

Supplementary Material

Understanding the Symptoms and Impacts Experienced by People with Relapsing– Remitting MS: A Qualitative Investigation Using Semi-Structured Interviews

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1 Literature review

Supplementary Table S1 Symptoms and impacts identified in PwMS, as reported in the literature

Citation	Study design	Brief summary of key symptoms/impacts identified
(A) CEI interviews and focus groups		
Westergaard et al. 2022 [1]	Focus groups and interviews (n=20; RRMS n=13, SPMS n=5, PPMS n=2) to evaluate the most important aspects of living with MS in Denmark.	Identified 28 symptoms/impacts, which were categorized into 5 domains: neurological symptoms, cognitive impairments, mental health and well-being, self-care activities, social challenges.
Hunter et al. 2021 [2]	Interviews exploring experiences of PwMS (n=14; RRMS n=7, SPMS n=5, PPMS n=2) and impacts on the family in the UK.	The central themes were feeling let down by healthcare, fears for the future, and finding a way forward. Fears about loss of autonomy and independence characterized the narratives.
Matza et al. 2019 [3]	CEIs with PwMS (n=14; RRMS n=6, SPMS n=6, PPMS n=1) in the development of the CROMS PRO (US).	Signs and symptoms of MS reported by at least 75% of participants related to: walking, coordination/balance, weakness, muscle impairment, sensory, mood/emotional functioning, fatigue/exhaustion/tiredness, and vision.
Hudgens et al. 2019 [4]	CEIs in people with RRMS (n=17) in the development of a fatigue-related symptoms and impacts PRO (US).	The most commonly reported fatigue-related symptoms were energy and weakness. Functional and emotional impacts of fatigue-related symptoms included difficulty walking, maintaining relationships, participating in social activities, performing general activities of daily living and difficulty with thought processes.
Al-Sharman et al. 2018 [5]	Focus group discussions with Jordanian PwMS (n=16; subtypes not reported).	Disease-related themes: physical decline, psychosocial withdrawal, and fear of the future. Physical symptoms reported included difficulty engaging in physical activities, inability to maintain balance and getting fatigued easily. Feelings of being unhappy, sad and withdrawn were reported, and concerns about the future in terms of disability, long-term consequences and financial status.
de Ceuninck van Capelle et al. 2016 [6]	Interviews relating to impact on family life for people with RRMS (n=10) diagnosed in the last 2 years (Netherlands).	Five clusters of experiences were reported: dwindling capacity for housekeeping and care; struggling to ask for or to accept help; countering awkward attitudes toward RRMS; suspecting family members of concealing feelings; watching family members wrestle with the effects of RRMS.
Harrison et al. 2015 [7]	Semi-structured telephone interviews to elicit accounts of	The five most frequently reported MS symptoms were fatigue, balance disruption, stiffness and spasms in muscles, cognitive impairment, and difficulties with speech. Many PwMS described

	pain in the UK (n=25; RRMS n=16, SPMS n=6, PPMS n=3).	pain as the worst symptom, and inherent to other symptoms such as optic neuritis, spasms, and sensory dysfunction. Interactions of pain, fatigue and sleep disruption were also highlighted. For many, pain had no discernable pattern and they felt pain would worsen over time. Frustration and anger were also linked to the unrelenting nature of the pain, and the fact that pain can prevent engagement in enjoyable activities.
Newland et al. 2012 [8]	Focus group to characterize symptoms in people with RRMS in the US (n=16).	Some symptoms were reported as occurring in isolation: heat intolerance, headache, foot drop, difficulty concentrating and twitching. Some symptoms were also identified as co-occurring including: fatigue and loss of cognition, heat intolerance and vision loss, heat intolerance and fatigue, feeling of heaviness and vision loss.
Coenen et al. 2011 [9]	Focus groups to identify ICF codes describing areas of functioning and disability important to PwMS in Germany (n=27; RRMS n=11, SPMS n=11, PPMS n=5).	Concepts were related to 106 second-level ICF categories: 35 <i>Body Functions</i> categories, 33 <i>Activities and Participation</i> categories, 38 <i>Environmental Factors</i> categories. ICF categories that were identified by all focus groups were emotional function, urinary function, walking, recreation and leisure, immediate family, health services, and systems and policies.
(B) Primarily symptom-related PROs		
Zhang et al. 2021 [10]	Symptoms with largest impact on HRQoL PROs AQoL-8D (n=1328; RRMS n=835, SPMS, n=183, PPMS n=123) and EQ-5D-5L (n=1985; RRMS=1242, SPMS n=272, PPMS n=188) were evaluated in PwMS in Australia.	Across all PwMS the five most severe symptoms were fatigue, balance problems, sensory symptoms, walking difficulties, bladder problems. There were slight differences in the 5 most severe symptoms between MS subtype. RRMS: fatigue, sensory symptoms, balance problems, cognitive problems, bladder problems. SPMS: walking difficulties, balance problems, bladder problems, fatigue, spasticity. PPMS: walking difficulties, balance problems, fatigue, bladder problems, sexual dysfunction.
Zhang et al. 2019 [11]	Survey on the differences in symptom severity between progressive-onset (n=231; PPMS and PRMS) and relapse-onset (n=1514; RRMS and SPMS) MS (total n=1985 including	The five most severe symptoms by MS onset type were: Progressive: walking difficulties, difficulty with balance, fatigue, bladder problems, sexual dysfunction. Relapsing: fatigue, sensory symptoms, difficulty with balance, bladder problems, walking difficulties.

