority groups may experience worse symptom severity and poorer quality of life (Frost et al., 2017; Koffman et al., 2013; Lavorgna et al., 2017).

Misdiagnosis, Re-Diagnosis, and Miscommunication

To add to the complexity of the diagnosis experience, there is the potential for misdiagnosis, and re-diagnosis—where a person was thought to be misdiagnosed and then was later diagnosed again with MS (Frost et al., 2017), There is even the chance for some unfortunate miscommunications, for example, a woman shared her medical chart stated she was diagnosed in 1979, but she wasn't told until 2003 (Frost et al., 2017, p. 323). However, no matter the diagnosis or label given to a patient's experience, they can still have their symptoms managed. As one provider explained, "'people are not textbooks," many of them "have a sprinkling of things …. they don't meet criteria for this disease or that disease, but they have features of autoimmunity…. you don't

need a label…we can still help you'" (Tucker, 2018) as cited in (Joyce & Jeske, 2020, p. 5). Providers can deliver care and symptom management with an uncertain or changing diagnosis (Joyce & Jeske, 2020).

Discussion

Summary of Key Findings

Every MS experience and diagnosis is unique to that individual, but there are some shared lived experiences and themes that may surface within these narratives. This review included 43 articles each with some aspect related to the pre-diagnosis and early diagnosis experience for people with MS. Six themes were identified: (1) change in self-image and role, (2) different reactions to diagnosis, (3) different readiness for learning about diagnosis, (4) need for support at many levels, (5) heterogeneity and complexity of symptom experience, and (6) difficulty with diagnosis and symptom management.

Interpretations

Most of the results were what we expected to see. Diagnosis MS can be a challenging journey for patients and providers. When faced with an MS diagnosis an individual's sense of self may be challenged, altering their plans and life course. Reactions to diagnosis may be greatly varied, including relief, acceptance, hope, increased spirituality, denial, defiance, overwhelm, fear, anger, frustration, and low mood. These initial reactions may persist for weeks, even years for the newly diagnosed. Readiness for learning varies based on the individual, their experiences, knowledge, and mindset, readiness for learning

about MS varies greatly. It was suggested that less information may be better to prevent individuals from feeling overwhelmed at the time of diagnosis, to give them time and space to process the experience, and that emotional needs with regards to adjusting to a life changing diagnosis may be a priority over information specific to MS.

The symptoms experienced by people diagnosed with MS are heterogeneous and complex. From this review over 60 early or initial MS symptoms were identified (more than we expected), changes in imaging, along with a few possible biomarkers. Considerations including different patterns of symptom type and severity, secondary and tertiary symptoms/consequences, comorbidities, and potential differences based on demographic characteristics. The time from initial symptoms to MS diagnosis is shortening, which was encouraging to observe, but patients continued to express frustration with their diagnostic journey. Patient-provider interactions where patients feel their concerns regarding odd or unexplained symptoms are ignored or dismissed and left unmanaged may be particularly damaging to the patient-provider relationship. Diagnostic delays result in increased psychological distress, delays in starting disease modifying drugs, possible damage to relationships, employment, and socialization, and may contribute to irreversible impairment from disease progression. Aspects of this experience that make diagnosis and symptom management difficult include the wide range of symptom presentation, encounters with different types of providers who may not consider MS right away,

subjective ‘invisible’ symptoms that may be difficult to describe, and the added complexities of diagnostic biases as well as potential misdiagnosis.

Implications for Research and Practice

The themes identified in this literature review help to contribute a clearer understanding of the pre- and early-diagnosis experience for people with MS. Of particular interest, the phenomena of feeling relief at having a diagnosis, even if that diagnosis is a serious one, may be worth further exploration. As well as the dichotomy where people may both accept their diagnosis, but also hope to restore their pre-MS identity and the impact these seemingly conflicting ideologies may have on the physical and psychological health of a person with MS.

This work helps to highlight the potential need for focus on the emotional health of individuals newly diagnosed with MS. Focusing on addressing depressive symptoms, fear, and coping instead of teaching about MS and attempting to make treatment decisions. To give people time, space, and support to process their diagnosis and avoid overwhelming them with too much additional information. Participants expressed feeling underqualified to make decisions regarding choosing a disease modifying drug. Perhaps it could be explored how to best introduce and assist patients in this decision process.

Another interesting area to consider is the concept of defiance against their diagnosis, where individuals take pride by doing things like taking part in marathons despite having MS. This supports a flawed ideal that one can

overcome their diagnosis, disease, or disability if you just try hard enough. Placing value and worth on being healthy and able, supporting the idea that disability is a moral failing, and slips into the realm of toxic positivity. It would be interesting to observe how individuals' attitudes and beliefs change with regards to defying their diagnosis in the event their disease progresses to where they cannot do the things they once did as defiance against their MS. Do they defy their disease in other ways? How have they coped with these changes?

The newly diagnosed value the knowledge, support, and advice of others with MS, but also fear seeing someone with more advanced MS symptoms. We could seek to better understand how peers are communicating with, supporting, and mentoring each other. As well as the role of those with more advanced MS symptoms in this support system. How do people with more advanced symptoms feel about taking part in these groups? How do the newly diagnosed feel if they do meet a person with more advanced MS symptoms?

With regards to the need for support at many levels, the potential complexity of relationships of those with MS and their friends and family may be able to be explored, as well as the potential importance of 'weak ties' within the community. People want support, but fear becoming a burden and do not want to be constantly reminded of declining abilities. They want to be treated how they were before their MS diagnosis as much as possible. Providing support and referrals for a person with MS and those close to them may be helpful to facilitate communication, boundaries, and expectations. Having informal 'weak tie'

relationships in the community like a mailman, cashier, or waitress, someone who does not necessarily know you have MS may be an unexpected source of support. Providing the person with a sense of belonging and independence as this ‘weak tie’ does not have reason to pity them or discuss aspects of their MS and treats them like everyone else.

This work strongly demonstrated the need for education of the public about MS, neurological symptoms, invisible symptoms, and disability as a whole. Increased public awareness of the complexities and heterogeneity of symptoms and disability may help to decrease fear and stigma, as well as to help people feel more comfortable in public spaces. Increased awareness of invisible symptoms and symptom clusters may help patients and providers better recognize potential early MS symptoms. Leading up to an MS diagnosis, individuals demonstrate increased health care utilization. Better understanding of these trends and types of encounters may aid in identifying those at risk for MS from health care utilization data. Additionally, exploring ways to better assess for underreported, stigmatizing, or embarrassing symptoms (like depression, suicidal ideation, cognitive problems, bowel and bladder issues) may be helpful.

For the rare times when misdiagnosis and re-diagnosis occur, it would be valuable to carefully consider these cases to understand and identify potential weak or blind spots, opportunities for improvement, and the emotional and psychological needs of these individuals.

Patients reported feeling their symptoms were ignored or dismissed by providers. To improve this aspect of the patient-provider partnership, this work identified the value of transparent and honest communication regarding the challenges encountered in the diagnosis process, symptom management, and problem solving. This will help to set clear expectations, help patients feel validated in their experience, recognize the complexity of this experience, and increase satisfaction. Patients may need reassurance from their providers that their concerns are being heard, acknowledged, and that providers will seek to help them to manage or alleviate those symptoms.

Reports that patients also experienced discrimination in the health care setting demonstrates the need for education of employees regarding discrimination and unconscious bias, as well as seeking to impartially examine potential trends with regards to the quality and type of care provided to marginalized groups to seek to alleviate any disparities in care.

Strengths and Limitations

It was reassuring that the themes identified in the 2017 review were reinforced by the 2020 review. The increase in the number of articles regarding the pre- and early-diagnosis experience for people with MS from 2012-2017 to 2017-2020 (13 to 43 articles respectively) was encouraging, demonstrating the increased interest and relevancy of this topic. Limitations to note include potential biases. Participant bias may be a factor, as well as the risk for confirmation bias with the inductive approach used to identify themes. Though discussion among

the research team helped to support the themes identified. The range in sample size between articles, differing countries where the research was conducted, and the number of different methods used make it possible to under or over emphasize the generalizability of results within the identified themes.

Conclusion

This review included 43 articles from the 535 found by combining searches of the literature done from 2012 to 2017 and from 2017 to 2020. Using an inductive approach, we identified six themes identified related to the pre-diagnosis and early diagnosis experience for adults with MS: (1) change in self-image and role, (2) different reactions to diagnosis, (3) different readiness for learning about diagnosis, (4) need for support at many levels, (5) heterogeneity and complexity of symptom experience, and (6) difficulty with diagnosis and symptom management. This study adds understanding and appreciation for the complexity of the symptom experience in adults with MS.

For our next steps and considerations for future research we would like to explore beliefs for those with MS that appear to be contradictory, like believing there will not be a cure, but hoping for a cure. We would like to investigate ways patients choose a disease modifying drug and how to make this process easier for the newly diagnosed. We would like to expand upon the concept of ‘defying your diagnosis,’ and how attitudes and beliefs about that defiance may change over time. We would like to observe how the newly diagnosed are supported by others with MS, and the roles of those with more advanced MS in this support

network. We would like to support efforts to increase awareness by the public about MS, neurological symptoms, invisible symptoms, and disability. We would like to explore discrimination and unconscious bias in MS care. Also, to develop a questionnaire or symptom tracking tool to better assess the complex symptoms experience for people with MS, and to better assess for underreported, stigmatizing, or embarrassing symptoms (like depression, suicidal ideation, cognitive problems, bowel and bladder issues). Moreover, to better understand how to best address depressive symptoms, fear, and coping with a serious medical diagnosis. We would like to explore ways to improve bilateral communication between patients and providers with regards to reporting symptoms or clusters of symptoms, and how providers respond to these disclosures. Furthermore, to explore trends in health care utilization to identify those at risk for MS. Finally, to better understand the misdiagnosis and re-diagnosis experience. We hope that with our work we will help to improve the diagnosis experience for people with MS.

CHAPTER 3: Symptoms of the First Multiple Sclerosis Attack, An Exploratory Factor Analysis

Introduction

Multiple sclerosis (MS) is a chronic neurodegenerative disease with no cure (J. R. Miller, 2004; Multiple Sclerosis International Federation, 2013; National Multiple Sclerosis Society, 2020d; World Health Organization, 2008). In the United States, nearly one million adults have a diagnosis of MS, and it is estimated over 2.5 million people in the world have MS (National Multiple Sclerosis Society, 2020d, 2020f). MS is the most common cause of non-traumatic disability in young adults (Dobson & Giovannoni, 2019; World Health Organization, 2008), with most being diagnosed between the ages of 20 and 50 (thought it may occur at any age) (National Multiple Sclerosis Society, 2020f).

The symptom experience for individuals with multiple sclerosis (MS) can be complex. Over 20 primary symptoms are attributed to MS (National Multiple Sclerosis Society, 2020c), including, but not limited to fatigue, problems walking, numbness or tingling, spasticity, vision problems, bowel and bladder problems, pain, cognitive and affective changes, hearing loss, problems with speech and swallowing, breathing problems, and seizures (National Multiple Sclerosis Society, 2020c). In addition to these primary symptoms, individuals may also experience secondary and tertiary symptoms. Secondary symptoms are “complications that can arise as a result of primary symptoms,” like bladder dysfunction (primary) leading to urinary tract infections (secondary) (National Multiple Sclerosis Society, 2020c). Tertiary symptoms are “the impact of the

disease on your life," like unemployment, lost friends, and social isolation (National Multiple Sclerosis Society, 2020c). A better understanding of the early symptom experience in adults with MS may help to improve symptom assessment, patient-provider communication, and symptom treatment and management.

Symptom Clusters

A symptom cluster is "a stable group of concurrent symptoms that are related to one another and distinct from other symptom clusters" (Kim et al., 2005). In chronic conditions like MS, individuals may experience symptom clusters, which are associated with poorer outcomes (Miaskowski et al., 2017). However, treatment of one symptom may alleviate other symptoms in the same cluster (Kwekkeboom et al., 2012; Miaskowski et al., 2017). A better understanding of symptom clusters may assist in the assessment, treatment, management, and prevention of impairment in people with MS to improve quality of life and maintain desired functionality. Identifying symptoms clusters has the potential to incorporate additional data like genomics, imaging, and other biomarkers to better understanding the biological underpinning of symptoms.

Aim

The aim of this study was to identify symptom clusters experienced by adults with multiple sclerosis (MS) during their first MS attack.

