Multiple Sclerosis and Related Disorders 62 (2022) 103793

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Challenges to Longitudinal Characterization of Lower Urinary Tract Dysfunction in Multiple Sclerosis

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ARTICLE INFO

Keywords:
Multiple sclerosis
bladder dysfunction
lower urinary tract symptoms
LUTS
lower urinary tract dysfunction
LUTD
quality of life
sex differences

ABSTRACT

Background: Neurogenic lower urinary tract dysfunction (LUTD) results in lower urinary tract symptoms (LUTS) that impact quality of life in people with multiple sclerosis (PwMS). The risk factors and the contribution of LUTD to multiple sclerosis (MS) disease progression are under-researched.
Objective: To identify clinical and demographic predictors of LUTS in PwMS and gaps in clinical ascertainment.
Methods: Participants were adults with MS enrolled in a prospective, multicenter study (SUMMIT, N=802), including a subset of N = 258 patients in the UCSF EPIC study for whom medical records were further reviewed. Demographic (age, sex, race, ethnicity), clinical (disease duration, MS type), and female-specific reproductive factors (e.g., parity) were evaluated to determine associations with bowel/bladder functional system score. Participants' medical records were analyzed to understand the patterns of LUTS ascertainment by physicians and the specific contribution of LUTS to overall bowel/bladder functional system scores.
Results: 802 participants (71.3% female) contributed to these analyses. Higher bowel/bladder functional system scores, indicating worsening symptoms and function, were significantly associated with female sex ($p=0.001$) and progressive MS type ($p\leq 0.001$). In the EPIC participants, female-specific reproductive exposures (parity, menopause) were not significantly associated with worse bowel/bladder functional system scores. Most (98%) bowel/bladder functional system scores reflected the severity of LUTS (relative to bowel dysfunction). LUTS were under-ascertained clinically, and more so in women ($X^2 = 5.02$, $p=0.08$).
Conclusions: Female sex and MS type are predictive of worsening LUTS. Symptoms may be less likely to be ascertained by clinicians in females compared to males.

Introduction

In people with multiple sclerosis (PwMS), adult neurogenic lower urinary tract dysfunction (LUTD), is a common result of demyelinating damage to the central nervous system, including the brain and spinal cord (Ginsberg, 2013). This may result in lower urinary tract symptoms (LUTS) including voiding symptoms, storage symptoms, or both (Panicker et al., 2015). Voiding symptoms include urgency, urinary incontinence, and nocturia. Storage symptoms include urinary hesitancy, urinary retention, sensation of incomplete emptying, and consequently, frequency (Ginsberg, 2013; Panicker et al., 2015). By 10 years of disease duration, 80% of PwMS report some degree of bladder/bowel

Abbreviations: LUTD, Lower urinary tract dysfunction; LUTS, Lower urinary tract symptoms; FS, Functional System.

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https://doi.org/10.1016/j.msard.2022.103793
Received 16 December 2021; Received in revised form 1 March 2022; Accepted 3 April 2022
Available online 11 April 2022

dysfunction, and 22% report moderate or severe dysfunction (Kister et al., 2013). LUTS, significantly impact quality of life (QOL) in PwMS (Hemmett et al., 2004), and may lead to increased social anxiety, isolation, and fall risk (Sung et al., 2016). LUTS can further synergistically worsen function in other domains such as sleep, consequently worsening fatigue and mood (Lin et al., 2019). In combination, these complications can reduce physical activity (Block et al., 2015). LUTS may also contribute to risk of infection, leading to increased morbidity and hospitalizations (De Sèze et al., 2007).