233 PwMS who were unsure of their MS onset type) in Australia.

Barin et al. 2018 [12]	Influence of symptoms on QoL using surveys from PwMS included in the Swiss MS registry (n=855; RRMS n=611, PMS n=244).	The five most commonly reported symptoms by MS subtype were: RRMS: paresthesia, fatigue, weakness, balance problems, memory problems. PPMS: gait problems, balance problems, fatigue, paresthesia, spasticity.
Prakash et al. 2019 [13]	Survey using self-reported measures of depression, anxiety, emotional dysregulation and HRQoL in PwMS (n=100; RRMS n=91, SPMS n=4, PPMS n=5) compared with community controls (n=98) in the US.	PwMS reported higher levels of depressive symptoms, greater emotion dysregulation, and lower HRQoL compared with community controls, after controlling for education. Differences in symptoms of depression were explained by greater use of maladaptive strategies, such as worry and rumination, expressive suppression and thought avoidance, and greater perceived emotion dysregulation among PwMS.
Rommer et al. 2019 [14]	Frequency and treatment of symptoms in PwMS in the German MS registry (n=35,755; RRMS n=21,261, SPMS n=7803, PPMS n=2289, unclassified n=2681).	Across all PwMS, the five most frequently reported symptoms over the course of the disease were fatigue, spasticity, voiding disorders, ataxia/tremor, and pain. There were slight differences in the most commonly reported symptoms per MS subtype: RRMS: fatigue, depression, voiding disorder, spasticity, pain. SPMS: spasticity, voiding disorder, fatigue, ataxia/tremor, pain. PPMS: spasticity, voiding disorder, fatigue, ataxia/tremor, pain.
Bethoux et al. 2016 [15]	Cross-sectional survey of PwMS in the NARCOMS registry (US; n=10,200; MS subtypes not reported) on the impact of spasticity.	Over 80% reported spasticity. There was greater difficulty with lower extremity symptoms versus upper extremity symptoms, with over 35% moderately or greatly bothered by stiffness, spasms, or pain. Spasticity was most frequently reported as moderately or greatly interfering with stair climbing, walking and sleep.
Chua et al. 2105 [16]	Retrospective analysis of a standard battery of PRO measures from the CLIMB study (n=537; RRMS 79.8%, SPMS 10.5%, PPMS 4.3%, PRMS 0.2%, CIS 5.2%) to develop a brief PRO measure of overall functioning in MS (US).	Eight factors explained 78% of the variance across the PROs and may represent overall function in mildly disabled PwMS: mental fatigue, physical activity, emotional functioning, social support, sexual functioning, health perceptions, health concerns, and tiredness.
Newland et al. 2016 [17]	Survey to assess symptom severity and co-morbidities of MS in the US (n=339; RRMS	The most severe symptoms reported were fatigue, imbalance, weakness, and disturbed sleep. Higher symptom severity was

