The Canadian Journal of Neurological Sciences (2025), 1–9
doi:10.1017/cjn.2025.48

Canadian Journal of Neurological Sciences
Journal Canadien des Sciences Neurologiques

Original Article

An Overview of Multiple Sclerosis Care in Rural and Urban Newfoundland and Labrador

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ABSTRACT: ***Introduction:*** Limited access to multiple sclerosis (MS)-focused care in rural areas can decrease the quality of life in individuals living with MS while influencing both physical and mental health. ***Methods:*** The objectives of this research were to compare demographic and clinical outcomes in participants with MS who reside within urban, semi-urban and rural settings within Newfoundland and Labrador. All participants were assessed by an MS neurologist, and data collection included participants' clinical history, date of diagnosis, disease-modifying therapy (DMT) use, measures of disability, fatigue, pain, heat sensitivity, depression, anxiety and disease activity. ***Results:*** Overall, no demographic differences were observed between rural and urban areas. Furthermore, the categorization of primary residence did not demonstrate any differences in physical disability or indicators of disease activity. A significantly higher percentage of participants were prescribed platform or high-efficacy DMTs in semi-urban areas; a higher percentage of participants in urban and rural areas were prescribed moderate-efficacy DMTs. Compared to depression, anxiety was more prevalent within the entire cohort. Comparable levels of anxiety were measured across all areas, yet individuals in rural settings experienced greater levels of depression. Individuals living with MS in either an urban or rural setting demonstrated clinical similarities, which were relatively equally managed by DMTs. ***Conclusion:*** Despite greater levels of depression in rural areas, the results of this study highlight that an overall comparable level and continuity of care is provided to individuals living with MS within rural and urban Newfoundland and Labrador.

RÉSUMÉ : Vue d'ensemble des soins pour la sclérose en plaques dans les zones rurales et urbaines de Terre-Neuve-et-Labrador. ***Introduction :*** L'accès limité aux soins destinés aux patients atteints de sclérose en plaques (SP) dans les zones rurales peut diminuer leur qualité de vie tout en influençant leur santé physique et mentale. ***Méthodes :*** Les objectifs de cette étude étaient de comparer entre eux les aspects démographiques et les résultats cliniques des personnes atteintes de SP résidant en milieu urbain, semi-urbain et rural dans la province de Terre-Neuve-et-Labrador. Tous les participants ont été évalués par un neurologue spécialiste de la SP. Les données recueillies comprenaient les antécédents cliniques des participants, la date du diagnostic, l'utilisation de traitements modificateurs de la maladie (TMM), des mesures de l'invalidité, de la fatigue, de la douleur, de la sensibilité à la chaleur, de la dépression et de l'anxiété, ainsi que des phases de la maladie. ***Résultats :*** Dans l'ensemble, aucune différence démographique n'a été observée entre les zones rurales et urbaines. En outre, la catégorisation de la résidence principale n'a révélé aucune différence en termes d'invalidité physique ou d'indicateurs des phases de la maladie. Un pourcentage significativement plus élevé de participants s'est vu prescrire des TMM à long terme dont l'efficacité est modérée (*platform DMTs*) ou des TMM à haute efficacité dans les zones semi-urbaines ; de plus, un pourcentage plus élevé de participants dans les zones urbaines et rurales s'est vu prescrire des TMM à efficacité modérée. Comparée à la dépression, l'anxiété était plus répandue dans l'ensemble de la cohorte. Des niveaux comparables d'anxiété ont été mesurés dans toutes les régions, mais les personnes vivant en milieu rural ont connu des niveaux de dépression plus élevés. En outre, les personnes atteintes de SP vivant en milieu urbain ou rural présentaient des similitudes cliniques, lesquelles ont été prises en charge de manière relativement égale par les TMM. ***Conclusion :*** Malgré des niveaux de dépression plus élevés dans les zones rurales, les résultats de cette étude montrent que les personnes atteintes de SP bénéficient d'un niveau et d'une continuité de soins globalement comparables dans les zones rurales et urbaines de Terre-Neuve-et-Labrador.

Keywords: depression; disease-modifying therapy; multiple sclerosis; patient and public involvement; quality of life; rural

(Received 17 December 2024; final revisions submitted 4 February 2025; date of acceptance 2 March 2025)

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Cite this article: Fifield KE, Fudge NJ, Arsenault ST, Anthony S, McGrath L, Snow NJ, Clift F, Stefanelli M, Ploughman M, and Moore CS. An Overview of Multiple Sclerosis Care in Rural and Urban Newfoundland and Labrador. *The Canadian Journal of Neurological Sciences*, https://doi.org/10.1017/cjn.2025.48

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Highlights

- Despite no overall demographic differences in MS patients living in a rural *vs*. urban setting, disease-modifying therapy (DMT) was varied.
- Compared to their urban counterparts, individuals with MS residing in rural Newfoundland and Labrador had greater levels of depression.
- Despite challenges associated with living outside an urban center, an overall comparable level and continuity of care is provided to individuals living with MS within rural and urban Newfoundland and Labrador.