Despite the documented prevalence of LUTS in PwMS and its impact on QOL, to date, there has been little consideration to identify who is at greatest risk based on clinical and demographic predictors. There are a number of barriers to accurately monitor LUTS over time in PwMS. First, while these symptoms typically worsen with increasing disease duration and disability status as measured by the Expanded Disability Status Scale (EDSS) (Mahajan et al., 2010), the bowel/bladder functional system (FS) used in prospective research cohorts does not granularly capture LUTS in the range of intervenable dysfunction (i.e, bowel/bladder FS scores 0-1, since a score of 2 warrants use of pads) (see Supplementary Table I), nor does it distinguish between bowel symptoms and LUTS. Further, as a functional score it does not indicate if symptoms are actively being treated (e.g, current usage of intradetrusor botulinum). Unfortunately however, in clinical practice, no single more granular symptomatic scale is widely collected (Aharony et al., 2017). Second, possibly due to their intimate nature, LUTS may less likely be appropriately ascertained and diagnosed in the clinical setting. Patients often neglect to volunteer information about LUTS, and clinicians are not likely to ask (Khalaf et al., 2015). Further, the prevalence of non-neurogenic and often sex-specific LUTS in the general population (Kagan et al., 2019, Lukacz et al., 2006, Patra and Patra, 2012) may confound recognition of MS-related contributions. In females, musculoskeletal pelvic floor dysfunction is correlated with increasing parity (Lukacz et al., 2006) and post--menopausal status (Kagan et al., 2019). The loss of pelvic floor muscle support contributes to the common problem of stress urinary incontinence which affects 46% of women across all ages, and its prevalence increases with age. Other risk factors include pregnancy, vaginal delivery, and elevated body mass index (Wu, 2021). In males, symptoms are typically related to bladder outlet obstruction including prostate abnormalities (De Nunzio et al., 2017). Males are more likely to experience symptoms of frequency and nocturia while females more commonly experience urge incontinence (Patra and Patra, 2012). In the MS population, some sex differences have been reported (Monti Bragadin et al., 2020; Nazari et al., 2020), but the evidence remains mixed (Khalaf et al., 2015; Nazari et al., 2020). While possible sex differences in symptoms and disease course may exist (Bove and Chitnis, 2014), it is unknown if such sex differences exist in the reporting and ascertainment of LUTS.

Given the unknowns relating to progression of LUTD in PwMS, we leveraged the prospectively collected data from a large multinational consortium (Bove et al., 2017), as well as a local prospective study monitoring patients seen both for research (Cree et al., 2016) and clinical care (Damotte et al., 2018) to explore potential factors that could inform our understanding of LUTD progression. From these resources, as summarized in Supplementary Table II, we developed 3 major objectives, each with two aims. First, we sought to understand the reliability of bowel/bladder FS assessments in research settings by (1a) comparing how LUTS are ascertained in a clinical versus research setting and (1b) evaluating the contribution of LUTD to the bowel/bladder FS. Second, we sought to understand the contribution of bowel/bladder FS scores to disease progression by (2a) evaluating if scores predict worsening disability as measured by the EDSS over the course of 5 years, and (2b) identifying specific demographic and clinical risk factors for developing LUTD in PwMS. Finally, we evaluated for sex-specific effects by (3a) comparing how LUTS are ascertained in females and males and (3b) assessing the contribution of female specific factors (parity and menopausal status) to overall bowel/bladder functional system scores.

Methods

Participants

Participants were adults with clinically isolated syndrome/MS (Polman et al., 2011) and enrolled in centers contributing to the Serially Unified Multicenter Multiple Sclerosis Investigation (SUMMIT) Consortium. SUMMIT is comprised of four prospectively enrolled cohorts, each with over a decade of comprehensive follow-up (Bove et al., 2018). As previously described (Bove et al., 2018), participants with MS are followed at least annually with clinical examinations, neuroimaging, and biosample collection.

Bowel/bladder FS scores are one of seven functional systems used to calculate the EDSS and addresses both bowel and bladder symptoms and function including urgency, hesitancy, incontinence and catheterization (Şen, 2018). A score of 0 indicates no problems, while a score of 6 indicates complete loss of bowel and/or bladder control (Supplementary Table I). While the bowel/bladder FS scores are not comprehensive of LUTS, these data were collected as part of the SUMMIT protocol and were used for retrospective analyses.

EDSS scores and bowel/bladder FS scores were available for three SUMMIT sites (Kurtzke, 1983) (Brigham and Women's Hospital CLIMB study, University of California, San Francisco [UCSF] EPIC study, and the American University of Beirut Medical Center AMIR study). Additionally, for the patients in the UCSF EPIC study, a subset contributed to clinical analyses (see Supplementary Figure 1 for descriptions of the subsets of particpants for each analysis).

Ethical review

The Committee on Human Research at each institution approved their respective protocol, and at UCSF approved analysis of the integrated dataset.