	n=221, SPMS n=50, PPMS n=29, PRMS n=25).	associated with comorbidities such as depression, arthritis, and migraine headaches.
Ng et al. 2012 [18]	Survey to compare patient-reported disability across motor neuron disease, Guillain-Barré syndrome and MS using the ICF classification in an Australian cohort (PwMS n=101; MS subtypes not reported).	A total of 63 ICF categories were identified in MS. ICF codes where at least 98% of PwMS experienced limitations included: body function – gait pattern functions; body structure – brain; activities and participation – handling stress and other psychological demands, walking, using transportation, moving around, driving; environmental factors – for personal consumption (food, medicines), climate.
(C) Primarily impact-related PROs		
Campos-Lucas et al. 2022 [19]	E-survey (2007: n=370, RRMS 56.7%; 2018: n=490, RRMS 77.1%) on the impact of living with MS (Spain).	In 2018, QoL was dependent on healthcare and current medications. Approximately one third of PwMS (33%) had stopped working due to MS symptoms; 53% of PwMS stated MS has little or no effect on work performance; 58% of PwMS stated they had suffered little or no financial difficulties as a result of MS diagnosis.
Maurino et al. 2020 [20]	Non-interventional, cross-sectional study (n=199; RRMS n=172, PPMS n=27) to assess the relationship between work difficulties, perceptions of MS-specific physical and psychological impact on HRQoL, levels of depressive symptoms, and perceptions of stigmatization in Spain.	Although 70.4% of PwMSs were employed at diagnosis, only 47.2% were still employed at the study visit. The mean (SD) retirement age was 43.6 (10.5) years. Positive correlations were observed between EDSS and MSIS-29 physical impact (large correlation), and between EDSS and MSIS-29 psychological impact (moderate correlation). Stigma was reported as often or always present by 20% of PwMS, and 41% were classified as being depressed.
Purmonen et al. 2020 [21]	Retrospective, cross-sectional mail survey relating to MS disease burden in Finland (n=498; RRMS n=244, SPMS n=160, PPMS n=94).	In total, 58% of participants had retired early. The mean time from first symptom to retirement was approximately 13 years. Fatigue was present in all MS subtypes and across all levels of disease severity. The total mean annual costs per person with RRMS, SPMS and PPMS were €36,492, €71,177 and €51,082, respectively.
Carter et al. 2021 [22]	Multi-center, cross-sectional study in the UK to assess a PRO measure across multiple neurological diseases (PwMS n=89).	A rating of 'fair' (on a scale of 'poor', 'fair', 'good', 'very good' or 'excellent') by PwMS was the most frequent rating for general health, physical health, mental health, QoL, social life and social activities. Over one quarter (27%) of PwMS reported not being able to carry out physical activities at all, 34% reported having emotional problems often or all of the time, and 87% had moderate to very

		severe levels of fatigue (very severe 5%, severe 34%, moderate 48%, mild 14%, none 0%).
Nickerson et al. 2015 [23]	Survey to assess the patient-perceived impact of an MS relapse, sent to eligible members of the NARCOMS registry (n=481; RRMS n=344, SSMS/PPMS/PRMS n=137).	The five most frequently reported symptoms associated with a relapse were related to fatigue, leg/foot weakness, numbness/tingling, walking, hand/arm weakness. Of the 163 respondents working or going to school, 55% reported missing work or school due to relapses, and 68% reported that the relapse impacted their ability to manage childcare or household tasks.
Karhula et al. 2013 [24]	Semi-structured interviews to identify the self-perceived problems in everyday activities and participation (linked to ICF categories) of PwMS in Finland (n=113; RRMS n=45, SPMS n=37, PPMS n=28, unknown n=3).	The first-level ICF categories with the highest frequency of most important problems were: community, social and civic life; mobility; and domestic life. The five second-level ICF categories with the highest frequency of most important problems were: recreation and leisure; moving around in different locations; doing housework; washing oneself; and caring for household objects.
van der Hiele et al. 2012 [25]	Set of questionnaires completed by Dutch PwMS (n=715; RRMS n=251, SPMS n=123, PPMS n=63, subtype unclear n=200) to assess the frequency, associated distress and type of daily hassles encountered during the past two months.	The Everyday Problem Checklist was used to measure the presence and distress caused by daily hassles. More than 50% of PwMS experienced a high frequency and total intensity of daily hassles. Males experienced person-dependent hassles more frequently and intensively than person-independent hassles. For females, person-dependent and person-independent hassles were experienced with equal frequency and intensity. Daily hassles noted by more than 50% of PwMS included 'your sleep was disturbed' (person-independent hassle), 'something brought back unpleasant memories' (person-dependent hassle) and 'you were asked to complete questionnaires' (person-independent hassle).
Oleen-Burkey et al. 2012 [26]	Online cross-sectional survey to characterize the impact of a MS relapse for people with RRMS in the US (n=711).	Employed respondents who experienced ≥ 1 relapse in the last 12 months missed more work during the last year (15 versus 5 days) and were more impaired at work (23% versus 14% of work time with reduced productivity) than employed respondents who were clinically stable. Relapses had a significantly negative effect on daily and leisure activities. Respondents who experienced ≥ 1 relapse in the last year reported impairment of about 45% in regular daily activities and 42% in leisure activities, while PwMS who were clinically stable

over the 12 months reported about a 30% impairment in regular daily activities and 27% impairment in leisure activities.