Methods

Sample and setting

Nine hundred seventy adults with multiple sclerosis were included in this secondary data analysis. Participants were part of the MURDOCK MS cohort of the larger MURDOCK Study Community Registry and Biorepository (NCT01723709 [Duke IRB Pro00023791], and NCT01708408 [Duke IRB Pro00011196] (Bhattacharya et al., 2012; Duke University, 2017, 2019). Data were collected from June 2010 to May 2017. Participants in the MURDOCK MS cohort were 18 and older, enrolled in the MURDOCK study, and diagnosed with MS. Participants completed an enrollment and annual follow-up questionnaire for the larger MURDOCK study, and did a one-time questionnaire for the MURDOCK MS sub-study; these questionnaires included symptom and demographic data (Duke University, 2017). The MURDOCK and MURDOCK MS study were sponsored by Duke University, and enrollment occurred at five study locations in North Carolina, USA (Concord, Davidson, Durham, Kannapolis, and Raleigh) (Duke University, 2017).

Measures

Symptoms

A 30-item symptom checklist was collected by self-report at enrollment for the MURDOCK MS cohort (MURDOCK, n.d.). For this checklist individuals were asked “What month/year did you have your first MS attack?” and “What symptoms did you experience with the first attack?” (MURDOCK, n.d.). An MS

attack (also known as a relapse, exacerbation, or flare-up) is “the occurrence of new symptoms or the worsening of old symptoms” (National Multiple Sclerosis Society, 2020a). Items were checked by the participant if they experienced the symptom during their first MS attack. The symptoms included in the checklist are shown in Table 6. The symptoms of the first MS attack were recalled at the time of enrollment, thus were a retrospective measure; yet other variables were collected for the time of enrollment (marital status, etc.) not for the time when the symptoms were first experienced (Figure 7).

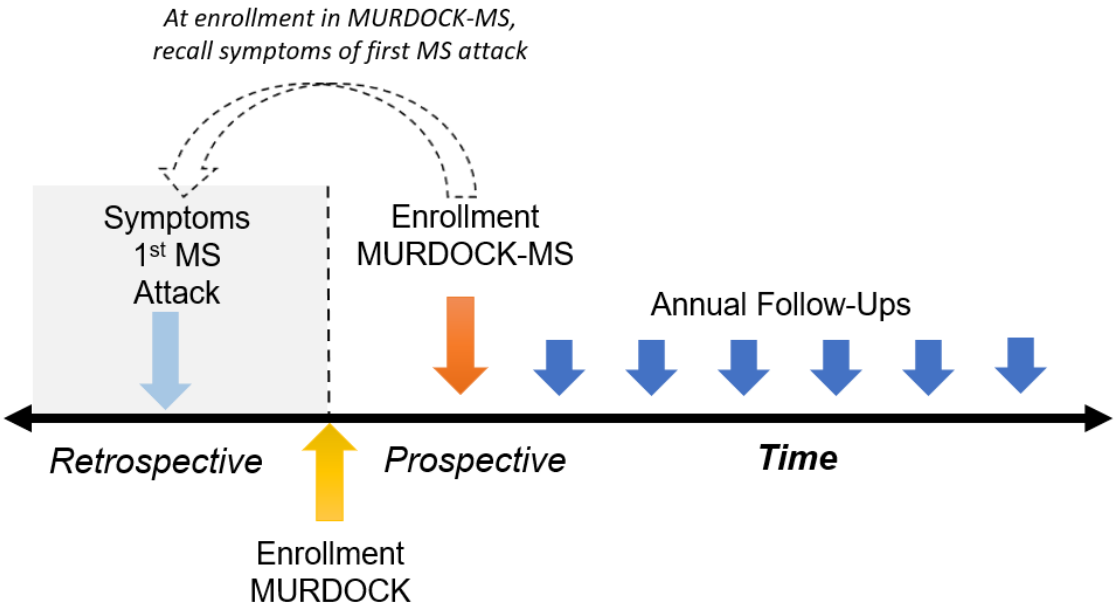


Figure 7: Timeline for One Participant in MURDOCK-MS

Table 6: MURDOCK MS Symptom Checklist (MURDOCK, n.d.)

1	Loss of balance	16	Uncontrollable rapid eye movements
2	Muscle spasms	17	Vision loss (usually affects one eye at a time)
3	Numbness/abnormal sensation in any area	18	Facial pain
4	Problems moving arms or legs	19	Painful muscle spasms
5	Problems walking	20	Tingling, crawling, or burning feeling in the arms and legs
6	Problems with coordination and making small movements	21	Decreased attention span, poor judgment, and memory loss
7	Tremor in one or more arms/legs	22	Difficulty reasoning and solving problems
8	Weakness in one or more arms/legs	23	Depression or feelings of sadness
9	Constipation and stool leakage	24	Dizziness and balance problems
10	Difficulty beginning to urinate	25	Hearing loss
11	Frequent need to urinate	26	Problems with erections
12	Strong urge to urinate	27	Problems with vaginal lubrication
13	Urine leakage (incontinence)	28	Slurred or difficult-to-understand speech
14	Double vision	29	Trouble chewing and swallowing
15	Eye discomfort	30	Fatigue

Demographic and Clinical Variables

Additional demographic and clinical variables obtained from the MURDOCK and MURDOCK MS studies included: age, sex, race, ethnicity, marital status, education, employment status, income, medical history, comorbidities, MS type, date of diagnosis, time since first MS attack, use of assistive devices, views about health/activities of daily living, and MS medications (MURDOCK, n.d.).

Data Analyses

All data analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Descriptive Statistics

Descriptive statistics were used to summarize demographic and other participant characteristics at enrollment. Symptom prevalence and correlation between symptoms were examined to ensure sufficient correlation for factor analysis as well as to identify potential issues related to collinearity (Osborne & Banjanovic, 2016).

Exploratory Factor Analysis

We conducted exploratory factory analyses (EFA) to analyze the underlying latent structure of these data using the method outlined by Osborne and Banjanovic (2016). Exploratory factor analysis is appropriate for exploring symptom clusters as it is a dimension reduction technique that compares pairwise relationships between individual variables to extract underlying latent constructs, in this case symptom clusters or co-occurring symptoms (Osborne & Banjanovic, 2016). The steps for an EFA as outlined by Osborne and Banjanovic (2016): 1) data cleaning, 2) decide on extraction method, 3) decide how many factors to retain for analysis, 4) decide on rotation method and rotating the factors, 5) interpret results, and 6) replication. The occurrence of symptoms was evaluated using dichotomous/binary variables (had vs. did not have the

symptom, 0/1), thus tetrachoric/polychoric correlations were used to create a matrix for EFA. To estimate the number of factors, iterated principal axes factor extraction was used, given that multivariate normality of the variables could not be assumed (Fabrigar et al., 1999; Osborne & Banjanovic, 2016, p. 14). The Heywood option was included to address errors of communality greater than one. The number of factors were selected using the cumulative variance of preliminary eigenvalues, scree plot, and what made sense conceptually and theoretically. Four possible models were run indicating the number of factors selected and using the oblique rotation method Promax, which allows factors to correlate (Osborne & Banjanovic, 2016, p. 63; SAS Institute Inc., 2015; B. Thompson, 2004). For this exploratory approach, the solution with the greatest interpretability and clinical meaningfulness was selected. To test model fit, a confirmatory factor analysis was done (CFA).

Confirmatory Factor Analysis

A confirmatory factor analysis allowed us to use the predetermined structure we found with our EFA with the original dataset (not the tetrachoric/polychoric correlation matrix) to explore model fit and see how well our EFA fit the data (University of California Los Angeles Statistical Consulting Group, 2021). The fit indices we will use are Goodness of Fit (GFI, >0.90), Adjusted Goodness of Fit Index (AGFI, >0.90), and Root Mean Square Error of Approximation (RMSEA, <0.80).

Results

Sample

Demographic characteristics of the 970 participants are presented in Table 7. The mean age of participants is 50 (SD=11) and range from a minimum of 18 to a maximum of 83 years of age. The majority are female 762 (79%), and white (817, 84%), which is reflective of the larger MS population (Harbo et al., 2013; National Multiple Sclerosis Society, 2020f). Most are married (654, 67%), and >47% have at least a bachelor's degree. Regarding employment, ~47% have worked for pay in the past year, 31% work full-time, and 35% are permanently disabled and unable to work. The mean number of months since their first MS attack is 183.24 months (~15 years) (SD=132.30 [~ 11 years]), with a minimum of one month since their first attack, and a maximum of 660 months (55 years). At the time of enrollment into the MURDOCK study individuals had 0 to 14 comorbidities (e.g., high blood pressure, heart attack, stroke, emphysema, liver disease, diabetes, kidney disease, cancer, obesity, asthma, depression, etc.) with a mean number of comorbidities of 4.41 (SD=2.54); 164 (16.91%) experienced three comorbidities, 153 (15.77%) experienced two comorbidities, and 135 (13.92%) reported four. Participants also reported 'Views About Health' using 13 questions scored by Likert scale. This included a general health rating, activities of daily living (ADLs), and satisfaction with ability to perform daily routine and leisure activities. From these 13 questions an ADL score was calculated, with a possible maximum score of 52. For Views About Health at

enrollment (*n*=919) the mean score was 21.27 (SD=11.85). Participants reported the use of assistive devices (cane, crutch, walker, and/or wheelchair), with 671 (73.25%) reporting using at least one assistive device.

Table 7: Baseline Demographics Characteristics of Participants

Variable	*N*=970
Age (minimum to maximum)	18 to 83
Mean age (standard deviation)*	50.21 (11.36)
Female	762 (78.56%)
Race	
White	817 (84.23%)
Black	145 (14.95%)
Asian	5 (0.52%)
Native American	20 (2.06%)
Other	12 (1.24%)
Hispanic	23 (2.41%)
Marital Status	
Married	654 (67.42%)
Domestic partner	21 (2.16%)
Divorced	126 (12.99%)
Separated	34 (3.51%)
Widowed	29 (2.99%)
Never married	106 (10.93%)
Highest Level of Education Completed	
Less than high school graduate	20 (2.06%)
High school graduate or GED	120 (12.37%)
Some college or associate degree	368 (37.94%)
Bachelor's degree	292 (30.10%)
Master's or higher professional degree	170 (17.53%)
Employment Status	
Employed past 12 months	462 (47.63%)
Permanently disabled	334 (34.54%)
Working full-time	297 (30.71%)
Retired	116 (12.00%)
Working part-time	88 (9.10%)
Stay at home for parenting, caregiving, or other responsibilities	63 (6.51%)
Unemployed looking for work	36 (3.72%)

Variable	*N*=970
Temporarily laid off or sick/maternity leave	14 (1.45%)
Student	13 (1.34%)
Household Income	
<$10,000	41 (4.23%)
$10,000-29,999	126 (12.99%)
$30,000-49,999	169 (17.42%)
$50,000-69,999	150 (15.46%)
$70,000-89,999	119 (12.27%)
$90,000 or more	291 (30.00%)
Type of MS	
Relapsing-Remitting	759 (78.25%)
Secondary-Progressive	92 (9.48%)
Primary-Progressive	70 (7.22%)
Clinically Isolated Syndrome	2 (0.21%)
Neuromyelitis Optica	1 (0.10%)
Take an MS medication (disease modifying drug)	896 (92.37%)
Mobility	
Can walk	889 (91.65%)
Can walk 500 meters without assistance	592 (61.03%)
Use a cane	326 (33.61%)
Use a walker	170 (17.53%)
Use a wheelchair	165 (17.01%)
Have family member with MS	253 (26.08%)
Have another autoimmune disease	159 (16.39%)
Have a family member with another autoimmune disease	385 (39.69%)
Have a history of Epstein Barr Virus	291 (30.00%)
Have a history of a serious infectious disease (Hep. B or C, HIV, chicken pox, measles, mumps, etc.)	879 (90.62%)
How well off growing up to age 12	
Poor	78 (8.04%)
Below average	147 (15.15%)
About average	553 (57.01%)
Above average	147 (15.15%)
Quite well off	15 (1.55%)
*Means and standard deviations reported for continuous variables, frequency and percentage presented for categorical variables	

Symptoms

The frequencies for the 30 symptoms are listed in Table 8. The most common symptom during the first MS attack was “numbness/abnormal sensation in any area” (494, 50.93%), followed by “tingling, crawling, or burning feeling in the arms and legs” (244, 25.15%). Individuals reported experiencing zero to 26 symptoms during their first MS attack, with a mean number of 2.78 (SD=2.98) symptoms per person. Three hundred and forty-one people (35.15%) experienced one symptom, 213 (21.96%) experienced two symptoms, and 135 (13.92%) experienced three symptoms.