Introduction

Multiple sclerosis (MS) is a chronic neurological disease characterized by attacks of central nervous system inflammation, demyelination and neuronal injury that can lead to neurodegeneration and result in physical and cognitive disability.[1] The extent of physical and/or cognitive disability in MS has been associated with traditional disease clinical subtypes, differing between individuals with relapsing-remitting MS (RRMS) and progressive MS, with the latter being more commonly associated with disability. Several factors have been previously suggested to mitigate long-term disability accumulation, including the early use of high-efficacy disease-modifying therapies (DMTs),[2,3] physical activity,[4] lifestyle modifications,[5] effective management of medical comorbidities[6] and access to adequate health care.[7–9] Specifically, access to a skilled MS neurologist and trained nursing staff at a specialized center can improve long-term outcomes.[10,11]

Limited access to MS-focused care in rural areas may represent a contributing factor in the progression of MS.[7–9] In a previous study of 1500 individuals with MS within the USA, physical and mental dimensions of health-related quality of life (HRQoL), including walking ability and independence in everyday activities, were surveyed within metropolitan and rural areas.[10] Patients living in rural areas reported reduced physical dimensions on the HRQoL construct. A similar study examined the unmet healthcare needs of 632 patients with MS in an urban area versus two rural counties in Ireland using the Needs Assessment Questionnaire to assess patients' access to physiotherapy, adequate physician care and social supports.[12] Unmet needs were associated with higher Expanded Disability Status Scale (EDSS) scores, the type of MS, duration of MS and living in a rural area. Interestingly, patients with progressive MS were reported to have unmet needs that were 3.2 times greater than people having RRMS.[12]

A multidisciplinary approach that includes access to a neurologist can improve patient-centered MS care.[13] In a study that investigated patient use of MS clinics, of 2841 persons diagnosed with MS in a province-wide health database (British Columbia, Canada), only 58% of patients registered with an MS clinic.[9] Interestingly, patients who did not use MS clinics had more comorbidities, and a mere 1% of these patients used DMTs specific for MS. In addition, Minden and colleagues examined access to a neurologist for 2156 persons diagnosed with MS, whereby approximately 72% reported that a neurologist was their primary care physician; patients without access to a neurologist were more likely to have a lower socioeconomic status and reside in a rural community while also lacking health insurance coverage, DMT use and outpatient physical rehabilitation.[7]

Several studies have previously reported that patients with MS experience increased depression and anxiety due to the clinical correlates of the disease and declines in physical health.[6,14,15] In a study conducted by Hoang *et al.,* an increased prevalence of both anxiety and depression and the use of anxiolytics/antidepressants were observed in patients with MS compared to the general population.[16] Interestingly, this was observed both prior and following a formal diagnosis of MS with the increased use of antidepressants occurring one year following diagnosis. Unfortunately, despite the elevated rates of anxiety and depression, mental health services are also often limited in rural areas,[17] with patients often being less satisfied with their access to mental health services compared to their urban counterparts.[18] Information observed from large databases suggests that feelings of anxiety and depression are either not associated with living in a rural or urban area[19,20] or are slightly higher in rural areas;[21] however, this has not been previously investigated in MS.

Health disparities have been previously identified in rural areas compared to urban centers.[22,23] In a recent study comparing DMT use between individuals living with MS in rural versus urban areas in Alberta, Canada, the authors reported that individuals residing in rural areas were less likely to have received a DMT (particularly an induction/higher-efficacy therapy), which could be explained by lower socioeconomic status and geography.[24] Specifically in Newfoundland and Labrador (NL), individuals living in rural areas have been reported to have increased risk factors associated with cardiovascular disease and poor clinical outcomes related to inadequate management of diabetes,[25,26] and it has been suggested to be related to the lack of regular access to a primary care physician.[27] In this research, our aim was to evaluate and compare demographic and clinical data of patients with MS living in urban, semi-urban and rural locations within NL. Importantly, all participants enrolled in this study had access to a neurologist within an urban center, which permits an investigation into the experience of living with MS in a rural versus urban setting, rather than access to MS-focused care.

Methods

Study participants

Study participants were enrolled in the Health Research Innovation Team in Multiple Sclerosis (HITMS) study during their routine clinical visits with an MS neurologist in St John's, NL, Canada, between February 2016 and March 2024. HITMS is a longitudinal patient registry and biorepository aimed to longitudinally assess various clinical and biological measures of participants with MS. The study was approved by the provincial and institutional health research ethics board (HREB #2015.103). All patient information was de-identified, and clinical and demographic data of interest were extracted from patients' MS clinic records. In addition to clinical and demographic data, participants completed self-reported questionnaires to rate their feelings of anxiety and depression (Hospital Anxiety and Depression Scale [HADS]), physical and psychological impact (Multiple Sclerosis Impact Scale-29 [MSIS-29]) and fatigue, pain and heat sensitivity (100 mm Visual Analogue Scale [VAS]).

Defining rural, semi-urban and urban populations

Participants were grouped into three categories (urban, semi-urban and rural) based on their primary residence and previously defined criteria.[27] Urban was defined as municipalities with a population greater than 100,000 residents with a major hospital and MS-focused care. Semi-urban was defined as an area with a population of 10,000–99,999 residents and with a hospital. Rural

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Table 1. Demographic and clinical characteristics of participants with MS

	RRMS (*n* = 264)	SPMS (*n* = 22)	PPMS (*n* = 12)
Age (years ± SD)	43.8 ± 10.5	52.3 ± 8.0	56.3 ± 10.5
Male (n (%))	68 (25.8%)	5 (22.7%)	6 (50%)
Female (n (%))	196 (74.2%)	17 (77.3%)	6 (50%)
BMI (kg/m^2)	29.1 ± 7.3	26.9 ± 6.5	27.1 ± 6.3
EDSS (median score, range)	2.0 (0.0–7.0)	6.0 (2.0–7.5)	6.0 (2.0–8.0)
MS duration (mean years ± SD)	14.8 ± 8.4	22.2 ± 8.8	11.8 ± 7.1
DMT			
None	60 (22.7%)	12 (54.5%)	9 (75.0%)
Platform	62 (23.5%)	4 (18.2%)	1 (8.3%)
Moderate efficacy	117 (44.3%)	5 (22.7%)	1 (8.3%)
High efficacy	25 (9.5%)	1 (4.5%)	1 (8.3%)

RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; PPMS = primary progressive multiple sclerosis; BMI = body mass index; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; DMT = disease-modifying therapy.

was defined as an area with a population less than 10,000 residents and greater than 100 km from a major hospital with MS-focused care. This definition aligns with the definition put forward by the US Office of Management and Budget.