Study Procedures

Reliability of Bowel/Bladder FS Scores in Research Assessments (EPIC subset)

Biases in Bowel/Bladder FS Score Ascertainment

Documented bowel/bladder FS scores are determined in part by patient self-reported symptoms—thus, we sought to determine possible ascertainment biases. For convenience, we focused on participants in the EPIC cohort who completed a Lifestyle Questionnaire that included detailed reproductive history (Supplementary Table III). We first noted bowel/bladder FS scores that were documented, or omitted, during all research EPIC visits (see Supplementary Table II for subgroups analyses). We then examined the electronic medical record within 6 months of the research visit for clinically documented scores as well as subjectively reported LUTS. We examined subjective reports of LUTS (e.g., patient spontaneously reports urinary leakage) and neurologist grading of bowel/bladder FS scores (e.g, graded as 0, i.e., no dysfunction) for discrepancies. Patient subjective reports were coded by one reviewer (AG) to match Neurostatus Scoring for Functional System scores: 0) no mention; 1) mild urinary urgency, hesitancy and/or constipation; 2) moderate urinary urgency, hesitancy and/or rare urinary incontinence and/or severe constipation; 3) frequent urinary incontinence and/or intermittent self-catherterizations and/or manual bowel evacuation.

For the same group of patients, we secondly evaluated whether LUTS noted to be present during a research (EPIC) visit, had been ommitted by their clinician during routine neurological care – or vice versa. We again reviewed the clinical and research record patients whose bowel/bladder FS scores were available from both research and clinical records within 6 months. We compared the research bowel/bladder FS scores with clinical scores within 6 months to identify any discrepancies.

Primary symptom driver of FS scores: bowel vs. bladder

Since the bowel/bladder FS scores account for both bladder and bowel dysfunction, we sought to understand whether the severity of LUTS could be reliably inferred by a participant's total score. For this analysis, we examined the electronic medical record for 89 female, and 43 male EPIC participants for whom self-reported, validated reproductive histories were available (Supplementary Table II), and calculated the percentage of clinical visits in which a bowel/bladder FS score was driven by LUTS (versus bowel).

The Role of Bowel/Bladder FS Score in Disease Progression (SUMMIT)

Effect of bowel/bladder FS score worsening on subsequent disability progression

To evaluate if bowel/bladder FS scores predict worsening disability as measured by the EDSS over the course of 5 years, the entire SUMMIT dataset was used to evaluate the association of a 1-point increase in scores between two annual visits, and odds of sustained EDSS worsening over the subsequent 4 years. We used Naïve Bayes' Classifier, adjusting for baseline age, MS type and sex. Clinically significant disability was defined as worsening by an increase in EDSS of 1.5 points if the baseline EDSS score was 0, 1.0 point if the baseline EDSS score was between 1.0 and 5.0, and 0.5 point for baseline EDSS scores of 5.5 or higher (Cree et al., 2019).

Demographic and Clinical Predictors of LUTS

To evaluate predictors of LUTS over time, we used the entire SUMMIT dataset and examined function at 10 years of disease duration since onset of MS symptoms. This timepoint was chosen given that previous studies have demonstrated a majority of PwMS will experience some LUTS by then; (Mahajan et al., 2010) additionally, it allowed for the largest number of SUMMIT participants with longitudinal data available to be included. We recorded the following data from all participants at 10 years disease duration: 1) clinical factors including date of first relapse, EDSS and FS scores, and MS disease course; 2) demographic factors including age, sex (biological sex and gender identity concordant in all participants), race, and ethnicity.

Sex Specific Effects (EPIC subset)

Female-specific contributors to LUTS

Since female-specific contributors to lower urinary tract function are common and may be influenced by pregnancy or age (Wu, 2021), we evaluated whether parity and menopausal status may influence bowel/bladder FS scores in females with MS. We included 117 female EPIC participants with self-reported, then validated, reproductive histories (Supplementary Table III), validated by electronic medical record review. Post-menopausal status was defined at least 12 months post-final menstrual period, according to the Stages of Reproductive Aging Workshop (Harlow et al., 2012), at the 10 years of disease duration. Parity was defined as the number of pregnancies reaching 20 weeks of gestation and beyond, regardless of the outcome (ACOG 2021).

Statistical analyses

The agreement between clinical and research ascertainment of bowel/bladder FS scores was obtained using a Chi-square test of independence. The association between bowel/bladder FS scores prospectively collected in the SUMMIT cohort at 10 years of disease duration and clinical and demographic factors (age, sex, and clinical MS type) was analyzed using an ordered logistic regression or proportional odds mode. The association between sex-related factors including menopausal status and parity were assessed using odds ratios. Statistical analysis of the results was conducted using the R 4.0.2 environment for statistical computing.