Table 8: Symptoms Experienced with First MS Attack (*N*=970)

	Symptom	Freq (%)
1	Numbness/abnormal sensation in any area	494 (50.93)
2	Tingling, crawling, or burning feeling in the arms and legs	244 (25.15)
3	Problems walking	225 (23.20)
4	Vision loss (usually affects one eye at a time)	214 (22.06)
5	Loss of balance	184 (18.97)
6	Weakness in one or more arms/legs	180 (18.56)
7	Fatigue	176 (18.14)
8	Dizziness and balance problems	135 (13.92)
9	Problems moving arms or legs	122 (12.58)
10	Problems with coordination and making small movements	93 (9.59)
11	Double vision	86 (8.87)
12	Decreased attention span, poor judgment, and memory loss	65 (6.70)
13	Muscle spasms	51 (5.26)
14	Slurred or difficult-to-understand speech	50 (5.15)
15	Eye discomfort	47 (4.58)
16	Depression or feelings of sadness	45 (4.64)
17	Painful muscle spasms	41 (4.23)
18	Difficulty reasoning and solving problems	29 (2.99)
19	Frequent need to urinate	28 (2.89)
20	Tremor in one or more arms/legs	28 (2.89)
21	Strong urge to urinate	25 (2.58)

	Symptom	Freq (%)
22	Uncontrollable rapid eye movements	23 (2.37)
23	Constipation and stool leakage	22 (2.27)
24	Urine leakage (incontinence)	22 (2.27)
25	Facial pain	19 (1.96)
26	Difficulty beginning to urinate	18 (1.86)
27	Hearing loss	13 (1.34)
28	Trouble chewing and swallowing	12 (1.24)
29	Problems with vaginal lubrication	8 (0.82)
30	Problems with erections	1 (0.10)

Exploratory Factor Analysis

To have sufficient variation and covariation to perform an exploratory factor analysis (EFA), only symptoms reported by at least 30 individuals were included in these analyses. Collinearity was suspected due to a high polychoric correlation between “depression or feelings of sadness” and “decreased attention span, poor judgment, and memory loss” (0.78), as well as failure of model convergence when “depression or feelings of sadness” remained in the analysis, so “depression or feelings of sadness” was excluded, leaving a total of 16 symptom variables in the analyses (listed in Table 9). Using a scree plot (Figure 8) and the preliminary eigenvalues we extracted three, four, five, and six factors and compare the results. The scree plot (Figure 8), with eigenvalues (y-axis) and number of factors (x-axis) shows an ‘elbow’ at three factors, which indicates a point where the slope of the curve is leveling off, indicating the number of factors to consider in the model (Rahn, 2012). The preliminary eigenvalues showed three factors explained 83.49% of the variance, four factors explained 91.59%, five factors explained 98.19%, and six factors explain 102.56% of the variance.

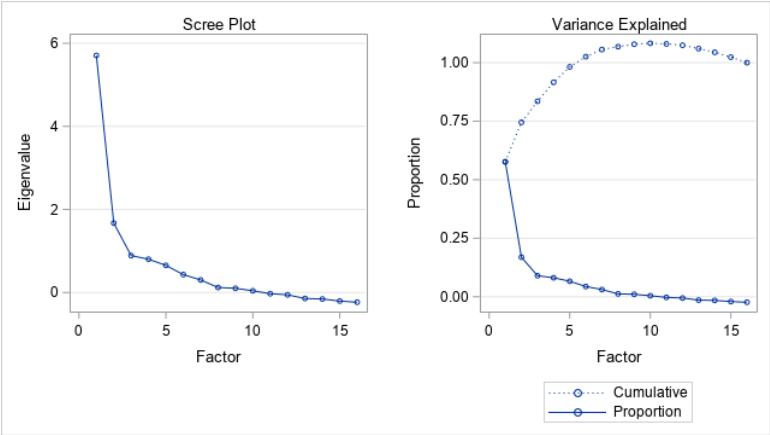


Figure 8: Scree Plot

Comparing the three, four, five, and six factor models, we chose the four-factor model EFA as the most interpretable and clinically meaningful model for these data. The four factors/symptom clusters identified were: 1) Intracranial Cluster, 2) Motor Cluster, 3) Spasticity Cluster, and 4) Paresthesia vs. Vision Loss Cluster (Table 9). The Intracranial Cluster is made up of six symptoms: 1) dizziness and balance problems, 2) decreased attention span, poor judgment, and memory loss, 3) double vision, 4) eye discomfort, 5) fatigue, and 6) slurred or difficult to understand speech. The Motor Cluster is made up of five symptoms: 1) problems walking, 2) problems moving arms or legs, 3) loss of balance, 4) problems with coordination and making small movements, and 5) weakness in one or more arms/legs. The Spasticity Cluster is made up of two symptoms: 1) painful muscle spasms, and 2) muscle spasms. The Paresthesia vs. Vision Loss is made up of three symptoms: 1) numbness/abnormal sensation in any area, 2) tingling, crawling, or burning feeling in the arms and legs, and 3) vision loss (usually affects one eye at a time). However, for the Paresthesia vs. Vision Loss

Cluster, Vision Loss has an inverse relationship with the other two symptoms (paresthesia), such that if a person has paresthesia like numbness/abnormal sensation and/or tingling, they do not have vision loss, and vice versa.

Table 9: Exploratory Factory Analysis (Rotated Factor Pattern [Standardized Regression Coefficients]), 4 Factors

Symptom		Cluster			
		Intracranial	Motor	Spasticity	Paresthesia vs. Vision Loss
1	Dizziness and balance problems	**0.70**	0.19	-0.09	-0.06
2	Decreased attention span, poor judgment, and memory loss	**0.70**	-0.17	0.33	0.15
3	Double vision	**0.67**	0.09	-0.14	-0.17
4	Eye discomfort	**0.55**	0.07	0.12	-0.25
5	Fatigue	**0.55**	-0.11	0.15	0.25
6	Slurred or difficult-to-understand speech	**0.43**	0.12	0.25	0.04
7	Problems walking	0.06	**0.79**	0.04	-0.01
8	Problems moving arms or legs	-0.13	**0.74**	0.23	0.17
9	Loss of balance	0.45	**0.49**	-0.16	0.02
10	Problems with coordination and making small movements	0.33	**0.45**	0.02	0.17
11	Weakness in one or more arms/legs	0.16	**0.42**	0.01	0.28
12	Painful muscle spasms	-0.05	-0.01	**0.84**	0.04
13	Muscle spasms	0.07	0.30	**0.72**	-0.22
14	Numbness/abnormal sensation in any area	-0.16	0.02	0.06	**0.74**
15	Tingling, crawling, or burning feeling in the arms and legs	0.18	0.05	-0.02	**0.61**
16	Vision loss (usually affects one eye at a time)	0.16	-0.20	0.15	**-0.55**

Confirmatory Factor Analysis

To validate the results of the exploratory factor analysis we did a confirmatory factor analysis using the original dataset (not the tetrachoric/ polychoric correlation matrix) and the four identified factors with their respective

associated symptoms (Figure 9, Table 10). According to the fit statistics, it appears this proposed model fits the data well. Fit statistics: Goodness of Fit (GFI)=1.95 (desired is >0.90), Adjusted Goodness of Fit Index (AGFI)=0.94 (desired >0.90), and Root Mean Square Error of Approximation (RMSEA)=0.50 (desired <0.80). Double vision (0.33), eye discomfort (0.29), and vision loss (-0.34) are on the low side, but all are statistically significant.

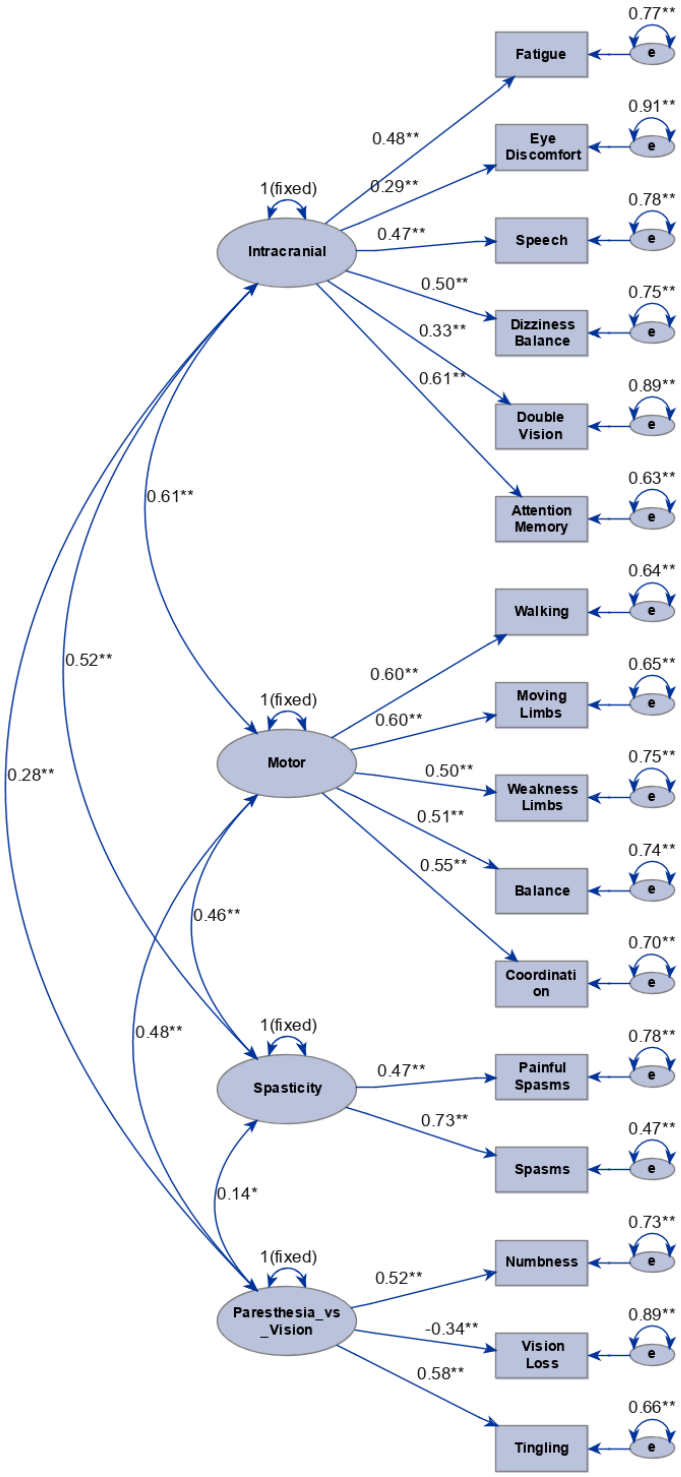


Figure 9: Standardized Solution for Confirmatory Factor Analysis

Table 10: Standardized Factor Loading Matrix for Confirmatory Factor Analysis

Factor	Symptom	Estimate	SE	t-value	p-value
Intracranial	Dizziness and balance problems	0.5	0	15.42	<0.0001
	Decreased attention span, poor judgment, and memory loss	0.61	0	20.18	<0.0001
	Double vision	0.33	0	9.21	<0.0001
	Eye discomfort	0.29	0	8.05	<0.0001
	Fatigue	0.48	0	14.63	<0.0001
	Slurred or difficult-to-understand speech	0.47	0	14.29	<0.0001
Motor	Problems walking	0.6	0	21.44	<0.0001
	Problems moving arms or legs	0.6	0	21.34	<0.0001
	Loss of balance	0.51	0	16.84	<0.0001
	Problems with coordination and making small movements	0.55	0	18.88	<0.0001
	Weakness in one or more arms/legs	0.5	0	16.32	<0.0001
Spasticity	Painful muscle spasms	0.47	0	11.46	<0.0001
	Muscle spasms	0.73	0.1	13.87	<0.0001
Paresthesia	Numbness/abnormal sensation in any area	0.52	0	11.94	<0.0001
Vs. Vision Loss	Tingling, crawling, or burning feeling in the arms and legs	0.58	0.1	12.78	<0.0001
	Vision loss (usually affects one eye at a time)	-0.34	0	-8.02	<0.0001

Discussion

This study is the first to use symptom data from the MURDOCK-MS cohort. These results suggest that symptoms may occur in clusters for adults during their first MS attack. With considerations for parsimony, interpretability, and clinical meaningfulness, we identified four symptom clusters to describe these data: 1) Intracranial, 2) Motor, 3) Spasticity, and 4) Paresthesia vs. Vision Loss. With regards to the symptoms in each group, some of them make sense to occur together due to their functional similarity, like the symptoms in the Motor Cluster (problems walking, problems moving arms or legs, loss of balance, problems with coordination and making small movements, weakness in one or more arms/legs) as they all have to do with muscle movement and strength. The symptoms in the Spasticity Cluster (painful muscle spasms, and muscle spasms) seem to logically go together in that they are almost the same symptom. However, the Intracranial Cluster (dizziness and balance problems, decreased attention span, poor judgement, and memory loss, double vision, eye discomfort, fatigue, and slurred or difficult-to-understand speech) and the Paresthesia vs. Vision Loss Cluster (numbness/abnormal sensation in any area, tingling, crawling, or burning feeling in the arms and legs, vs. vision loss) are not as straight forward. If we considered looking at them in terms of functional systems (visual, sensory, brainstem, motor, cerebellar, cognition, ambulation, and bowel and bladder)

(Stoppe et al., 2017). The Paresthesia vs. Vision Loss Cluster would encompass the visual (vision loss) and sensory (numbness/abnormal sensation, tingling, crawling, or burning feeling) functional systems, and the Intracranial Cluster would encompass visual (double vision, eye discomfort), cerebellar (dizziness and balance problem), brainstem (slurred or difficult-to-understand speech), cognition (decreased attention span, poor judgement, and memory loss), but fatigue doesn't fit neatly into these functional systems (possibly cerebellar and/or brainstem, could also be secondary to other functional systems). So functional systems do not seem to align well with these identified clusters. More investigation is required to explore possible underlying mechanisms or latent factors that may tie these co-occurring symptoms together.