Statistical analysis

Data were analyzed using GraphPad Prism 5.0 software (GraphPad Software Inc., La Jolla, CA) and SPSS v.29 software (IBM SPSS Statistics, Illinois, CH). Statistical significance was determined at $p < 0.05$. D'Agostino and Pearson omnibus normality test was used to assess data for normal distribution. For normally distributed data, parametric Student's t-tests or one-way ANOVA were performed to compare groups. Normally distributed data were expressed as mean ± standard deviation (SD). For non-normalized data, nonparametric Mann–Whitney U tests or Kruskal–Wallis tests were performed to compare groups. Non-normal data were expressed as median with interquartile range (IQR). Pearson chi-square tests were performed to assess categorical data across groups. To explore associations between variables, parametric Pearson correlation and nonparametric Spearman correlations, with a line of best fit, were performed on normal and non-normal data, respectively.

Results

Demographic and clinical characteristics of participants with MS

Demographic and clinical characteristics are summarized in Table 1. A total of 298 individuals diagnosed with MS were recruited and included in the analyses. The majority of recruited individual participants were diagnosed with RRMS ($n = 264$, 88.6%), with fewer patients diagnosed with primary progressive MS (PPMS) ($n = 12$, 4.0%) or secondary progressive MS (SPMS) ($n = 22$,7.4%). Data for SPMS and PPMS were combined as progressive MS (PMS) for the analysis. Individuals diagnosed with RRMS were significantly younger (43.8 years) compared to PMS (54.2 years) ($t(294) = 5.38, p < 0.0001$). In keeping with the known demographic profile of MS, 73.5% of participants were female, and 26.5% were male; no significant differences were observed between the types of MS ($X^2(2, N = 298) = 3.6, p = 0.16$). Furthermore, no significant differences in body mass index (BMI) were observed between RRMS and PMS. As expected, the median EDSS for RRMS was 2.0 (IQR = 2.5), while a median EDSS score of 6.0 (IQR = 0.5) was recorded in both SPMS and PPMS; participants with PMS had a significantly higher EDSS compared to RRMS ($U = 396.5, p < 0.0001$). Patients diagnosed with PMS also had a longer disease duration compared to RRMS ($U = 3485, p = 0.04$). The percentage of participants on a DMT differed between the types of MS ($X^2(2, N = 298) = 24.83, p < 0.0001$); 22.7% of participants with RRMS were not taking a DMT, which contrasted with SPMS and PPMS where 54.5% and 75.0% were not on a DMT, respectively. DMTs were categorized as platform, moderate efficacy or high efficacy based on the known mechanism of action. Platform DMTs include interferon-beta (IFN-beta) and glatiramer acetate; moderate-efficacy DMTs include teriflunomide, dimethyl fumarate and fingolimod; and high-efficacy DMTs include natalizumab, ocrelizumab, ofatumumab, alemtuzumab and cladribine.

Table 2. Demographic and clinical characteristics of participants with MS living in urban, semi-urban and rural areas

Urban (*n* = 186)	RRMS *n* = 168	SPMS *n* = 13	PPMS *n* = 5
Age (years ± SD)	43.7 ± 10.7	53.1 ± 4.7	62.0 ± 6.3
Male	45 (27%)	3 (23%)	1 (20%)
Female	123 (73%)	10 (74%)	4 (80%)
BMI (kg/m^2)	28.6 ± 7.1	27.5 ± 5.7	28.3 ± 9.5
EDSS (median score, range)	2.0 (0.0–7.0)	6.0 (2.0–7.5)	6.0 (6.0–6.5)
MS duration (mean years ± SD)	14.4 ± 8.3	24.8 ± 8.2	12.4 ± 4.9
Semi-urban (*n* = 48)	*n* = 43	*n* = 4	*n* = 1
Age (years ± SD)	43.3 ± 10.3	47.5 ± 6.4	72
Male	7 (16%)	1 (25%)	0 (0%)
Female	36 (84%)	3 (75%)	1 (100%)
BMI (kg/m^2)	29.3 ± 7.8	28.4 ± 7.9	33.9
EDSS (median score, range)	2.0 (0.0–5.5)	6.0 (5.5–6.5)	6.5 (6.5–6.5)
MS duration (mean years ± SD)	15.5 ± 9.3	12.3 ± 7.4	4.0
Rural (*n* = 64)	*n* = 53	*n* = 5	*n* = 6
Age (years ± SD)	44.6 ± 10.2	54.0 ± 14.5	48.8 ± 7.9
Male	16 (30%)	1 (20%)	5 (83%)
Female	37 (70%)	4 (80%)	1 (17%)
BMI (kg/m^2)	30.5 ± 7.6	24.1 ± 7.7	25.1 ± 3.1
EDSS (median score, range)	2.0 (0.0–6.0)	6.0 (3.0–7.0)	6.0 (2.0–8.0)
MS duration (mean years ± SD)	15.8 ± 7.9	23.6 ± 6.4	12.5 ± 8.9

RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; PPMS = primary progressive multiple sclerosis; BMI = body mass index; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis.