LaRocca et al. 2011 [27]	Online survey to assess the impacts of walking difficulties in PwMS (n= 1011; RRMS n=695, SPMS n=176, PPMS n=58, PRMS n=27, 'other'/'not sure' n=53) in the US.	The most commonly experienced MS symptoms experienced at least twice a week were fatigue, abnormal sensations and losing balance. Negative impacts in the last 6 months experienced by most PwMS included the ability to perform household chores, shopping, participating in sports, physical activities or exercise. Most PwMS experienced impacts on everyday activities in the last 6 months including maintaining balance, running, walking long-distances, climbing up and down stairs, sleeping and standing.
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AQoL-8D Assessment of Quality of Life with Eight Dimensions. *CEI* concept elicitation interview, *CIS* clinically isolated syndrome, *CRoMS* Clinician Rating of Multiple Sclerosis, *EDSS* Expanded Disability Status Score, *EQ-5D-5L* European Quality of Life with Five Dimensions and Five Levels for Each Dimension, *HAQUAMS* Hamburg Quality of Life Questionnaire in Multiple Sclerosis, *HRQoL* health-related quality of life, *ICF* International Classification of Functioning, Disability and Health, *MS* multiple sclerosis, *MSIS* Multiple Sclerosis Impact Scale, *NARCOMS* North American Research Committee on Multiple Sclerosis, *PMS* progressive multiple sclerosis, *PPMS* primary–progressive multiple sclerosis, *PRMS* primary relapsing multiple sclerosis, *PRO* patient-reported outcome, *PwMS* people with multiple sclerosis, *QoL* quality of life, *SPMS* secondary progressive multiple sclerosis, *US* United States

2 Interview guide

Supplementary Table S2 Excerpt of semi-structured interview guide

Primary topic	Questions/probes
Symptoms experienced	• What symptoms of MS do you experience currently? • What symptoms of MS have you experienced in the past but no longer experience? • What symptoms do you experience only during a flare or relapse? • Can you tell me more about your [<i>each symptom reported</i>]? • Where do you experience or feel [<i>symptom with potentially variable location e.g., pain</i>]? • Which of your MS symptoms would be most important to treat? • Of all of the MS symptoms we have discussed, which symptom bothers (or affects) you the most? How about the next/second most bothersome? Third most bothersome? [<i>Probe why each symptom is bothersome</i>].
Impacts of MS	• How does having MS affect you? • Are there things that you still do, but they are more difficult for you because of your MS? Can you tell me about that? • Are there things that you would like to do but don't attempt because of your MS? Are there things that you cannot do? What are they? • Are there things that you normally can do but can't when you are experiencing an MS flare or relapse? • What is the most important impact or effect of MS for you?

MS multiple sclerosis

3 Extended tables of physical function- and fatigue-related concepts

Supplementary Table S3 Specific physical function-related concepts

Physical function concepts and examples from PwMS	Supportive quotations
Difficulty walking	<i>My walking got hard to walk from, like, A to B. I would, like, look out my window and think, 'How am I going to walk to my mailbox?' (CEI-01-Mild)</i>
1) Cannot walk very far; hard to walk to the mailbox and back. 2) Has fallen. 3) Stumbles frequently. 4) Must concentrate on walking; no high heels. 5) Must watch the ground closely while walking. 6) Has difficulty moving around. 7) Must have a cart to hold on to in the grocery store or have a person to hold on to. 8) Cannot walk without assistance.	<i>I just can't do much of it. Legs feel like they're going to fall off. (CEI-03-Mild)</i> <i>I can't wear high heels. (CEI-01-Mild)</i> <i>I can't walk, like, we go on vacation, anything longer than maybe two blocks. (CEI-01-Mild)</i> <i>I do sometimes stumble. I lose, if I'm walking, I might lose... the knee might go out or something. My leg feels like it's going, and I'll stumble. (CEI-06-Mod)</i> <i>I was walking kind of at an angle. Always needed to support, so I would walk to the right. It was always to a wall. (CEI-07-Sev)</i> <i>So I've fallen twice. (CEI-08-Mod)</i> <i>And I'm noticing more in the last 6 months that I stumble around more. (CEI-09-Mild)</i>
Balance problems/ instability	<i>Which gets me to balance, coordination. That's what I experience. (CEI-01-Mild)</i>
1) Balance off, not stable, "wobbly". 2) Needs to touch walls when walking down a hall. 3) Balance while standing or sitting is poor. 4) Poor balance and coordination; cannot carry anything while walking. 5) Cannot look to the side while walking.	<i>And if I'm walking on an unstable surface, like sometimes I'll grab my husband just to make sure. (CEI-02-Mild/Mod)</i> <i>Yeah. I was a little wobbly when you had to go down one foot. (CEI-03-Mild)</i> <i>Carrying a laundry basket upstairs is not an easy task. (CEI-03-Mild)</i> <i>I really usually can't work both legs. I just walk kind of to the side. But yeah, here and there, I'll have the balance issue. (CEI-04-Mild)</i> <i>I cannot walk straight, period. I'm tripping over my own feet literally. (CEI-04-Mild)</i>
Daily/household activities	<i>Probably a lot of the cleaning at home. Like, it's just because I'm getting too warm. My husband keeps up with all that. (CEI-02-Mild/Mod)</i>
1) Cannot mow the grass. 2) Cannot garden. 3) Has difficulty cooking because of dropping things. 4) Cannot do any cooking or cleaning. 5) Difficulty with housekeeping. 6) Cannot drive.	<i>My husband usually does most of the [household chores]. I don't know. I just don't, just because I can't see to do things as well as I used to. I definitely limit a lot of what I do. (CEI-02-Mild/Mod)</i> <i>Household chores are, well, the chores are like back shelf kind of thing. Like I don't remember the last time I dusted. (CEI-05-Mild/Mod)</i>