For the first three clusters (Intracranial, Motor, and Spasticity) the symptoms clustered together occurred together. However, for the fourth cluster (Paresthesia vs. Vision Loss), Vision Loss has an inverse relationship with Paresthesia (numbness/abnormal sensation and tingling), such that if a person had "numbness/abnormal sensation in any area" and/or "tingling, crawling, or burning feeling in the arms and legs" was associated with not having "vision loss (usually affects one eye at a time)," and vice versa. To our knowledge, this inverse relationship between numbness and tingling versus vision loss has not previously been reported in the literature. "Numbness/ abnormal sensation in any area" and "tingling, crawling, or burning feeling in the arms and legs" were the two most reported symptoms (50.93% and 25.15% respectively), while "vision

loss (usually affects one eye at a time)" was the fourth most reported symptom (22.06%). These results are clinically interesting given the assumption that vision loss is an alarming symptom often associated with MS diagnosis (optic neuritis) (National Multiple Sclerosis Society, 2020c), (though the 2017 McDonald Criteria do not include optic neuritis as a finding indicative of MS diagnosis (Jordan & Sharma, 2021)). Yet, individuals who were predominantly in the Paresthesia vs. Vision Loss group were better able to maintain employment than the other groups (an outcome of importance to many people with chronic illnesses), despite demonstrating less ability to perform ADLs independently, and being more likely to use a wheelchair (not the motor group as one may expect). Though we have observed these trends, we are neither able to draw cause and effect conclusions, nor to determine the mechanisms for this finding. There may be potential biases we have not accounted for, for example differences within this group regarding the type of skills required for their specific type of employment. Additionally, this may be a result of appropriate symptom prevention and management within this group, effective use of occupational therapy, effectiveness of workplace accommodations and home health or informal caregiver assistance. This inverse relationship for this cluster is certainly one worth further thought and investigation.

Exploring how symptoms at first MS attack cluster has implications for clinical care, to aid in assessment of co-occurring symptoms, and may provide potential targets for symptom treatment, prevention, and management.

Recognizing that early MS symptoms may occur in clusters may aid in the diagnostic process both from the perspective of healthcare providers and patients. The diagnostic process experience for people with MS is a challenging one for many, riddled with self-doubt, especially when symptoms are difficult or embarrassing to describe, and/or cannot be easily observed by others. Symptoms that are not painful or do not yet interfere with a person's ability to perform activities of daily living may not be perceived as worthy of medical attention. Fear of being perceived as a hypochondriac may also leave individuals hesitant to share their symptom experience with providers. Recognizing that symptoms may occur in clusters may help to validate and legitimize the patient's symptom experience, helping them to feel more confident to communicate their symptoms to providers, aiding in creating a more trusting and collaborative patient-provider care experience. Legitimization of a patient's symptom experience may also help accelerate the diagnostic process and prevent symptoms from progressing to a level of impairment. Recognizing the potential meaningfulness of seemingly benign sensory symptoms along with the more readily observable or fear inducing symptoms (like problems walking and vision loss) may aid in encouraging individuals to seek care, and aid providers to assess for potential MS more readily. Early recognition of MS and utilization of disease modifying drugs is associated with better outcomes. Thus, steps that can be taken by both patients and providers to diagnose and treat MS as soon as possible may be beneficial for patients, their families, as well as for society as a

whole, helping individuals maintain their desired level of functionality in their personal and professional lives.

Study Limitations

Several limitations to this study must be noted. First, there is the potential for recall bias of symptoms of the first MS attack. This may be more likely due to some individuals completing the symptom questionnaire as far as 55 years out from their first MS. Conversely researchers note that initial symptom experiences are particularly memorable if it is high-stress or traumatic, making it a ‘flashbulb’ (Hirst & Phelps, 2016) or ‘super-encoded’ memory that is particularly vivid (Chatterjee, 2018), though some feel that even high-stress memories are prone to distortion over time like ‘memory amplification’ where the experience is remembered with more trauma than was initially reported, with the potential even for symptoms of medically induced post-traumatic stress disorder (PTSD) where the body itself and/or experiences related to seeking medical care (vs. a past event) trigger re-experiencing of trauma, an ‘Enduring Somatic Threat (EST) model of PTSD’ (Bernstein, 2020; Edmondson, 2014; Strange & Takarangi, 2015; Untethered, 2020; Willard Virant, 2019). There may be hyperawareness or hyperarousal regarding one’s own body causing severe anxiety about illness worsening or developing a new symptom or new disease, and disillusionment with regards to healthcare providers (Cordova et al., 2017; Untethered, 2020).

Second, though the symptom assessment tool was created by clinical experts, it did not go through a formal instrument validation process, thus

potentially limiting the reliability and generalizability of this work. Items in the symptom checklist were not mutually exclusive, and there seemed to be more emphasis on some areas than others. For example, there were multiple options for different aspects of urination, but cognitive issues were combined into only one option ("decreased attention span, poor judgment, and memory loss") instead of three. Of note, there was also an "other" category for the symptoms with a free text option for individuals to list/describe symptoms they were experienced that were not included on the 30-item checklist. A review of this "other" category revealed some potential symptoms to be included in future symptom check lists, in particular headaches or migraines (experienced by at least 17 people), pain (~24 people), blurry vision, change in ability to taste or smell, facial numbness, foot drop/dragging foot/or floppy foot, heat sensitivity/intolerance, nausea, optic neuritis, trigeminal neuralgia, change in temperature sensation, and Lhermitte's sign. This "other" category also highlighted the differences in language patients use to describe the symptoms they experience, as well as possible health literacy considerations and differences between the language used by patients and clinicians to describe symptoms. It may be worth attempting to recode or explore this other category in more detail, to expand the 30-item symptom checklist, as well as to include definitions/descriptions for each symptom or the kinds of symptoms patients experience to aid in finding a common language/understanding between patients and providers with regards to MS symptoms.

Third, our analyses identified clustering symptoms, but does not identify the characteristics of the individuals who may experience these clusters as the factor scores for each individual are spread across the four clusters. However, now that these clusters have been identified, they may be explored further as ‘a priori’ identified clusters to be explored with other types of analyses, like Latent Profile Analysis, such that we can incorporate characteristics like sex, race, ethnicity, level of education, income, etc. into our analyses.

Finally, our original hypothesis or measurement model may need to be revised, or more a larger sample size may be needed. This was demonstrated by exclusion of 13 symptom variables due to small sample sizes, and the exclusion of one variable (“depression and feelings of sadness”) for potential issues with collinearity.

Future Directions

For our future work we would like to explore the subpopulations and covariates within this sample based on variables like sex, race, ethnicity, level of education, income, MS type, and time since diagnosis. We would like to explore the “other” option for reported early symptoms in more detail, and consider using or creating a validated symptom assessment tool for people with MS. We would like to see if theses symptom clusters may be replicated in another MS population, and explore the transferability of these clusters to other chronic conditions. We would like to better understand how these symptom clusters may aid in MS diagnosis, treatment selection, symptom management, and to relate

them to other outcomes that are of importance to patients and providers. Additionally, we would like to explore the possible underlying biological mechanisms within and between these symptom clusters.

This area of research using the MURDOCK MS dataset is ripe for future exploration and extension. There are additional variables within the dataset that may be explored, including data related to hospitalizations, medications (MS-specific and medications for other issues), comorbidities, pain, diet, use of alcohol and tobacco, family history of MS and other diseases, history of other autoimmune disorders, history of infectious diseases, and symptoms of their second MS attack. There is also the potential to access biological samples (including genetic/genomic data), imaging, and the electronic health record. Longitudinal measures of some variables are also available including symptoms (anxiety, depression, fatigue, sleep disturbance, pain, and anger), views about health, ability to perform activities of daily living, and satisfaction with ability to perform daily routine and leisure activities.

Conclusion

This study highlights the occurrence of symptoms during the first MS attack as being in clusters (Intracranial, Motor, Spasticity, and Paresthesia vs. Vision Loss). Recognizing that symptoms may occur in clusters may aid in assessment, diagnosis, and treatment of MS as well as to provide a potential starting point for additional work related to exploring biological underpinnings of symptoms that may apply across diagnoses.

CHAPTER 4: Trajectory Typologies of Pervasive Symptoms in Adults with Multiple Sclerosis, A Latent Class Growth Analysis

Introduction

Nearly one million adults in the United States have a diagnosis of multiple sclerosis (MS), with an estimate of over 2.5 million people in the world (National Multiple Sclerosis Society, 2020d, 2020f). MS is neurodegenerative, with no cure (J. R. Miller, 2004; Multiple Sclerosis International Federation, 2013; National Multiple Sclerosis Society, 2020d; World Health Organization, 2008), and is the most common cause of non-traumatic disability in young adults (Dobson & Giovannoni, 2019; World Health Organization, 2008). Most are diagnosed between the ages of 20 and 50 (though it may occur at any age) (National Multiple Sclerosis Society, 2020f). Despite having no cure, early diagnosis and initiation of disease modifying drugs may aid in slowing disease progression (Beiki et al., 2019; Healy et al., 2013; van Capelle et al., 2017; van der Vuurst de Vries et al., 2018). The identification and management of MS's associated symptoms helps to advance early diagnosis, prevent disability, and maintain quality of life.

The symptom experience for individuals with multiple sclerosis (MS) can be complex, with primary, secondary, and tertiary symptoms (National Multiple Sclerosis Society, 2020c). The course of disease progression and severity of disability developed over time by a person with MS varies greatly between individuals. However, the first appearance, severity, and progression of

symptoms over time and the relationship between the trajectory of symptom experience and long-term impairment is not known. A better understanding of how symptoms progress over time for a person with MS may help to identify those at risk for poor outcomes such that interventions and limited resources may be more aptly targeted to help prevent or delay impairment. Additionally, a better understanding of the patterning of symptoms for people with MS, regardless of their severity, degree of disability, or risk for poor outcomes, may allow for interventions and symptom management to be better tailored to the needs of the individual to improve their well-being and quality of life.

Aim

The aim of this study is to identify and describe symptom trajectory typologies for people with MS based on pervasive symptom severity, and to explore sociodemographic differences between the typologies identified.

Methods

Design and Sample

We conducted a secondary data analysis of a longitudinal observational study of 970 adults with multiple sclerosis taking part in the MS cohort of the MURDOCK study (NCT01723709 [Duke IRB Pro00023791], and NCT01708408 [Duke IRB Pro00011196] respectively) (Duke University, 2017, 2019). Data were collected from June 2010 to May 2017. Participants in the MURDOCK MS cohort were 18 and older, enrolled in the MURDOCK study, and diagnosed with MS. The MS cohort completed a one-time MS-specific questionnaire, and as part of

the larger MURDOCK study completed an enrollment questionnaire and an annual questionnaire; these questionnaires included symptom and demographic data. The MURDOCK MS study was sponsored by Duke University, and enrollment occurred at five study locations in North Carolina, USA (Concord, Davidson, Durham, Kannapolis, and Raleigh).

Measures

Data on six pervasive symptoms (anxiety, depression, fatigue, pain, sleep disturbance, and anger) were collected at baseline and annually for the larger MURDOCK study. Pervasive symptoms are more generalized symptoms that are not necessarily specific to MS. Items consisted of one to four questions for each pervasive symptom, scored with a five-point Likert scale (Table 11). Demographic variables obtained from the MURDOCK study included age, sex, race, ethnicity, marital status, education, employment status, income, medical history/comorbidities, and MS type. The MS-specific questionnaire included date of diagnosis, and MS medications.

Table 11: Pervasive Symptom Assessment Questions (All Measured at Enrollment and Follow-Up)

Pervasive Symptom	Questions	Likert Scale
Anxiety	(1) I felt fearful [0-4] (2) I found it hard to focus on anything other than my anxiety [0-4] (3) My worries overwhelmed me [0-4] (4) I felt uneasy [0-4]	Never [0], Rarely [1], Sometimes [2], Often [3], Always [4]. Anxiety sub-score range from [0 to 16].
Depression	(1) I felt worthless [0-4] (2) I felt unhappy [0-4] (3) I felt depressed. [0-4] (4) I felt hopeless [0-4]	Never [0], Rarely [1], Sometimes [2], Often [3], Always [4]). Depression sub-score range from [0 to 16].