Clinical characteristics of participants with MS living in urban, semi-urban and rural areas

In terms of regional living delineation, 186 participants were categorized as living in an urban area, 48 were categorized as

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Table 3. DMTs for participants with MS living in urban, semi-urban and rural areas

		None	Platform*	Moderate efficacy**	High efficacy***
Urban	RRMS	39 (23.2%)	38 (22.6%)	77 (45.8%)	14 (8.3%)
	SPMS	9 (69.2%)	1 (7.7%)	3 (23.1%)	0 (0%)
	PPMS	5 (100%)	0 (0%)	0 (0%)	0 (0%)
Semi-urban	RRMS	11 (25.6%)	14 (32.6%)	9 (20.9%)	9 (20.9%)
	SPMS	0 (0%)	2 (50%)	2 (50%)	0 (0%)
	PPMS	1 (100%)	0 (0%)	0 (0%)	0 (0%)
Rural	RRMS	10 (18.9%)	10 (18.9%)	31 (58.5%)	2 (3.8%)
	SPMS	3 (60%)	1 (20%)	0 (0%)	1 (20%)
	PPMS	3 (50%)	1 (16.7%)	1 (16.7%)	1 (16.7%)

*Platform DMTs include interferon-beta and glatiramer acetate. **Moderate-efficacy DMTs include teriflunomide, dimethyl fumarate and fingolimod. ***High-efficacy DMTs include natalizumab, ocrelizumab, ofatumumab, alemtuzumab and cladribine. Values for DMT expressed as a number with percentages. RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; PPMS = primary progressive multiple sclerosis.

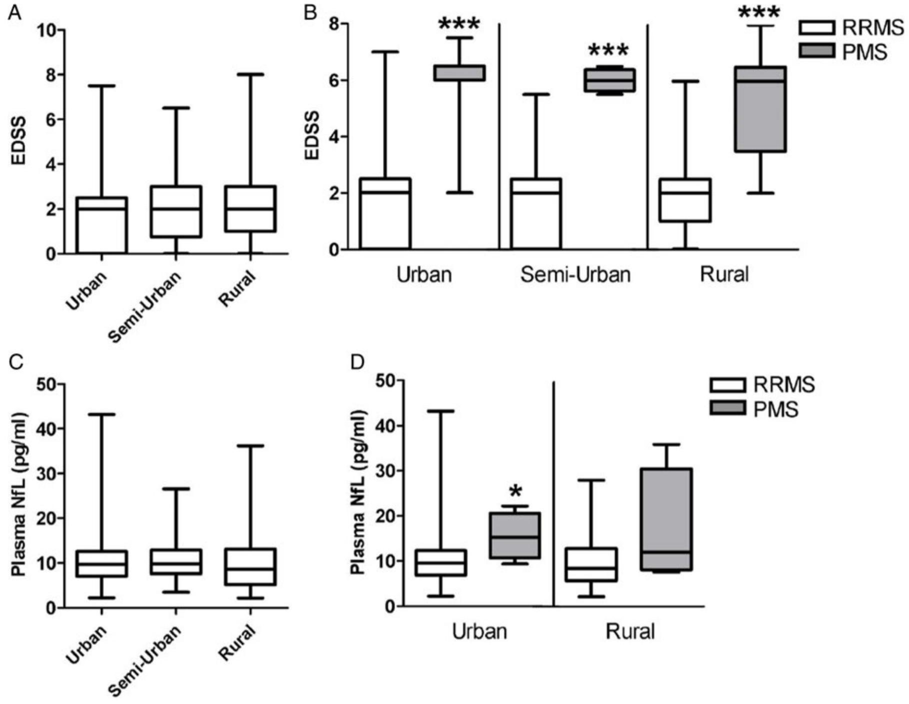

Figure 1. Clinical disability scores and biomarkers among MS patients living in urban, semi-urban and rural areas. (A) EDSS for MS patients within urban, semi-urban and rural areas. (B) EDSS for RRMS and PMS patients in the three areas. (C) Plasma NfL biomarker for MS patients within urban, semi-urban and rural areas. (D) Plasma NfL for RRMS and PMS patients within urban and rural areas. Data are expressed as whisker box plot with median and minimum to maximum values. *p<0.05, ***p<0.001. EDSS: Expanded Disability Status Scale. MS: Multiple Sclerosis. NfL: Neurofilament light chain. PMS: Progressive MS. RRMS: Relapse Remitting Multiple Sclerosis.

living in a semi-urban area and 64 were categorized as living in a rural area (Table 2). No differences in age, sex, disease duration or BMI were observed between regions. The majority of participants were diagnosed with RRMS within urban (90.3%), semi-urban (89.6%) and rural (82.8%) areas, with no significant differences observed across regions ($X^2(4,\ N = 298) = 6.247$, $p = 0.1814$).

We next assessed disability by comparing the neurologist-scored EDSS between participants with MS within urban, semi-urban and rural areas. No significant differences were observed between the areas Figure 1A). As was the case with the entire cohort, EDSS was significantly greater in patients with PMS versus RRMS, regardless of region (urban: [$U = 119.5$, $p < 0.001$]; semi-urban: [$U = 0.5$, $p < 0.001$]; rural: [$U = 40.5$, $p < 0.001$]) (Figure 1B).

Plasma neurofilament light (NfL) levels, a suggested biomarker of axonal injury and disease activity, were also measured in all participants;[28] a positive correlation between EDSS and NfL levels was observed ($r(155) = 0.1653$, $p = 0.0385$) (not shown). We then assessed plasma NfL levels in participants living between areas, and no differences were observed (Figure 1C). In participants designated as living in urban areas, a significantly increased plasma NfL was observed in PMS compared to RRMS ($U = 71.0$, $p < 0.05$; Figure 1D); no differences were observed in rural areas. Semi-urban was excluded from this analysis as there was only a single patient with PMS with a reported NfL level.