I used to wash the walls. I used to get on the floor and wash tile, make sure the grout was spotless and it doesn't happen anymore. It gets a quick runover with the, you know, it doesn't get that thorough cleaning. (CEI-05-Mild/Mod)

So, I don't wash dishes. I mean, you know, I live alone, so I don't wash dishes every day. I decided to focus my energy. I'm not trying to do everything at once. (CEI-08-Mod)

So, before I would clean all of my bathrooms the same day, and now it's like, okay, downstairs today. (CEI-08-Mod)

I used to take care of the flowers outside, you know, pulling weeds and stuff like that. (CEI-02-Mild/Mod)

I started getting, like, a double vision and it just kept getting more and more severe to the point where I couldn't drive. (CEI-02-Mild/Mod)

Leisure activities (hobbies, vacations)	<i>Yeah. I don't know. It just feels extra warm in stores to me now. So that sometimes affects it. (CEI-02-Mild/Mod)</i>
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1) Cannot take trips with friends, travel/sightsee. 2) Cannot camp. 3) Cannot bowl. 4) Cannot shop. 5) Cannot do arts and crafts. 6) Cannot paint or sculpt.	<i>I can't really go bowling. (CEI-01-Mild)</i> <i>I'm an amateur artist. I love to draw. I love to paint. I love to sculpt. And I feel like I don't even do that anymore because I can't get my hands to do it. (CEI-05-Mild/Mod)</i> <i>Just I guess not having the stamina to get some stuff done and to go on some of the trips, you know. (CEI-10-Mod)</i> <i>I used to do a lot more hiking and I used to do a lot of camping and stuff. (CEI-10-Mod)</i>
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Supplementary Table S4 Specific fatigue-related concepts

Fatigue concepts and examples from PwMS	Supportive quotations
Mental fatigue/cognitive dysfunction	<i>I have no desire to, it is so hard for me to, like, focus or care. (CEI-04-Mild)</i>
1) Mentally tired. 2) Unable to concentrate. 3) Unable to focus. 4) Difficulty learning new concepts.	<i>Yeah. I feel like my mind just goes blank. I've noticed it, like, down to even doing my bills for the month. (CEI-04-Mild)</i>
	<i>Almost like trying to solve a complicated math problem when you have a migraine, you know? You just can't do it. (CEI-05-Mild/Mod)</i>
	<i>I would call it cognitive issues where I feel like it takes me a long time to grasp a new concept and hang onto it. (CEI-05-Mild/Mod)</i>
Feeling of weakness or heaviness in extremities and body	<i>And then sometimes when I'm fatigued, and my body just feels really heavy, like it's hard to move. (CEI-11-Mod)</i>
1) Muscle weakness. 2) Heaviness in arms, hands, legs.	<i>And my legs get real tired. They feel like there is a wet blanket tied around them. They feel really heavy. (CEI-01-Mild)</i>
	<i>Just feeling weak and tired and not being able to... tired as far as hands feeling heavy. I mean my arms or your legs or stuff like that. (CEI-01-Mild)</i>
	<i>Just my legs are sometimes, they feel very heavy where I have to lift them up in the car. I can't physically lift it in, that kind of thing. (CEI-06-Mod)</i>

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