Pervasive Symptom	Questions	Likert Scale
Fatigue	(1) How fatigued were you on average? [0-4] (2) How run-down did you feel on average? [0-4] (3) How tired did you feel on average? [0-4]	Not at all [0], A little bit [1], Somewhat [2], Quite a bit [3], Very much [4]. Fatigue sub-score range from [0 to 12].
Pain	(1) How much did pain interfere with your day-to-day activities? [0-4] (2) How much did pain interfere with your ability to participate in social activities? [0-4] (3) How much did pain interfere with your enjoyment of life? [0-4]	Not at all [0], A little bit [1], Somewhat [2], Quite a bit [3], Very much [4]). Pain sub-score range from [0 to 12]
Sleep disturbance	(1) I was satisfied with my sleep [0-4]	Not at all [4], A little bit [3], Somewhat [2], Quite a bit [1], Very much [0]. Sleep disturbance sub-score range from [0 to 4] (Reverse coded so that is more comparable to other variables [high is worse, low is better])
Anger	(1) I felt angry [0-4]	Never [0], Rarely [1], Sometimes [2], Often [3], Always [4]. Anger sub-score range from [0 to 4]
Total: Scores may range from 0 to 64 (high is worse, low is better)		

Data Analyses

All data analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). We conducted a latent class growth analysis (LCGA) using SAS Proc Traj (Jones & Nagin, 2016) to identify latent class trajectories (subgroups of people) based on their six pervasive symptoms over time. There were up to eight follow-up visits. The sample size at enrollment was 970 and decreased to two for the eighth follow-up visit. This decreasing sample size was due to a rolling enrollment and study closeout when the original

MURDOCK MS registry and biorepository met its enrollment goals (which were not dependent on the longitudinal data) (Newby, 2016). Due to the sample sizes, the seventh (*n*=19) and eighth (*n*=2) follow-up visits were excluded from our analyses. LCGA was conducted for seven timepoints (from enrollment [*N*=970] to the sixth follow-up [*n*=100]). See the sample sizes at each follow-up visit in Table 12. We used a censored normal distribution (cnorm) as the variables were continuous (pervasive symptom scores). Based on empirical summary plots, we tested intercept, linear, and quadratic trend models and chose the number of latent groups based on Akaike Information Criteria (AIC), Bayesian Information Criteria (BIC), and judgement of the study team (Yang, 2006). We modeled trajectories of pervasive symptoms simultaneously using a multi-trajectory model.

To examine the relationships between participant characteristics, clinical variables, and the latent class trajectory group membership we conducted bivariate analyses for age, sex, race, ethnicity, marital status, education, employment, income, MS type, if taking MS medications, date since diagnosis, and comorbidities (heart attack, congestive heart failure, stroke, emphysema, liver disease, diabetes, kidney disease, cancer, etc.). Participants also reported their 'Views About Health' using 13 questions scored with a point Likert scale (score from 0 to 52) that included general health rating, activities of daily living (ADLs [ex. ability to climb stairs, walking distance, carrying groceries, bending, etc.]), and satisfaction with ability to perform daily routine and leisure activities.

Results

Sample

Characteristics of the 970 participants are presented in Table 14. They range in age from 18 to 83 years (mean=50.21, SD=11.36). The majority are female (762, 78.56%), white (817, 84.23%), not Hispanic (926, 97.58%), and married or in a domestic partnership (675, 69.59%). Most participants had a bachelor's degree or higher (462, 47.73%). Nearly half (462, 47.73%) had worked for pay in the previous 12 months, 334 (34.72%) were permanently disabled (unable to work), and 297 (30.71%) worked full time. Approximately a third (336, 30.71%) had a household income of less than $50,000 US dollars. The majority reported having relapsing-remitting MS (759, 82.41%), 92 (9.99%) reported secondary-progressive MS, and 70 (7.60%) reported primary-progressive MS. They ranged from one month to 660 months (55 years) since their first MS attack (mean=183.24 [15.27 years], SD=132.30 [11.03 years], median=164 [13.67 years], mode=107 [8.92 years]). Most (896, 92.47%) participants were taking a disease modifying drug for their MS, and 165 (17.33%) used a wheelchair at least some of the time. The mean score for Views About Health for all participants at all time points ranged from 19.76 (SD=11.88) to 21.74 (SD=11.18) with a maximum possible score of 52 (higher score indicates a worse health rating, more challenges with performing ADLs on their own, and less satisfaction).

Pervasive Symptoms

The mean symptom severity score and standard deviation for each pervasive symptom, as well as a total score for each time point (enrollment to the sixth follow-up), are shown in Table 12. Considering the maximum possible scores for each symptom, the means are generally low.

Table 12: Pervasive Symptom Severity Score at Each Follow-Up, Mean (Standard Deviation)

Symptom	Max Score	Follow-Up, Mean (Standard Deviation)						
		Enrollment (*N*=970)	**1** (*n*=755)	**2** (*n*=607)	**3** (*n*=384)	**4** (*n*=310)	**5** (*n*=208)	**6** (*n*=100)
Anxiety	16	3.78 (3.32)	3.35 (3.17)	3.34 (3.20)	3.17 (3.04)	3.32 (3.23)	3.23 (3.18)	3.45 (3.21)
Depression	16	3.52 (3.38)	3.25 (3.26)	3.37 (3.48)	3.20 (3.26)	3.49 (3.46)	3.14 (3.31)	3.40 (3.62)
Fatigue	12	6.20 (3.10)	5.96 (3.17)	6.04 (3.26)	5.77 (3.16)	5.90 (3.18)	5.90 (3.24)	6.00 (3.34)
Pain	12	3.21 (3.31)	3.12 (3.32)	3.30 (3.37)	3.03 (3.27)	3.25 (3.29)	3.48 (3.40)	4.06 (3.56)
Sleep Disturbance	4	2.00 (1.17)	2.01 (1.21)	1.93 (1.18)	1.92 (1.16)	1.84 (1.14)	1.92 (1.16)	2.23 (1.10)
Anger	4	1.12 (0.86)	1.03 (0.86)	1.05 (0.86)	1.04 (0.83)	1.06 (0.86)	1.03 (0.86)	1.05 (0.88)
Total	64	19.81 (11.52)	18.58 (11.27)	18.97 (11.77)	17.99 (11.01)	18.78 (11.60)	18.60 (11.37)	20.14 (11.98)

Symptom Severity Trajectory Typologies

Empirical summary plots for the six pervasive symptoms (Figure 10: Empirical Summary Plots (Mean and Standard Error), Pervasive Symptoms Over Time) show the overall trends (symptoms appear together in the figure if they are scored on the same scale). Anxiety and depression (with a range score of 16) were both low, between two and four, and appear to be linear. Fatigue and pain each have a maximum score of 12, with pain low (between three and four, slight increase over time [worse severity]), and moderate fatigue (around six, linear).

Sleep disturbance and anger each have a range score of four, with anger low (around one, linear), and sleep disturbance moderate (around two, slight increase over time). When considering the scale of each pervasive symptom, anxiety, depression, pain, and anger are rated low, while fatigue and sleep disturbance were rated at a higher relative severity. The overall trends appear to be linear for all six symptoms over six years, with little change over time for anxiety, depression, fatigue, and anger, and a slight worsening for pain and sleep over time.

Considering all six symptoms together, we chose to model these data with three pervasive symptom trajectories at the intercept and linear level based on indices and clinical relevance: 35.88% (*n*=367) were in the first trajectory (Low Severity Trajectory), 41.84% (*n*=428) were in the second trajectory (Moderate Severity Trajectory), and 22.28% (*n*=223) were in the third trajectory (High Severity Trajectory). We also considered the trajectories for two and four trajectories; however, the three-class model was chosen based on judgement, parsimony, and model fit (AIC and BIC) (Table 15). The three class symptom severity trajectories for the six pervasive symptoms are shown in Figure 11, where the Low Severity Trajectory is Group 1 (red), Moderate Severity Trajectory is Group 2 (green), and the High Severity Trajectory is Group 3 (blue). Solid lines are the estimated trajectories, and dashed lines are the 95% pointwise confidence intervals on the estimated trajectories.

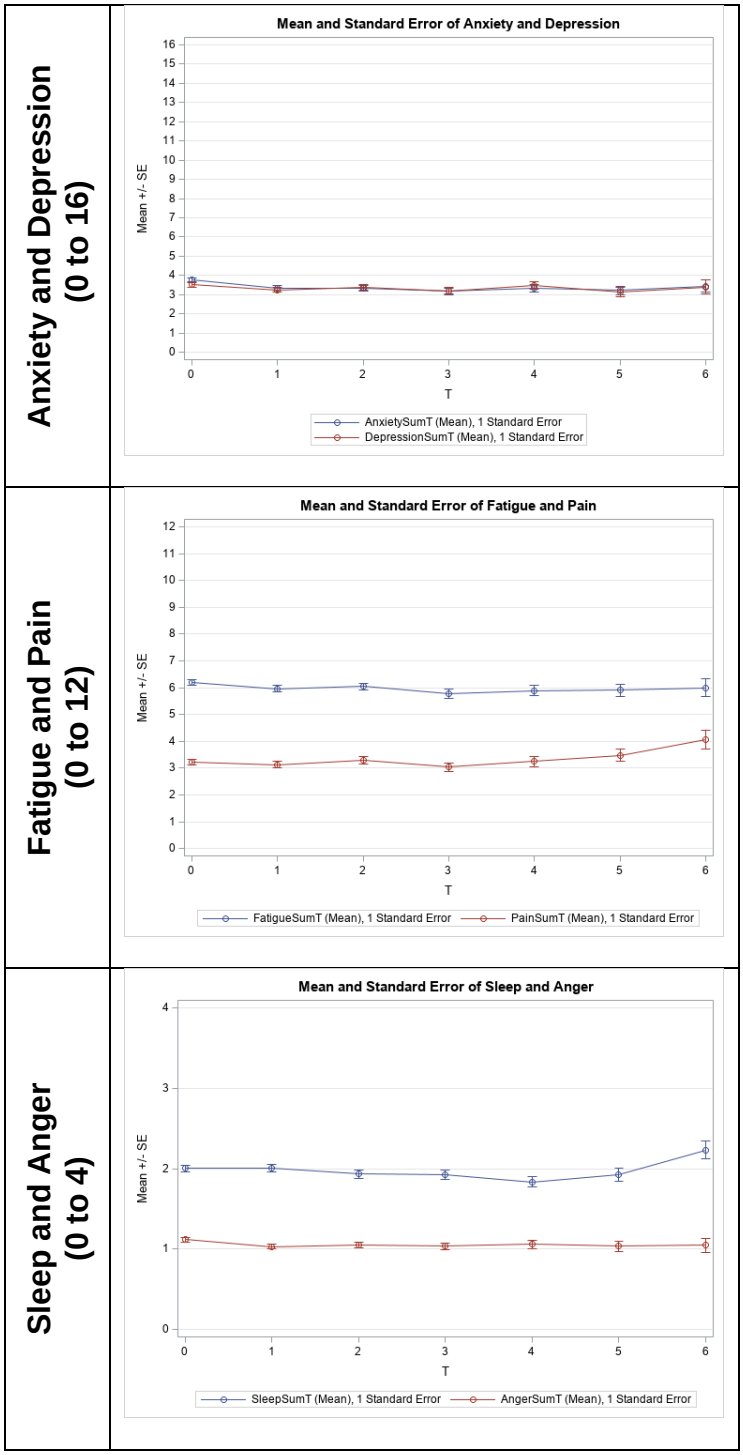
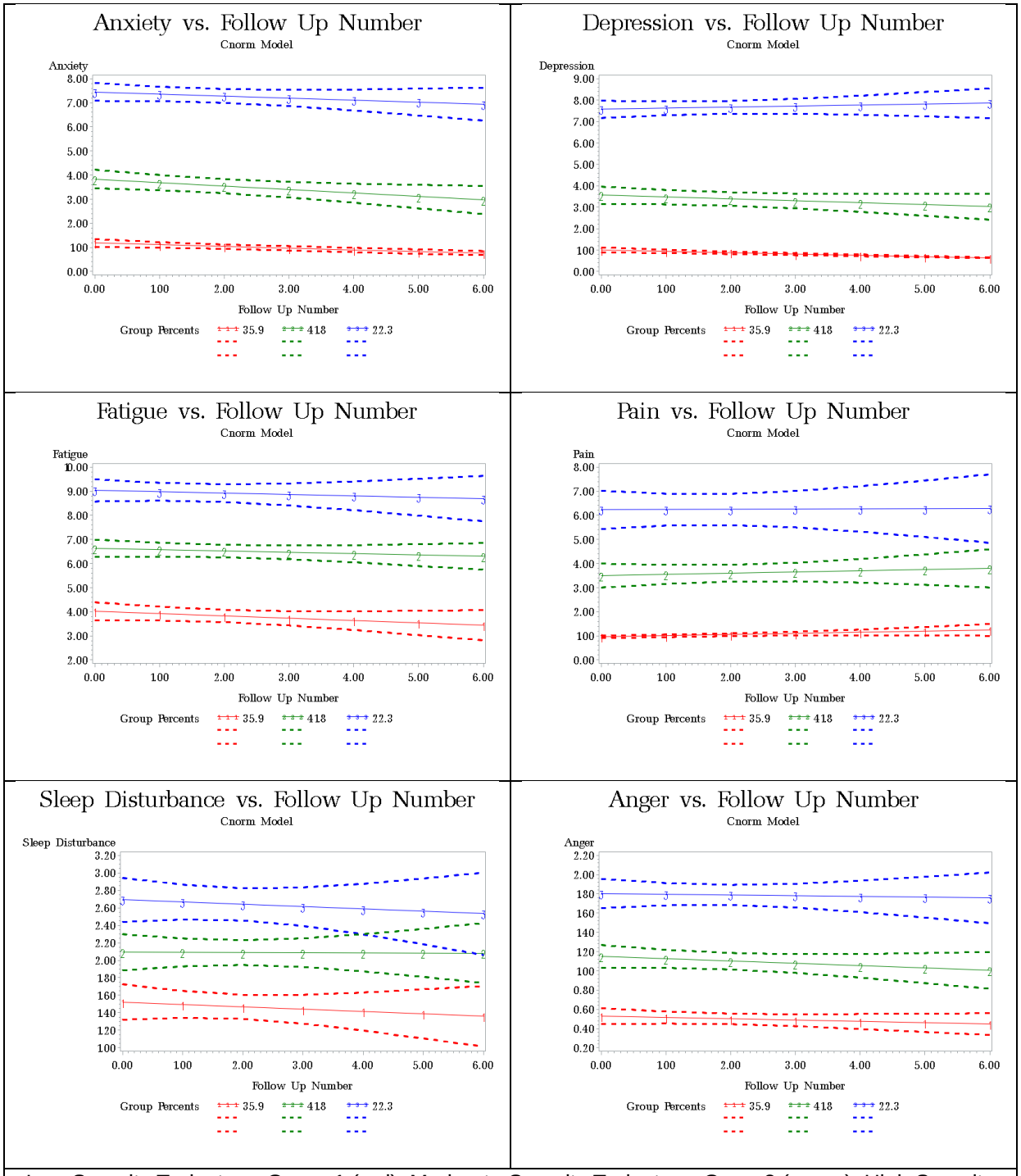