We next assessed DMT use in the subtypes of MS across different areas (Table 3). Overall, the percentage of participants with RRMS not taking a DMT was similar across locations (urban: $n = 39$, 23.2%; semi-urban: $n = 11$, 25.6%; rural: $n = 10$, 18.9%); however, a significant difference between DMT type and location was observed, with a higher percentage of participants prescribed a platform DMT in semi-urban areas compared to

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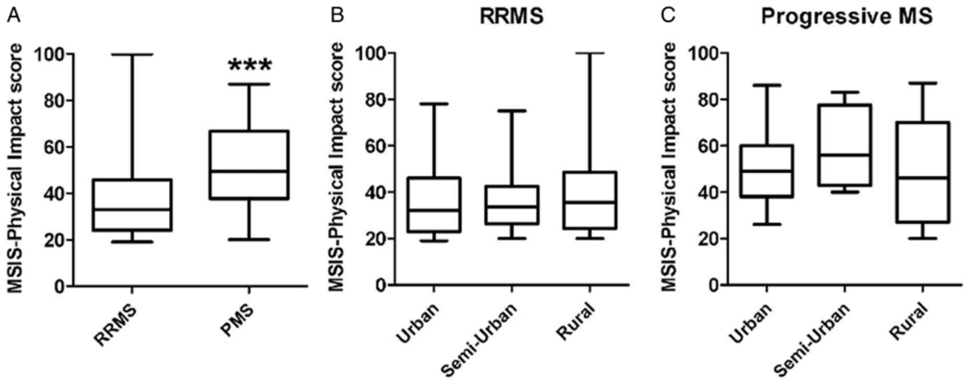

Figure 2. Physical and psychological impact of MS on patients within urban, semi-urban and rural areas. A: MSIS-29 Physical impact score for patients with RRMS or progressive MS. B: Physical impact scores for patients with RRMS within urban, semi-urban and rural areas. C: Physical impact scores for progressive MS (SPMS and PPMS) within the three locations. D: MSIS-29 Psychological impact score for patients with RRMS or progressive MS. E: Psychological impact score for RRMS within three locations. F: Psychological impact for progressive MS within three locations. Data are expressed as whisker box plot with median and minimum to maximum values. ***$p<0.001$. MS: Multiple Sclerosis. MSIS: Multiple Sclerosis Impact Scale. PMS: Progressive Multiple Sclerosis. RRMS: Relapse Remitting Multiple Sclerosis.

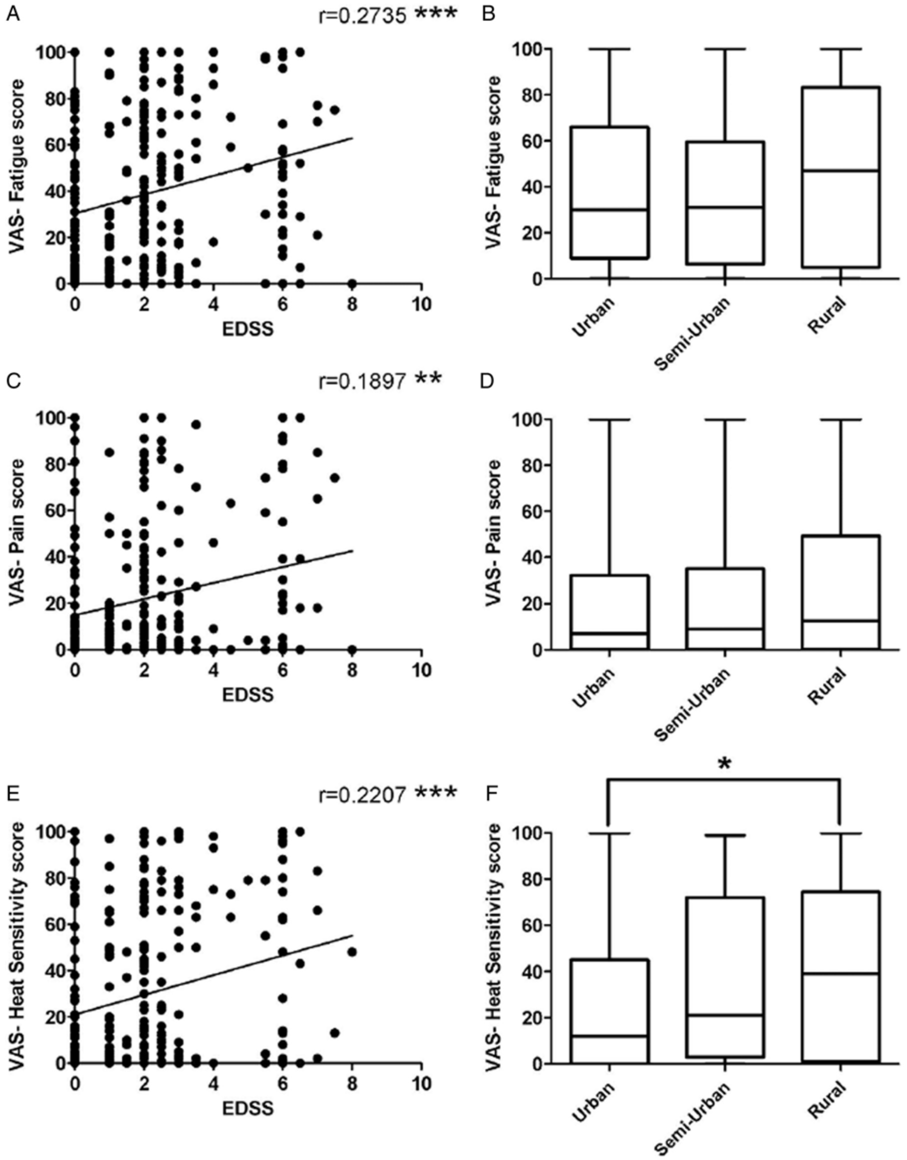

Figure 3. Fatigue, pain, and sensitivity to heat among patients living with MS. A: Correlation between fatigue on the HYF scale and EDSS. B: HYF fatigue score for MS patients living in urban, semi-urban and rural areas. Data are plotted aswhisker box plot with median and minimum to maximum values. C: Correlation between pain on the HYF scale and EDSS. D: HYF pain score for MS patients living in the three locations. Data are plotted as whisker box plot with median. E: Correlation between heat sensitivity on the HYF score and EDSS. F: HYF heat sensitivity score for MS patients living in the three different areas. Data are plotted as whisker box plot with median and min to max values. *$p<0.05$, **$p<0.01$, ***$p<0.001$. EDSS: Expanded Disability Status Scale. HYF: How You Feel.