Results

Reliability of Bowel/Bladder FS Scores in Research Assessments (UCSF Patients)

Biases in Bowel/Bladder FS Score Ascertainment

We evaluated the concordance between the research bowel/bladder FS scores and any clinically ascertained scores within 6 months, for 479 total research and clinical visits for 132 patients (Supplementary Table II).

Of 479 total corresponding research/clinical visits analyzed, 277 recorded both clinic and research bowel/bladder FS scores (64% female, 36% male). Of these 277 visits, the clinical and research bowel/bladder FS scores agreed in 172 cases (67% female, 53% male). For females, the research bowel/bladder FS score was lower for 17%, and higher for 16%. For males, the research score was lower for 19% and higher for 28%. Overall, rater agreement was present in only 60.1% of visits. For males, there appeared to be under-scoring in the clinic relative to the research visit. A chi-square test of independence to examine the relation between sex and bowel/bladder FS score agreement between research and clinical data trended towards significance ($X^2 = 5.02$, $p=0.08$).

Further, in the clinical visits, there was no mention of LUTS for 15% of the female patient visits; while at the same timepoint, 58% of these had a research bowel/bladder FS scores above 0, (42%=0, 33%=1, 11%=2, 13%=3), indicating that LUTS were present. For males, there was no recorded ascertainment of LUTS in 8% of clinical notes, while research bowel/bladder FS scores were above 0 for 43% of these timepoints (57%=0, 29%=1, 14%=2). While LUTS were under-ascertained clinically for both females and males, there appeared to be a higher percentage of under recorded, moderate to severe LUTS in females.

Primary symptom driver of FS scores: bowel vs. bladder

When both LUTS and bowel symptoms in 284 clinical visits of 89 EPIC female participants were scored, (Supplementary Table II), bowel/bladder functional system scores severity matched LUTS severity for 280 (98.6%) scores; in contrast, bowel symptoms were more severe than LUTS in only 4 visits (1.4%). In the majority of cases, the severity of bowel/bladder functional system scores indicated the severity of LUTS.

The Role of Bowel/Bladder FS Scores in Disease Progression (SUMMIT Participants)

SUMMIT Participant characteristics

Data from 802 participants were available for the primary timepoint of interest, 10 year (±1) disease duration; this included EPIC (n=295), CLIMB (n=425), and AMIR (n=82) cohorts. A majority of participants were female (71.3%) and self-identified as white (96.55%). At 10 years of disease duration, most had relapsing remitting MS (RRMS) disease type (83.29%), and median EDSS was 2.0 [IQR 1.0, 3.0] (Table 1). Among the 572 female, 490 (85.7%) had a bowel/bladder FS score between 0 and 1, and 82 (14.3%) had a score >1 at 10Y. Median EDSS was 2.0 [IQR 1.0, 3.0]. Among the 230 males, 211 (91.7%) had a bowel/bladder FS score between 0-1 and 19 (8.3%) had a score >1; median EDSS was 2.0 [IQR 1.0, 2.5].

Table 1
Comparison of demographic and clinical characteristics of 802 across 3 SUMMIT Consortium sites.