Figure 10: Empirical Summary Plots (Mean and Standard Error), Pervasive Symptoms Over Time



Low Severity Trajectory=Group 1 (red), Moderate Severity Trajectory=Group2 (green), High Severity Trajectory=Group3 (blue). Solid lines are the estimated trajectories, dashed lines are the 95% pointwise confidence intervals on the estimated trajectories.

Figure 11: Pervasive Symptom Severity Trajectories, 3 Classes

Low Severity Trajectory

In the Low Severity Trajectory (Table 13), individuals were low for all symptoms (anxiety intercept=0.10, depression intercept=-0.30, fatigue intercept=3.91, pain intercept=-1.30, sleep disturbance intercept=1.43, and anger intercept=0.26). This trajectory shows a slight decrease in slope over time (improvement in symptom severity) for five out of the six symptoms: 1) anxiety (slope=-0.15, *p*=0.01), 2) depression (slope=-0.15, *p*=0.01), 3) fatigue (slope=-0.11, *p*=0.04), 4) sleep disturbance (slope=-0.03, *p*=0.19), and 5) anger (slope=-0.02, *p*=0.23) that was statistically significant for anxiety, depression, and fatigue. For the sixth symptom, pain (slope=0.12, *p*=0.15), it started low with a slight increase over time (increased severity). However, for pain this increase was not statistically significant.

Moderate Severity Trajectory

In the Moderate Severity Trajectory (Table 13), individuals' symptom severity was moderate to low (but less than the High Severity Trajectory, and more than the Low Severity Trajectory) (anxiety intercept=3.71, depression intercept=3.89, fatigue intercept=6.65, pain intercept=3.06, sleep disturbance intercept=2.11, and anger intercept=1.09). This trajectory shows a slight decrease over time (improvement in symptom severity) for five out of the six symptoms: 1) anxiety (slope=-0.17, *p*=0.0001), 2) depression (slope=-0.10, *p*=0.03), 3) fatigue (slope=-0.06, *p*=0.22), 4) sleep disturbance (slope=-0.001, *p*=0.94), and 5) anger (slope=-0.03, *p*=0.08) that was statistically significant for

anxiety and depression. For the sixth symptom, pain (slope=0.06, *p*=0.33), it showed a slight increase over time (increased severity). However, for pain this increase was not statistically significant.

High Severity Trajectory

In the High Severity Trajectory (Table 13), individuals' symptom severity was moderate to high, and higher than both the Low and Moderate Severity Trajectories, (anxiety intercept=7.45, depression intercept=7.56, fatigue intercept=9.28, pain intercept=6.25, sleep disturbance intercept=2.84, and anger intercept=1.80). This trajectory shows a slight decrease over time (improvement in symptom severity) for four out of the six symptoms: 1) anxiety (slope=-0.08, *p*=0.21), 2) fatigue (slope=-0.07, *p*=0.36), 3) sleep disturbance (slope=-0.03, *p*=0.33), and 4) anger (slope=-0.01, *p*=0.72). For the remaining two symptoms, there is a slight increase over time (increased severity): 5) depression (slope=0.05, *p*=0.49), and 6) pain (slope=0.01, *p*=0.72). For the High Severity Trajectory, no slope values were statistically significant.

Table 13: Latent Class Growth Analysis Multi-Trajectory Model Results for Three Pervasive Symptom Severity Typologies

Trajectory Typology	Pervasive Symptom	Parameter	Estimate (b)	SE	t-value	*p*-value
Low	Anxiety	intercept	0.10	0.16	0.62	0.54
		slope	-0.15	0.06	-2.59	**0.01****
	Depression	Intercept	-0.30	0.16	-1.86	0.06
		slope	-0.15	0.06	-2.45	**0.01****
	Fatigue	Intercept	3.91	0.14	28.34	0.00
		slope	-0.11	0.05	-2.06	**0.04****
	Pain	Intercept	-1.30	0.23	-5.75	0.00
		slope	0.12	0.08	1.43	0.15
	Sleep Disturbance	Intercept	1.43	0.07	21.74	0.00

Trajectory Typology	Pervasive Symptom	Parameter	Estimate (b)	SE	t-value	*p*-value
		slope	-0.03	0.03	-1.30	0.19
	Anger	Intercept	0.26	0.05	5.07	0.00
		slope	-0.02	0.02	-1.21	0.23
Moderate	Anxiety	Intercept	3.71	0.14	25.67	0.00
		slope	-0.17	0.05	-3.43	**0.001****
	Depression	Intercept	3.89	0.15	22.36	0.00
		slope	-0.10	0.05	-2.11	**0.03****
	Fatigue	Intercept	6.65	0.14	48.10	0.00
		slope	-0.06	0.05	-1.23	0.22
	Pain	Intercept	3.06	0.19	16.45	0.00
		slope	0.06	0.06	0.98	0.33
	Sleep Disturbance	Intercept	2.11	0.06	33.42	0.00
		slope	-0.001	0.02	-0.07	0.94
	Anger	Intercept	1.09	0.01	24.45	0.00
		slope	-0.03	0.02	-1.75	0.08
High	Anxiety	Intercept	7.45	0.18	42.48	0.00
		slope	-0.08	0.07	-1.27	0.21
	Depression	Intercept	7.56	0.19	40.45	0.00
		slope	0.05	0.07	0.70	0.49
	Fatigue	Intercept	9.28	0.18	52.79	0.00
		slope	-0.07	0.07	-0.92	0.36
	Pain	Intercept	6.25	0.25	24.96	0.00
		slope	0.01	0.09	0.12	0.91
	Sleep Disturbance	Intercept	2.84	0.09	32.03	0.00
		slope	-0.03	0.03	-0.98	0.33
	Anger	Intercept	1.80	0.06	31.44	0.00
		slope	-0.01	0.02	-1.36	0.72

Note: Akaike Information Criteria (AIC)= -37,580.80,
Bayesian Information Criteria (BIC)= -37,689.10

Participant Characteristics vs. Symptom Severity Trajectory Typology

Bivariate results are presented in Table 14. Symptom severity trajectory was not significantly associated with age, sex, ethnicity, marital status, type of MS, months since first MS attack, and number of follow-up visits attended.

Race

For race (white vs. minority racial groups) there was a higher percentage of white people in the Low Severity Trajectory (309, 88.03%) than the Moderate (325, 80.85%) and High Severity (161, 77.03%) Trajectories. Minority racial

groups were more likely to be in the High Severity Trajectory (62, 22.97%). Using a Chi-Square test, the relationship between these variables was significant ($X^2(2)=12.60$, $p=0.002<0.05$).

Level of Education

There were more individuals with a bachelor's degree (126, 35.69%) and a master's degree or higher (84, 23.80%) in the Low Severity Trajectory. Individuals with some college or an associate degree are more likely to be in the High (97, 45.54%) and Moderate (159, 39.36%) Severity Trajectories. Using a Chi-Square test, the relationship between these variables was significant ($X^2(8)=67.69$, $p<0.0001<0.05$).

Employed for Pay Last Year

Those who were employed for pay in the last 12 months (205, 58.07%) were more likely to be in the Low Severity Trajectory than the Moderate (189, 47.01%) or High Severity (68, 31.92%) Trajectories. Using a Chi-Square test, the relationship between these variables was significant ($X^2(2)=36.55$, $p<0.0001<0.05$).

Employment Status

Individuals who report being permanently disabled (unable to work) were more likely to be in the High Severity Trajectory (110, 52.38%) than the Moderate (156, 38.90%) and Low Severity (68, 19.37%) Trajectories. Those working full-time were more likely to be in the Low Severity Trajectory (150, 42.74%). Using a

Chi-Square test, the relationship between these variables was significant ($X^2(14)=112.75$, $p<0.0001<0.05$).

Household Income

Those with a higher household income (≥$50,000) were more likely to be in the Low Severity Trajectory (235, 66.57%), while those whose household of less than $50,000 per year were more likely to be in the High Severity Trajectory (97, 50.52%). Using a Chi-Square test, the relationship between these variables was significant ($X^2(2)=23.68$, $p<0.0001<0.05$).

Table 14: Participant Characteristics, All Together and by Symptom Severity Trajectory Typology

Characteristics	***N***	**All**	**Low** (*n*=367)	**Moderate** (*n*=428)	**High** (*n*=223)	**F or χ^2**	***p*-value**
Number of Participants							
Enrollment	970	970 (100)	353 (36.39)	404 (41.65)	213 (21.96)	1.45	0.49
Follow-Up One	755	755 (77.84)	283 (37.48)	328 (43.44)	144 (19.07)	13.73	**0.001****
Follow-Up Two	607	607 (62.58)	232 (38.22)	251 (41.35)	124 (20.43)	3.63	0.16
Follow-Up Three	384	384 (39.59)	150 (39.06)	156 (40.63)	78 (20.31)	2.56	0.28
Follow-Up Four	310	310 (31.96)	107 (34.52)	135 (43.55)	68 (21.94)	0.53	0.77
Follow-Up Five	208	208 (21.44)	68 (32.69)	95 (45.67)	45 (21.63)	1.65	0.44
Follow-Up Six	100	100 (10.31)	30 (30.00)	47 (47.00)	23 (23.00)	1.84	0.40
Age (18 to 83)	970	50.21 (11.36)	50.68 (11.96)	50.31 (11.14)	49.23 (10.73)	1.11	0.33
Female	970	762 (78.56)	267 (75.64)	320 (79.21)	175 (82.16)	3.53	0.17
Race, White	962	817 (84.23)	309 (88.03)	325 (80.85)	161 (77.03)	12.60	**0.002****
Ethnicity, Hispanic	949	23 (2.41)	11 (3.19)	7 (1.78)	5 (2.38)	1.55	0.46
Married/Domestic Partner	970	675 (69.59)	257 (38.07)	283 (41.02)	135 (20.00)	5.64	0.06
Body Mass Index (BMI) at Enrollment	967	28.21 (6.54)	27.27 (6.09)	28.42 (6.70)	29.39 (6.73)	7.38	**0.0007****
Highest Level of Education Completed	970					67.69	**<0.0001****