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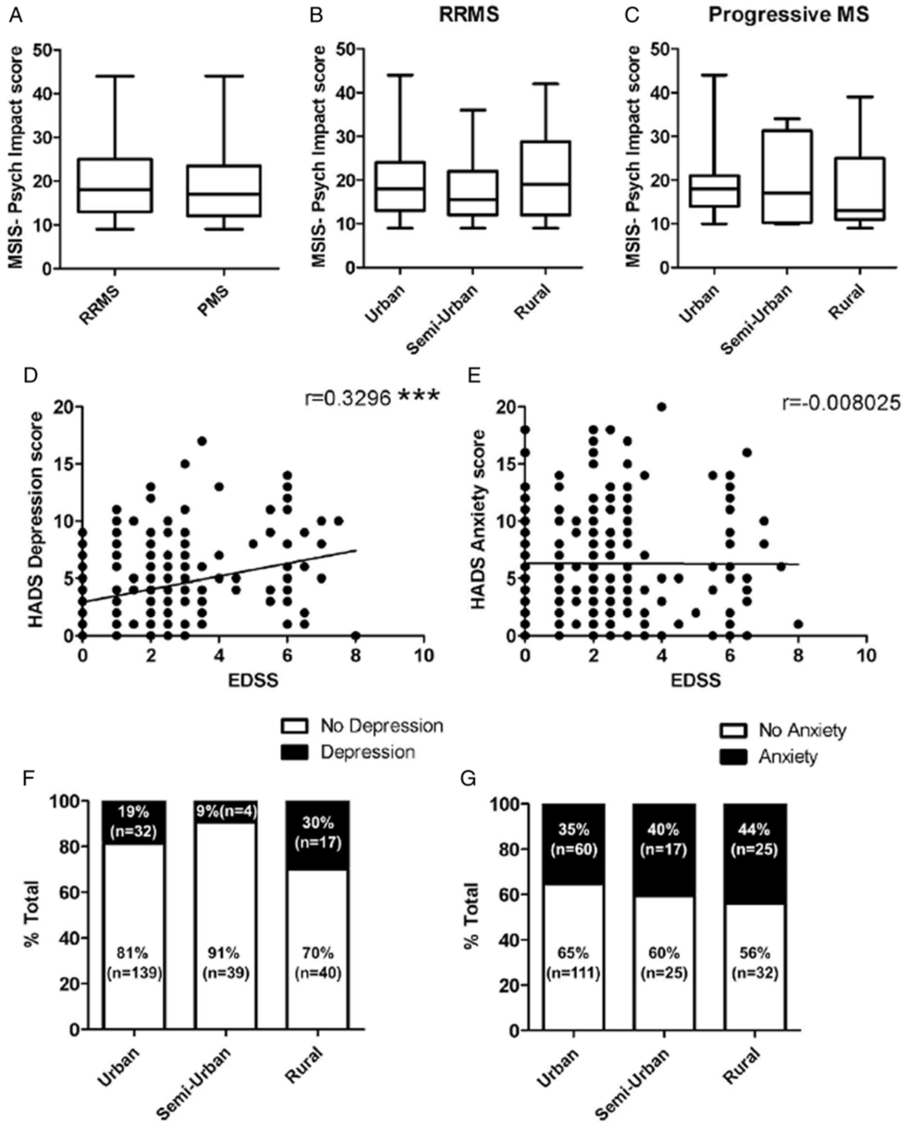

Figure 4. Depression and anxiety among patients living with MS. A: Correlation between duration of MS diagnosis and depression assessed using HADS. B: Correlation between duration of MS diagnosis and anxiety assessed using HADS. C: Correlation between EDSS and depression for MS patients. D: Correlation between EDSS and anxiety for MS patients. E: Percentage of MS patients living with and without depression in urban, semi-urban and rural areas. F: Percentage of those with or without anxiety in the three different locations. *p<0.05, ***p<0.001. MS: Multiple Sclerosis. HADS: hospital anxiety and depression scale.

urban and rural areas (X^2(6, $N = 264$) = 18.366, $p = 0.005$; Table 3). Furthermore, a lower percentage of participants in semi-urban areas were prescribed moderate-efficacy DMTs. In semi-urban areas, a greater percentage of participants were prescribed a high-efficacy DMT ($n = 9$, 20.9%) compared to urban ($n = 14$, 8.3%) and rural areas ($n = 2$, 3.8%) (X^2(6, $N = 264$) = 18.366, $p = 0.005$; Table 3).

Physical impact of MS on participants living in urban, semi-urban and rural areas

We next assessed the impact of living with MS using the MSIS-29 and VAS score for physical symptoms of MS. Overall, participants with PMS had a significantly greater physical impact score compared to RRMS ($U = 1919$, $p < 0.0001$; Figure 2A), which was not influenced by area (Figure 2B,C).

For the VAS score analysis, a significant positive correlation was observed between the level of fatigue and EDSS ($r(268) = 0.2735$, $p < 0.0001$) (Figure 3A). Within urban, semi-urban and rural areas, no significant differences in fatigue scores were recorded between areas (Figure 3B). Furthermore, no significant difference in fatigue were recorded in participants with RRMS or progressive MS (not shown). A significant positive correlation was also observed between pain and EDSS ($r(268) = 0.1897$, $p = 0.0017$), yet no differences were observed between areas (Figure 3C–D). No significant differences in fatigue were recorded in participants with RRMS or PMS (not shown). A significant positive correlation between heat sensitivity and EDSS was also observed (Figure 3E; r (268) = 0.2207, $p = 0.0003$), which was associated with area (H(2, $n = 274$) = 6.766, $p = 0.0339$), whereby individuals residing in rural areas had an overall significantly greater heat sensitivity score compared to their urban counterparts (Figure 3F). As previously mentioned, the type of MS did not influence heat sensitivity (not shown).