Characteristics	EPIC (n=295)	CLIMB (n=425)	AMIR (n=82)	Total (n=802)	p-value
Sex, n (%)					
Female	199 (67.46)	319 (75.06)	54 (65.85)	572 (71.32)	
Male	96 (32.54)	106 (24.94)	28 (34.15)	230 (28.68)	0.044*
Race, n (%)					
White	279 (98.59)	395 (94.50)	82 (100.00)	756 (96.55)	
Not white	4 (1.41)	23 (5.50)	0 (0.00)	27 (3.45)	0.003*
Unknown	12	7	0	19	
Ethnicity, n (%)					
Hispanic	24 (8.14)	16 (3.77)	0 (0.00)	40 (4.99)	
Not Hispanic	271 (91.86)	408 (96.23)	82 (100.00)	761 (95.01)	0.002*
Unknown	0	1	0	1	
Years of Education, n (%)					
<= 4	1 (0.34)	0 (0.00)	0 (0.00)	1 (0.15)	
5 to 10	0 (0.00)	1 (0.28)	0 (0.00)	1 (0.15)	
11 to 15	82 (27.80)	94 (26.63)	9 (30.00)	185 (27.29)	
> 15	212 (71.86)	258 (73.09)	21 (70.00)	491 (72.42)	0.875
NA	0	72	52	124	
Alcohol use status, n (%)					
Never	42 (14.24)	0 (0.00)	0 (0.00)	42 (14.24)	
Former	8 (2.71)	0 (0.00)	0 (0.00)	8 (2.71)	
Current	245 (83.05)	0 (0.00)	0 (0.00)	245 (83.05)	
NA	0	425	82	507	< 0.001*
Tobacco status, n (%)					
Never	169 (57.29)	245 (58.33)	0 (0.00)	414 (57.90)	
Former	89 (30.17)	0 (0.00)	0 (0.00)	89 (12.45)	
Current	37 (12.54)	175 (41.67)	0 (0.00)	212 (29.65)	< 0.001*
NA	0	5	82	87	
Clinical features at 10-year disease duration					
Age, mean (sd)	45.82 (9.10)	46.25 (9.91)	39.68 (10.87)	45.42 (9.91)	< 0.001*
Disease duration, mean (sd)	10.38 (0.76)	10.89 (0.38)	10.37 (0.79)	10.65 (0.64)	< 0.001*
Disease course					
CIS	17 (5.76)	13 (3.06)	2 (2.44)	32 (3.99)	
RR	241 (81.69)	354 (83.29)	73 (89.02)	668 (83.29)	
PP	13 (4.41)	16 (3.76)	1 (1.22)	30 (3.74)	
SP	24 (8.14)	42 (9.88)	6 (7.32)	72 (8.98)	0.343
Bowel/Bladder FSs					
0 - 1	257 (87.12)	365 (85.88)	79 (96.34)	701 (87.41)	
> 1	38 (12.88)	60 (14.12)	3 (3.66)	101 (12.59)	0.032
EDSS, median [IQR]	2.0 [1.5, 3.5]	1.5 [1.0, 2.5]	1.0 [0.0, 2.0]	2.0 [1.0, 3.0]	< 0.001*

Legend: CIS: clinically isolated syndrome, RR: relapsing remitting, PP: primary progressive, SP: secondary progressive, Bowel/Bladder FSs: Bowel and Bladder Functional System score, EDSS: Expanded Disability Status Scale, IQR=interquartile range
*Indicates statistical significance

Demographic and Clinical Predictors of LUTS

To evaluate predictors of higher bowel/bladder functional system scores at 10 years of disease duration, both a proportional odds regression and binary logistic regression (0-1 and >1) were conducted. Using the binary logistic regression, a higher bowel/bladder FS score was significantly associated with female sex ($p=0.001$), and MS type [primary progressive (PPMS) and secondary progressive (SPMS) versus RRMS; $p\leq 0.001$ for each] but not age of MS onset ($p> 0.10$) (Table 2). Compared to males, females were significantly more likely to have a score >1 than 0-1 (OR 2.82, CI 1.60-5.22, $p=0.001$) by 10Y. The sex difference remained when scores were analyzed as ordinal values (0-4), ($p=0.012$).

Sex differences in bowel/bladder FS scores remained statistically significant in both the binary logistic regression ($p=0.001$) and the proportional odds regression ($p=0.013$) after adjusting for walking speed using the Timed 25 Foot Walk (T25FW).

Effect of Bowel/Bladder FS Score worsening on subsequent disability progression

A 1-point increase in bowel/bladder FS scores between the baseline study visit and follow up visit at year 1 was associated with an increased risk of clinically meaningful EDSS progression over the subsequent year (i.e year 1 to year 2) (n = 617, AUC=0.63). Change in score was also predictive of worsening EDSS from follow up visits at 1 year compared to 3 years (n = 572, AUC=0.64) and the 5-year on-study visit (n =575, AUC=0.61).