Characteristics	*N*	All	Low (*n*=367)	Moderate (*n*=428)	High (*n*=223)	F or χ^2	*p*-value
Less than High School		20 (2.06)	2 (0.57)	9 (2.23)	9 (4.23)		
High School Graduate or GED		120 (12.37)	29 (8.22)	44 (10.89)	47 (22.07)		
Some College or Associate Degree		368 (37.94)	112 (31.73)	159 (39.36)	97 (45.54)		
Bachelor's Degree		292 (30.10)	126 (35.69)	122 (30.20)	44 (20.66)		
Master's or Higher Professional Degree		170 (17.53)	84 (23.80)	70 (17.33)	16 (7.51)		
Employed for Pay Past 12 Month	968	462 (47.73)	205 (58.07)	189 (47.01)	68 (31.92)	36.55	**<0.0001****
Employment Status	962					112.75	**<0.0001****
Permanently Disabled		334 (34.72)	68 (19.37)	156 (38.90)	110 (52.38)		
Working Full-Time		297 (30.71)	150 (42.74)	111 (27.68)	36 (17.14)		
Retired		116 (12.06)	55 (15.67)	41 (10.22)	20 (9.52)		
Working Part-Time		89 (9.25)	31 (8.83)	49 (12.22)	9 (4.29)		
Stay at Home (Parent, Caregiver, or Other)		62 (6.44)	31 (8.83)	21 (5.24)	10 (4.76)		
Unemployed, Looking for Work		37 (3.85)	9 (2.56)	12 (2.99)	16 (7.62)		
Temporarily Laid Off, Sick or Maternity Leave		14 (1.46)	2 (2.56)	5 (1.25)	7 (3.33)		
Student		13 (1.35)	5 (1.42)	6 (1.50)	2 (0.95)		
Household Income	896					23.68	**<0.0001**
< $50,000		336 (37.50)	97 (29.22)	142 (38.17)	97 (50.52)		
≥ $50,000		560 (62.50)	235 (66.57)	230 (56.93%)	95 (44.60%)		
Type of MS	921					2.46	0.65
Relapsing-Remitting		759 (82.41)	279 (83.28)	321 (82.95)	159 (79.90)		
Secondary-Progressive		92 (9.99)	29 (8.66)	41 (10.59)	22 (11.06)		
Primary-Progressive		70 (7.60)	27 (8.06)	25 (6.46)	18 (9.05)		
Total Number of Follow-Up Visits	1017	3.28 (1.83)	3.33 (1.78)	3.32 (1.83)	3.12 (1.92)	1.12	0.33
Comorbidities at Enrollment (0 to 13)	970	3.65 (2.15)	3.16 (1.89)	3.64 (2.15)	4.46 (2.30)	25.67	**<0.0001**
Views About Health Score at Enrollment (0 to 52)	919	21.27 (11.85)	15.26 (11.19)	22.30 (10.47)	29.26 (11.19)	110.58	**<0.0001****
Views About Health Score at Follow-Up Six (0 to 52)	100	21.74 (11.18)	16.03 (11.90)	21.62 (8.97)	29.43 (10.07)	11.30	**<0.0001****
Months Since First MS Attack (1 to 660)	945	183.24 (132.30)	187.91 (137.70)	189.30 (136.93)	163.83 (111.15)	2.85	0.06

Characteristics	*N*	All	Low (*n*=367)	Moderate (*n*=428)	High (*n*=223)	F or χ^2	*p*-value
Take an MS Disease Modifying Drug	969	896 (92.47)	325 (92.33)	373 (92.33)	198 (92.96)	0.09	0.95
Use a Wheelchair	952	165 (17.33)	42 (12.10)	68 (17.17)	55 (26.32)	18.40	**<0.0001****

Table 15: Model Fit by Number of Latent Classes Modeled for Anxiety, Depression, Fatigue, Pain, Sleep Disturbance, and Anger

Classes	AIC	BIC (*N*=1015)	Percent Per Class
2	-38258.66	-38334.96	52.50/47.50
3	-37580.80	-37580.80	35.88/41.84/22.28
4	-37145.38	-37285.67	31.37/17.40/28.59/22.63
Note: AIC = Akaike information criterion; BIC = Bayesian information criterion. Sample size per class based on the most likely class membership			

Number of Comorbidities

A one-way ANOVA was done to compare the number of comorbidities at enrollment in the three symptom severity trajectories. There was a significant difference in the number of comorbidities for all three symptom severity trajectories ($F(2,967)=25.67$, $p<0.0001<0.05$). Those with a higher number of comorbidities at enrollment were more likely to be in the High Severity Trajectory (*n*=213, mean=4.46, SD=2.3), followed by the Moderate Severity Trajectory (*n*=404, mean=3.64, SD=2.15), then the Low Severity Trajectory (*n*=353, mean=3.15, SD=1.89). Post hoc analyses show that the number of comorbidities is statistically significant between all three groups. For the High vs. Moderate Severity Trajectories the difference between means is 0.82, with simultaneous 95% Confidence Limits of 0.40 and 1.23. For the High vs. Low Severity Trajectories the difference between means is 1.30, with simultaneous 95% Confidence Limits of 0.88 and 1.73. For the Low vs. Moderate Severity

Trajectories, the difference between means is 0.48, with simultaneous 95% Confidence Limits of 0.13 and 0.84.

Body Mass Index

A one-way ANOVA was done to compare the Body Mass Index (BMI) at enrollment in the three symptom severity trajectories. There was a significant difference in the BMI between the groups ($F(2, 964)=7.38$, $p=0.0007<0.05$). Those with higher BMIs at enrollment were more likely to be in the High Severity Trajectory ($n=212$, mean=29.39, SD=6.73) and the Moderate Severity Trajectory ($n=404$, mean=28.42, SD=6.70), than the Low Severity Trajectory (mean=27.27, SD=6.09). Post hoc analyses show significant differences between the High and Low Severity Trajectories (difference between means=2.12, simultaneous 95% confidence limits 0.79 and 3.44), and the Moderate and Low Severity Trajectories (difference between means is 1.15, simultaneous 95% confidence limits are 0.04 and 2.26). There was not a statistically significant difference between the High and Moderate Severity Trajectories.

Views About Health Score, Enrollment

A one-way ANOVA was done to compare the Views About Health score at enrollment in the three symptom severity trajectories. There was a significant difference in the Views About Health score at enrollment between the groups ($F(2, 916)=110.58$, $p<0.0001<0.05$). A higher (worse) Views About Health score was associated with the High Severity Trajectory at enrollment ($n=199$, mean=29.26, SD=10.03), followed by the Moderate Severity Trajectory ($n=389$,

mean=22.30, SD=10.47), and the Low Severity Trajectory (*n*=331, mean=15.26, SD=11.19). Post hoc analyses show Views About Health is statistically significant between all three groups. For the High vs. Moderate Severity Trajectories the difference between means is 6.96, and the simultaneous 95% Confidence Limits are 4.78 and 9.14. For the High vs. Low Severity Trajectories the difference between means is 14.00, and the simultaneous 95% Confidence Limits are 11.76 and 16.24. For Moderate vs. Low Severity Trajectories the difference between means is 7.04, and the simultaneous 95% Confidence Limits are 5.17 and 8.91.

Views About Health Score, Follow-Up Six

A one-way ANOVA was done to compare the Views About Health score at follow-up six in the three symptom severity trajectories. There was a significant difference in the Views About Health score at enrollment between the groups ($F(2, 97)=11.30$, $p<0.0001<0.05$). At the sixth follow-up, a higher (worse) Views About Health score was associated with the High Severity Trajectory (*n*=23, mean=29.43, SD=10.07), followed by the Moderate Severity Trajectory (*n*=47, mean=21.62, SD=8.97), then the Low Severity Trajectory (*n*=30, mean=16.03, SD=11.90). Post hoc analyses (Tukey) show there is a statistically significant difference between the High Severity vs. Low Severity Trajectories (difference between means is 13.40, simultaneous 95% Confidence Limits is 6.70 and 20.11), and there is statistically significant difference between the High Severity and Moderate Severity Trajectories (difference between means is 7.85,

simultaneous 95% confidence limits are 1.67 and 13.98). There is not a significant difference between the Low and Moderate Severity Trajectories.

Wheelchair Use

A Chi-Square test was done to compare wheelchair at enrollment in the three symptom severity trajectories. There was a significant difference in wheelchair use between the groups ($X^2(2)=18.40$, $p<0.0001<0.05$). A wheelchair was used at least some of the time at enrollment by 165 participants (17.33%). Those in the High Severity Trajectory are most likely to use a wheelchair. Out of 209 participants in the High Severity Trajectory 26.32% (55) used a wheelchair at least some of the time at enrollment, versus 17.17% (68) in the Moderate Severity Trajectory, and 12.10% (42) in the Low Severity Trajectory. So, though most wheelchair users are in the Moderate Severity Trajectory (68, 41.21% of wheelchair users), proportionately this is less than the number of wheelchair users in the High Severity Trajectory, as the Moderate Severity Trajectory is the largest overall group.

Discussion

Using a latent class growth analysis, we identified symptom severity trajectories for adults with MS from the MURDOCK-MS dataset. We identified three distinct, stable symptom severity trajectory typologies: Low Severity, Moderate Severity, and High Severity for the six pervasive symptoms (anxiety, depression, fatigue, pain, sleep disturbance, and anger). Anxiety, fatigue, sleep disturbance, and anger decreased slightly over time for all three severity

trajectories. From the clinical perspective this may mean that these symptoms are generally being managed well among adults with MS taking part in the MURDOCK-MS study. However, there is the possibility that the reported symptom severity does not necessarily reflect the impact the symptom has on an individual's quality of life. For example, when patients live with symptoms like chronic pain, a zero to 10 pain scale may not adequately describe their pain experience (Hurt & Prasad, 2020; Neighmond, 2018). Thus, the Likert scale used to assess these pervasive symptoms may not adequately reflect the symptom experience.

Pain was the one symptom that showed an increase over time in all three severity trajectories. This trend may be worth investigating further to understand if it is an artifact of a decreasing sample size over time or is truly an increase. In the High Severity Trajectory, there is also an increase in depression over time that warrants further investigation. Once again to determine if this is an artifact of the decreasing sample size, or if it is truly an increase. It may be valuable to explore these patterns in more detail to better understand the impact of these symptoms over time for adults with MS.

The symptoms with the highest mean symptom severity scores proportionately (considering the maximum for each score) were fatigue and sleep disturbance, while anxiety, depression, pain, and anger all fell in the bottom halves of their respective scales. The trend of anxiety, depression, and anger being in the bottom half of the scale, as well as decreasing (improving) over time

for most individuals indicates that these symptoms may not be as much of a concern for individuals with MS, or that they are being better assessed, managed, or prevented over time within this group. For fatigue and sleep disturbance it may be helpful to explore these tendencies further to determine if they are contributing more to overall symptom severity and impact and the possible explanations as to why this may be.

Bivariate analyses showed a significant difference in groups based on race, level of education, worked for pay in the last 12 months, employment status, household income, number of comorbidities at enrollment, BMI, Views About Health at enrollment and at the sixth follow-up, and wheelchair use. Statistically significant relationships were not observed based on age, sex, ethnicity, marital status, type of MS, months since first attack, months since first MS attack, and number of follow-up visits attended.

Minority racial groups were more likely to be in the High Severity Trajectory (worse severity of the three severity trajectories), this is consistent with the literature that minority groups with MS are at a higher risk for more severe symptoms (Koffman et al., 2013; National Multiple Sclerosis Society, 2020f). For level of education, those in the Low Severity Trajectory had completed more education than the Moderate and High Severity Trajectories. This may be due to several factors, keeping in mind that with these data we are unable to determine cause and effect. However, it has been found that a higher education (an indicator of socioeconomic status) (Shavers, 2007) is associated with a lower

MS risk (Abbasi et al., 2016; Bjørnevik et al., 2016). Those in the Low Severity Trajectory are also more likely to have worked for pay in the last year, which may indicate that higher symptom severity interferes with an individual's ability to attend work, meet job requirements, or may negatively impact job performance. For employment status, those working full-time are more likely to be the Low Severity Trajectory, and those who are permanently disabled (unable to work) in the High Severity Trajectory. Those with a higher annual household income (≥$50,000) were more likely to be in the Low Severity Trajectory, and those with lower income (<$50,000) were more likely to be in the High Severity Trajectory. These findings support previous research that show greater levels of impairment with increased disease severity (Nicholas et al., 2019), and higher levels of unemployment, decreased work participation, diminished productivity, and less paid work for people with MS (Vijayasingham & Mairami, 2018).