Levels of depression and anxiety in participants with MS living in urban, semi-urban and rural areas

We next assessed the impact of MS on mental health using the psychological portion of the MSIS-29 and HADS measures. In contrast to the physical scores of the MSIS-29, no differences in psychological impact scores were observed between RRMS and PMS, nor were the scores impacted by area (Figure 4A–C). When

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Table 4. Anxiety and depression reported by participants with MS living in urban, semi-urban and rural areas

Anxiety	**Urban** *n* = *171*	**Semi-urban** *n* = *42*	**Rural** *n* = *57*
None	111 (65%)	25 (60%)	32 (56%)
Anxiety reported	60 (35%)	17 (40%)	25 (44%)
Mild	39 (22%)	7 (16%)	11 (19%)
Moderate	13 (8%)	8 (19%)	10 (18%)
Severe	8 (5%)	2 (5%)	4 (7%)
Depression	*n* = *171*	*n* = *43*	*n* = *57*
None	139 (81%)	39 (91%)	40 (70%)
Depression reported	32 (19%)	4 (9%)	17 (30%)*
Mild	25 (15%)	2 (4.5%)	12 (21%)
Moderate	7 (4%)	2 (4.5%)	3 (5%)
Severe	0 (0%)	0 (0%)	2 (4%)
Anti-depressants	*n* = *171*	*n* = *43*	*n* = *57*
None	130 (76%)	32 (74%)	37 (65%)
Prescribed	41 (24%)	11 (26%)	20 (35%)

Values are expressed as a number of participants with percentages. Anxiety and depression that are reported are categorized as mild, moderate or severe (shaded area). $^{*}p < 0.05$.

assessing depression among the entire cohort, no correlation was observed between depression scores and disease duration; however, a significant negative correlation was observed with anxiety ($r(267) = -0.1358$, $p = 0.0260$) (not shown). Participants diagnosed with MS for greater than 15 years had lower anxiety scores compared to those with a diagnosis of less than 15 years [$U = 7575$, $p < 0.05$] (not shown). A significant positive correlation between depression scores and degree of disability was observed ($r(265) = 0.3296$, $p < 0.0001$), but not with anxiety scores (Figure 4D–C). Participants living in rural areas reported greater depression (HADS) (Figure 4F, $X^2(2, N = 271) = 6.771$, $p = 0.0339$); however, there were no differences between geographic groups in anxiety scores (Figure 4G; Table 4). Of those experiencing depression in rural areas, the HADS depression scores were mostly categorized as mild at 21% (Table 4). Despite an increase in depression scores in rural areas, anti-depressant use was not statistically different across locations ($X^2(2, N = 271) = 2.731$, $p = 0.2553$; Table 4).

Discussion

The aim of this study was to assess and compare the physical health (disability, symptoms), mental health (anxiety, depression) and clinical status (DMT use, plasma NfL) of participants with MS living in urban, semi-urban and rural areas within the province of Newfoundland and Labrador, Canada. Overall, the results of this study suggest that the disability of persons with MS living within an urban or rural setting is comparable. This contrasts with a previous study that demonstrated greater physical disability in patients with MS living within rural areas lacking access to an MS-focused clinic.[10] In the current study, disability was measured by both a neurologist (EDSS) and the patient (MSIS-29-Physical) and was similar in patients across geographic areas, suggesting that patient access to MS-focused clinical care, even at a distance from one's home, helps to maintain optimal health.

An important and noteworthy aspect of this study was that despite study participants having their primary residence in one of these areas, all participants were monitored by one of only a few specialized MS neurologists located within a tertiary healthcare setting. As such, inter-assessor clinical and/or treatment bias is less of a concern, which is often a major limitation in cohort studies designed to assess health outcomes in rural versus urban settings. The results of this study suggest that despite individuals with MS living in a rural area, their disease is well-managed when seeking care within an urban setting. However, the results of this study also suggest that specific considerations need to be taken into account when treating certain comorbidities, including depression, which is known to be highly prevalent within the MS patient population.[14]

Notably, NfL, which is an objective measure of axonal injury and relapse activity,[29] was similar between participants in the geographic regions, supporting the notion that MS can be managed effectively using a hub-and-spoke model of care (*i.e.*, one centralized tertiary healthcare setting servicing urban, semi-urban and rural populations) as an approach to healthcare delivery.[30] Interestingly, participants with RRMS residing within semi-urban areas were more often prescribed platform DMTs compared to urban or rural areas; however, this result did not impact the overall disability scores and symptom management of patients.