Sex Specific Effects (EPIC Cohort)

Female-specific contributors to LUTS

Finally, we examined the relationship between reproductive variables (age of menopause and parity) and bowel/bladder FS scores at 10 years of disease duration (n=117) (Supplementary Table II). Menopausal status at 10 years of disease duration is summarized in Table 4. Post-menopausal status at 10 years of disease duration was not significantly associated with increased odds of higher bowel/bladder FS scores in both a proportional odds regression, (OR 1.88, $p=0.24$) or in a binary logistic regression (bowel/bladder FS score 0 vs >0, OR 1.89, $p=0.27$ and bowel/bladder FS score 0-1 vs >1, OR 1.98, $p=0.37$). Similary, parity was not significantly associated with increased odds of higher scores in a proportional odds regression (OR 0.90, $p=0.86$) or using a

Table 2
Proportional odds regression of bowel/bladder functional score and sex, age of onset, disease course, and timed 25 foot walk

Bowel/Bladder Functional Score (0-4)			
Predictors	*Odds Ratios*	*95% Confidence Interval*	*p-value*
Intercept: 0|1	4.75	3.41-6.23	<0.001*
Intercept: 1|2	25.00	24.63-25.38	<0.001*
Intercept: 2|3	232.91	104.69-518.16	<0.001*
Intercept: 3|4	126.84	594.89-2685.04	<0.001*
Sex (F/M)	1.52	1.10-2.13	0.013*
Age of onset	1.02	1.00-1.03	0.046*
Disease course (CIS/RR)	0.84	0.36-1.81	0.676
Disease course (PP/RR)	11.06	5.23-23.70	<0.001*
Disease course (SP/RR)	6.95	4.16-11.68	<0.001*
T25FW	1.00	1.00-1.003	0.069
Observations	777		
R (Panicker et al., 2015) Nagelkerke	0.21		

Legend CIS: clinically isolated syndrome, RR: relapsing remitting, PP: primary progressive, SP: secondary progressive, T25FW: timed 25 foot walk test
* Indicates statistical significance

Table 3
Binary logistic regression of bowel/bladder functional score and sex, age of onset, disease course, and timed 25 foot walk

Bowel/Bladder Functional Score (0 vs >0)				Bowel/Bladder Functional Score (0-1 vs >1)		
Predictors	*Odds Ratios*	*95% Confidence Interval*	*p-value*	*Odds Ratios*	*95% Confidence Interval*	*p-value*
Intercept	0.25	0.13-0.46	<0.001*	0.02	0.01-0.05	<0.001*
Sex (F/M)	1.27	0.90-1.80	0.176	2.85	1.60-5.40	0.001*
Age of onset	1.01	0.999-1.03	0.059	1.02	0.995-1.04	0.12
Disease course (CIS/RR)	0.76	0.32-1.63	0.492	1.66	0.47-4.56	0.37
Disease course (PP/RR)	8.25	3.28-25.15	<0.001*	13.81	5.78-33.63	<0.001*
Disease course (SP/RR)	5.34	3.02-9.91	<0.001*	9.13	4.94-16.91	<0.001*
T25FW	1.00	0.998-1.002	0.885	1.002	1.000-1.004	0.06
Observations	777			777		
R (Panicker et al., 2015) Tjur	0.089			0.174		

Legend CIS: clinically isolated syndrome, RR: relapsing remitting, PP: primary progressive, SP: secondary progressive, T25FW: timed 25 foot walk test
* Indicates statistical significance

Table 4
Menopausal Status at 10 Years Disease Duration

	N
Total Female Patients Included in Analysis	117
Menopausal status at 10 years disease duration:	
Post Menopause (i.e. final menstrual period at least 12 months prior to visit)	34
Natural	21
Surgical	8
Radiation or chemotherapy	2
Endometrial ablation	2
Unavailable	1
Cycling or Premenopause	74
Unknown	9

binary logistic regression (number of pregnancies: bowel/bladder FS score 0 vs >0, OR 1.07, p=0.66 and bowel/bladder FS score 0-1 vs >1, OR 1.12, p=0.60; number of deliveries: bowel/bladder FS score 0 vs >0, OR 1.14, p=0.84 and bowel/bladder FS score 0-1 vs >1, OR 0.83, p=0.88). Altogether then, it did not appear that reproductive factors contributed to bowel/bladder FS scores at 10 years of disease duration.

Discussion

In this exploration of LUTS in MS, we uncovered a number of potential biases that could obscure our understanding of LUTD progression. First, we identified discordance between clinical and research notes, with under-ascertainment of LUTS in the clinical setting as well as inaccurate scoring in the research setting. Second, we confirmed that in most cases, the severity of LUTS and not bowel symptoms 'drove' the severity of the bowel/bladder FS scores. Third, we found that unexpectedly, at 10 years of disease duration females had worse bowel/bladder FS scores than males, and in a focused sub-cohort in women this did not appear related to reproductive factors such as menopausal status or parity. It is not clear whether this could be however due to differences in patient reporting and ascertainment of LUTS. Finally, with respect to disability progression, we showed that worsening in bowel/bladder FS scores is associated with subsequent worsening in overall disability.