A higher number of comorbidities at enrollment was more likely in the High Severity Trajectory, supporting previous work showing comorbidities significantly contribute to symptom severity in people with MS (Lo et al., 2021). Those with higher BMIs were more likely to be in the higher severity trajectories, supporting previous work that demonstrates BMI has been associated with higher clinical disability and increased inflammatory biomarkers (Stampanoni Bassi et al., 2020). For Views About Health scores, those with higher (worse) scores were more likely to be in the High Severity Trajectory at enrollment and at their sixth follow-up than those with lower scores. This relationship between worse

symptom and worse Views About Health is consistent with work that shows decreased health-related quality of life in people with MS (Berrigan et al., 2016). Those who use a wheelchair at least some of the time were more likely to be in the High Severity Trajectory, consistent with research that shows people with moderate or severe MS were more likely to use a wheelchair (Conradsson et al., 2018).

With regards to the variables that were not significantly associated with the symptom severity trajectories, these findings are also worth additional thought and consideration. The variables that were not significantly associated with symptom severity trajectory were: age, sex, ethnicity, marital status, type of MS, months since first MS attack, and number of follow-up visits attended. Some of these were not quite what we would have expected. For instance, as MS is a progressive disease for most, as well as the increased potential for developing comorbid conditions (Multiple Sclerosis Trust, 2020a), we expected that age may be associated with a worse trajectory (Scalfari et al., 2011), but we did not observe that with these data. Additionally, it has been reported that men experience worse symptom severity than women (Abbasi et al., 2016; Multiple Sclerosis Trust, 2016; Ribbons et al., 2015), however we did not observe this trend. With regards to ethnicity (Hispanic or not), we would have expected that as a minority group those who report Hispanic ethnicity may be more likely to experience a more severe symptom trajectory (Amezcua & McCauley, 2020; National Multiple Sclerosis Society, 2020e; Rivas-Rodríguez & Amezcua, 2018),

we did not observe this trend. Though our results did not reflect this, it has been reported in some health conditions that being married may be protective (Abbasi et al., 2016; Abdollahpour et al., 2018). For months since first MS attack, we did not find there to be a significant relationship with symptom severity, such that having MS for a long time did not mean worse symptom severity, further reflecting the heterogeneity in symptom experiences between individuals with MS. Though results have been somewhat mixed, age at onset, rather than time since first MS attack, may be better at predicting MS severity (Abbasi et al., 2016; Albatineh et al., 2020). For number of follow-up visits attended we may have expected that those in the High Severity Trajectory would attend fewer follow-up visits, but this was not what we observed.

For type of MS, we expected that those with PPMS would be more likely to be in the more severe symptom trajectory (Holland et al., 2010; National Multiple Sclerosis Society, 2020e; Raghavan et al., 2015), but for these data this was not this case. Potentially this may be a result of the PPMS group being so small (*n*=70) vs. the RRMS and SPMS group (*n*=854). Interestingly, looking at the PPMS group, the majority of them are in the Low Severity Trajectory (*n*=27, 38.57% of PPMS group), followed by the Moderate Severity Trajectory (*n*=25, 35.71%), then the High Severity Trajectory (*n*=18, 25.71%). Those who did not have PPMS were more likely to be in the Moderate Severity Trajectory (*n*=364, 42.62%), followed by the Low Severity Trajectory (*n*=308, 36.07%), then the High

Severity Trajectory (*n*=182, 21.31%). Thus, the general belief that PPMS is worse than other types of MS may not be accurate.

Limitations and Strengths

Limitations of this work include lack of statistical significance for the LCGA linear slopes, especially for there being no significant values for the High Severity Trajectory group. Thus, one should be mindful in drawing definitive conclusions about the Moderate Severity Group. With regard to the survey, there is no assessment of the validity and reliability of the questions used to assess pervasive symptoms; though some of the questions are the same as those used in the PROMIS measures (Pilkonis et al., 2011) the entire tool is not included (please note, however, that it appears the PROMIS tools were still in development when the MURDOCK study was already collecting data). This work may be limited in its generalizability due to the patient characteristics (tend to be high income, highly educated, etc.), and the relatively short time of data collection (up to six years) considering the natural history of MS (Leray et al., 2016).

Strengths in using latent class growth analysis include that it is a data driven and person-centered approach, allowing for the gathering of individuals into similar groups (Jung & Wickrama, 2008). LCGA helps to identify underlying latent groups or subpopulations within a larger, heterogeneous population (Jung & Wickrama, 2008). Strengths of these data include the sample size at

enrollment (*N*=970), though this does decrease to 100 people by the sixth follow-up visit.

Conclusion and Future Directions

This study identified pervasive symptom trajectory typologies for adults with MS taking part in the MURDOCK-MS study. Three distinct symptom severity trajectory typologies were identified: Low Severity, Moderate Severity, and High Severity. Fatigue and sleep disturbance showed higher (worse) scores proportionately than the other pervasive symptoms. Anxiety, fatigue, sleep disturbance, and anger decreased slightly over time (symptom improvement). Depression showed a slight increase only in the High Severity Trajectory. Pain is the only symptom that showed increasing severity over time in all three trajectory typologies.

This exploratory work provides ideas and guidance regarding future exploration of these data, as well as aspects to consider for future data collection and analyses. These patterns are worth further investigation to better understand the impact of these symptoms, for example incorporating outcomes or endpoints as well as covariates into theses analyses. We would like to explore other potential differences between the three identified groups, to better understand if there are ways to predict which individuals are most at risk for being in the High Severity Trajectory. We are interested in considering subgrouping based on time since diagnosis, for instance, less than 5 years, 5 to 15 years, and greater than 15 years. We would like to attempt to replicate these results in another MS

dataset, as well as to compare the applicability of these symptom severity trajectories to other disease states. Additionally, we may want to explore patient-provider communication with regards to reporting and assessing symptoms. We would like to investigate the effectiveness of various management and treatment options for symptom severity trajectories for people with MS. We may specifically want to target those in the High Severity Trajectory (the highest severity group), to help to meet the needs of the group experiencing the worse symptom severity, as well as to explore aspects of symptom treatment and management for the Low Severity Trajectory to potentially identify modifiable differences between the groups that may be helping to keep their symptom severity low.

CHAPTER 5: Conclusions

The aim of chapter five is to synthesize the findings from each chapter, discuss the limitations of the study, and provide implications for practice and future research.

Purpose of Dissertation

The purpose of this dissertation is to provide the foundation for my program of research on the symptom experiences of people with Multiple Sclerosis. This work will identify MS symptom phenotypes, incorporating both early MS-specific and subsequent pervasive symptom trajectories. The resulting symptom phenotypes will describe MS symptom experiences and inform my future research regarding symptom self-management and prevention of adverse symptoms in adults with MS.

Summary of Key Findings

Chapter 2: A Literature Review of the Symptom Experience in Adults with Multiple Sclerosis

The aim of this chapter was to conduct a literature review exploring the diagnosis experience of people with MS and identifying themes. The six themes identified related to the pre-diagnosis experience for people with MS were: (1) change in self-image and role, (2) different reactions to diagnosis, (3) different readiness for learning about diagnosis, (4) need for support at many levels, (5) heterogeneity and complexity of symptom experience, and (6) difficulty with diagnosis and symptom management.

Chapter 3: Symptoms of the First Multiple Sclerosis Attack, An Exploratory Factor Analysis

The aim of this chapter was to conduct an exploratory factor analysis to cluster the 30 MS-specific symptoms from the first MS attack according to possible latent factors. With considerations for parsimony, interpretability, and clinical meaningfulness, we identified four symptom clusters:

1. Intracranial Cluster: Dizziness and balance problems, decreased attention span, poor judgement, and memory loss, double vision, eye discomfort, fatigue, and slurred or difficult-to-understand speech.
2. Motor Cluster: Problems walking, problems moving arms or legs, loss of balance, problems with coordination and making small movements, weakness in one or more arms/legs.
3. Spasticity Cluster: Painful muscle spasms and muscle spasms.
4. Paresthesia vs. Vision Loss: Numbness/abnormal sensation in any area, tingling, crawling, or burning feeling in the arms and legs, vs. vision loss (usually affects one eye at a time).

For the first three clusters (Intracranial, Motor, and Spasticity) the symptoms occurred together. However, for the fourth cluster (Paresthesia vs. Vision Loss), Vision Loss has an inverse relationship with paresthesia (numbness/abnormal sensation and tingling), such that if a person has numbness and/or tingling, they do not have vision loss, and vice versa. These results suggest that symptoms may occur in clusters for adults during their first MS attack.

Chapter 4: Trajectory Typologies of Pervasive Symptoms in Adults with Multiple Sclerosis: A Latent Class Growth Analysis

The aim of chapter four was to conduct a Latent Class Growth Analysis to classify longitudinal pervasive symptom trajectory typologies. Using LCGA we identified three distinct, stable symptom severity trajectory typologies: Low Severity, Moderate Severity, and High Severity for the six pervasive symptoms (anxiety, depression, fatigue, pain, sleep disturbance, and anger). However, there was a lack of statistical significance for the linear slopes in the latent class growth analysis, with no significant values for the High Severity Trajectory group.

Anxiety, fatigue, sleep disturbance, and anger decreased slightly over time for all three severity trajectories. Pain was the only symptom that showed an increase over time in all three severity trajectories. In the High Severity Trajectory depression also showed a slight increase over time. Symptoms with the highest mean symptom severity scores proportionately (considering the maximum for each score) were fatigue and sleep disturbance, while anxiety, depression, pain, and anger all fell in the bottom halves of their respective scales. The trend of anxiety, depression, and anger being in the bottom half of the scale, as well as decreasing (improving) over time for most individuals indicates that these symptoms may not be as much of a concern for individuals with MS, or that they are being better assessed, managed, or prevented over time within this group.

Statistically significant bivariate analyses showed a significant difference in groups based on race, level of education, worked for pay in the last 12 months,

employment status, household income, number of comorbidities at enrollment, BMI, Views About Health scores at enrollment and at the sixth follow-up, and wheelchair use. Statistically significant relationships were not observed based on age, sex, ethnicity, marital status, type of MS, and months since first attack.

We would like to incorporate outcomes and covariates into theses analyses, to explore other potential differences between the three identified groups, and to better understand if there are ways to predict which individuals are most at risk for being in the High Severity Trajectory. Additionally, we would like to explore aspects of symptom treatment and management for the Low Severity Trajectory to potentially identify modifiable differences between the groups that may be helping to keep their symptom severity low.

Limitations and Strengths

Regarding the limitations of this work, the data for chapters three and four used a secondary/existing dataset (MURDOCK-MS), which was not specifically designed for the aims of this research project, and we were not the original group to collect the data. Thus, there may be nuances regarding these data of which we are not aware (Cheng & Phillips, 2014). There is also the potential for confirmation bias, especially in chapter two, the literature review. For chapter three, the exploratory factor analysis, there is the potential for recall bias for participants recalling their initial MS symptoms. For chapter four, the latent class growth analysis, we are limited by the decreasing sample size over time, and the

lack of statistical significance of aspects of the selected model (especially for the High Severity Trajectory).

Strengths of this research for chapters three and four include this is the first use of the already existing MURDOCK-MS symptom data, and the large sample size (*N*=970). For chapter two, confirmation of the previously identified themes in the second search shows stability within the six themes identified by the literature review.

Implications and Future Research

Implications of this work include improved understanding of a complex symptom experience for adults with MS. This work serves as a foundation for future work, providing evidence for gaps in certain areas of MS-related research. This work offers insight into symptoms in adults with MS including themes related to the pre-diagnosis and early diagnosis experience, symptom clusters from the early MS experience, and symptom severity trajectories over time. These hypothesized themes, clusters, and trajectories may be further explored, incorporating covariates into analyses, seeking to confirm these findings in a new MS population, as well as potentially exploring if these themes, clusters, and trajectories are applicable for other health conditions.

The priority next steps in this work would be to utilize statistical approaches to analyzing these data that will allow the incorporation of covariates and outcomes into the symptom clusters of the first MS attack and the symptom trajectory typologies. I would like to combine the symptom clusters with the

symptom trajectory data to create a more comprehensive symptom phenotype for adults with MS. I would like to identify and incorporate outcomes into this work to allow for the use of the Symptom Phenotype Trajectory Model (Figure 5). I would like to explore the next step of the NIH Symptom Science Model (biomarker discovery) (Figure 4) using genetic/genomic and imaging data, and learning how to incorporate these types of data into my analyses to better understand the biological underpinnings of symptoms, clusters, and trajectories.

I would like to explore the ways patients and providers communicate regarding symptoms and their management, seeking to improve reporting and assessment of symptoms, as well as pharmaceutical and nonpharmaceutical methods used to help manage symptoms and improve quality of life. I am interested as well in exploring ways to educate the public regarding symptoms, clusters of symptoms, and disability with the hopes to clarify misconceptions and help to improve the symptom experience for people with MS. The journey to diagnosis for MS is often a challenging and potentially traumatic one, with many frustrations and setbacks along the way. I would like my research to help to improve this experience, and to improve the quality of life and symptom management for people with multiple sclerosis.

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Biography

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