In MS, disability is classically assessed by a neurologist using the EDSS. Unfortunately, this scale is heavily weighted toward pyramidal symptoms associated with MS and neglects other common symptoms (*e.g.*, cognitive impairment) that can influence/impair function.[31] To account for subjective impairments not well-captured by the EDSS, we also used the MSIS-29 and VAS scores to obtain a patient's self-assessment of their physical and psychological symptoms. In urban versus rural, our data support that the physical impacts of MS are experienced similarly between areas, which is inconsistent with previous studies, whereby patients showed worse physical disability when residing in rural locations.[10,12] Compared to our findings, the major limitation of these previous studies was that not all study participants accessed specialized MS-focused care. As mentioned, patients with MS-focused care by a specialized team have better management of MS symptoms with more appropriate prescribing of individual DMTs.[7–9]

In addition to EDSS and the MSIS-29, the VAS scale was also used to obtain a patient's subjective assessment of their physical symptoms. Using this scale, we found that participants with MS residing in rural NL had increased sensitivity to heat; no differences in fatigue or pain were observed. It has previously been demonstrated that increased heat sensitivity is a presenting symptom of MS, especially in those with greater lesion burden or atrophy.[32] While this result was unexpected, it is worth noting that all patients recruited for this study completed their VAS scales during their MS clinic visit with the neurologist in an urban area. While a relatively lengthy travel period was required for some individuals, a commute from rural to urban centers to seek medical care could be perceived as stressful, thus exacerbating MS symptoms[33] and, in turn, aggravating heat sensitivity symptoms. Of note, repeated elevations in cortisol levels following a stressful event can induce glucocorticoid resistance, which may lead to increased inflammation and relapses.[33,34] A possible explanation to further explain this intriguing finding may be that patients from rural areas could be more non-adherent to their DMT prescription. Critch and colleagues assessed predictors of heat sensitivity that were self-reported by patients with MS and concluded that patients

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with heat sensitivity were nine times more likely to be not taking a DMT.[32] While multiple reasons for this are plausible, this may be due to difficulties in accessing specific DMTs in rural areas and/or non-adherence. Finally, a previous study demonstrated that several factors and/or triggers are attributable to heat sensitivity in patients with MS.[35,36] Chacko and colleagues have demonstrated an exacerbation of MS symptoms with increasing environmental temperatures,[36] which is known to occur within urban centers and has been previously described as the urban heat island effect.[37] Given that individuals within urban centers have also been previously described as having a greater heat sensitivity,[38] these two factors combined may explain our results and suggest that clinicians should be mindful and consider clinical disparities that are differentially influenced by a patient's residence in a rural versus urban setting.

Previous studies have shown that the physical symptoms of MS can be detrimental to mental health, particularly where mental health services are limited.[15,17] In this study, our results demonstrated that anxiety levels were comparable between patients living in urban, semi-urban and rural areas, yet levels declined with increased disease duration and may be the result of patients being more able to cope with the anxiety symptoms that often accompany a recent MS diagnosis.[39] This is further supported by the comparable psychological impact experienced by participants with RRMS and PMS, despite a greater degree of disability observed with PMS. We also demonstrated that patients residing in rural areas experienced greater depression compared to semi-urban and urban areas, which is consistent with previous studies whereby depression and a worsening mental health status were more prevalent within rural locations.[13,15,17] Interestingly, despite greater self-reported depression in rural areas, there was no significant difference in the proportion of individuals with antidepressant prescriptions; patient access and use of psychotherapy and/or counseling were not recorded. Due to the difficulty and/or lack of access to mental health services in rural areas, these results are not unsurprising. In addition, it has been previously reported that patients with MS living in rural areas have less access to and satisfaction with mental health services compared to their urban counterparts.[13] These findings could reflect systemic barriers to care in rural NL, such as disproportionately poor access to primary care providers in rural areas.[40]

While several additional potential barriers must be overcome for patients with MS living in rural areas when seeking medical care in urban centers (*e.g.*, transportation, additional expenses, personal stress, *etc.*), insights may be gained by looking at other diseases. A study conducted by Mathews and colleagues assessed patients' decisions in regard to cancer treatment in rural NL and found that travel costs were indeed a deciding factor for care.[41] It has also been previously reported that nearly one in four individuals (24%) within the province of NL do not have a family doctor, while the largest proportion of individuals (37%) without a family doctor was in rural areas.[40] Due to the current doctor shortage, the increased rates of depression in patients with MS living in rural NL may also be due in part to the lack of a primary physician who can diagnose, prescribe and submit referrals for mental health services.

There are limitations in our study, including the use of a database that does not include control participants. Patients in the current study are seen by a neurologist in an MS clinic within an urban hospital. The length between visits may vary; however, information is collected from participants upon their visit to that neurologist. Using the HITMS database limits the comparison of patients with MS with no neurologist or comparison of mental health to the general population of NL. We therefore cannot compare with those who have undiagnosed MS or those not seeing an MS neurologist. HITMS collects data from patients over multiple visits expanding over years. This study analyzed data at the initial visit and recruitment to the study. It is unknown how outcomes change over time throughout the progression of MS.

In summary, the results of this study demonstrate that within the province of NL, individuals with MS who have a primary residence in either an urban or rural setting experience no significant differences in overall physical disability and were equally managed by DMTs despite a significantly higher percentage of patients prescribed platform DMTs in semi-urban areas. Individuals residing in rural areas self-reported a greater heat sensitivity while also having a higher prevalence of depression. Together, these findings should be considered by clinicians when treating patients, given the limited access to primary and specialized health services outside of an urban center. Overall, while some discrepancies in mental health outcomes were measured between individuals living in an urban versus rural setting, the results of this study highlight that when seeking specialized MS care within an urban center, a comparable level of continuity of care is provided to patients residing in both rural and urban NL. We believe that our results are likely to mirror other Canadian provinces with a similar patient demographic and that our study design provides a framework for others to investigate similar research questions across Canada.

Author contributions. **KF:** Conceptualization, data analysis, writing – original draft, review, editing. **NF:** Data collection. **STA:** Patient information and data collection. **SA:** Patient information and data collection. **LG:** Patient information and data collection. **NJS:** Patient information and data collection, writing – review, editing. **FC:** Patient information and data collection. **MS:** Patient information and data collection. **MP:** Patient information, writing – review, editing. **CSM:** Supervision, conceptualization, dData analysis, writing – review, editing.

Funding statement. This work was supported by the Canada Research Chair Program.

Competing interests. The authors declare no competing interests.

Disclosures. The authors have no relevant disclosures.

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