The observed sex differences in LUTS are of interest because large cohort studies (Ribbons et al., 2015) demonstrated that males seem to accumulate global MS-related disability more quickly than females. On the contrary, here, female participants had worse bowel/bladder FS scores.

Of note, these worse bowel/bladder FS scores were not associated with slower walking speed, as measured by the T25FW. Gait speed and lower extremity function have been shown to correlate with measures of MS disease progression (Kalinowski et al., 2022; Block et al., 2017). The association found between progressive MS subtypes and bowel/bladder FS scores may suggest that LUTS do not correlate with pyramidal damage and lower limb disability as previous studies suggested (Giannantoni et al., 1999).

Suspecting possible ascertainment biases or confounders for the sex differences, two possible scenarios were investigated. First, we considered the possible contribution of female reproductive variables (parity and menopause) to LUTS. At our selected timepoint, worsening bowel/bladder FS scores did not correlate significantly with parity or menopausal status. In a cohort of older females, we might expect to find associations between reproductive exposures and LUTS, as in the general population, or worsening in neurological function due to menopause (Bove et al., 2016; Baroncini et al., 2019), but at 10 years of disease duration, this did not appear to explain apparent higher scores in females. Second, we evaluated for possible ascertainment biases. Overall, it appeared that females' LUTS were under ascertained in the clinic relative to males' and that clinicians may miss some instances of mild to moderate LUTS severity. Nonetheless, even though LUTS appeared more often ascertained in males, the severity of their symptoms could have been under-appreciated by clinicians.

Despite the high prevalence of LUTD in MS, there are limited clinical guidelines for the screening and prevention of MS related lower urinary tract dysfunction, and management consensus guidelines vary widely (De Sèze et al., 2007). This may be partly due to neurologists feeling ill-equipped to manage or identify LUTS. It is notable that only limited research (Ginsberg, 2013, Mahajan et al., 2010) exists that has directly addressed the etiology or appropriate management of LUTS in MS. While LUTS have an adverse impact on QOL of PwMS, our existing QOL instruments fail to capture patients' concerns adequately. In fact, amongst patient-reported outcomes, there is only one question of the 54 questions included in the Multiple Sclerosis Quality of Life Instrument (MSQOL-54) related to both bowel and bladder symptoms (Vickrey et al., 1995). Improved screening tools may be available to ascertain LUTS in PwMS, and this should be a priority for clinicans given that QOL scores in all domains are noted to decrease as overactive bladder symptom scores increase (Mahajan et al., 2010). Systematically evaluating for LUTS and ultimating treating patients appropriately may help address overall QOL.

Our data found a significant association between worsening LUTS and subsequent disability progression. These data raise the possibility that bowel/bladder FS scores worsening might herald the onset of "silent progression" in RMS (University of California et al., 2019) or evolution to SPMS; additional prospective studies will be required to confirm this observation. Results also suggest that LUTS could subsequently lead to decreased activity, conditioning, and psychological well-being (Tubaro, 2004) – which can all worsen QOL (Hemmett et al., 2004).

Limitations of this study included the retrospective nature of the sensitivity analyses, the imprecise and insensitive measure of LUTD used (bowel/bladder FS scores), as well as the preponderance of white patients in all cohorts limiting generalizability. In particular, the bowel/bladder FS score is widely used in MS cohorts, but has a number of limitations in its ability to capture all aspects of LUTS or in a granular and objective manner. However, the cohort size and longitudinal data collection allowed for valuable analyses on predictors of LUTS. Future, prospective studies should include aforementioned, comprehensive assessments of LUTS.

More detailed analyses are needed to disentangle possible effects of inflammatory lesions, neurodegeneration, treatment biases, and other sex-specific factors. Further, the mechanisms through which bladder dysfunction could contribute to worsening of overall disability require clarification. Overall, our study suggests that while there may be increasing awareness of bladder dysfunction and LUTS in MS, both male and female patients remain underserved.

CRediT authorship contribution statement

Tamara B. Kaplan: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **Arpita Gopal:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Valerie J. Block:** . **Anne M. Suskind:** Validation, Writing – review & editing. **Chao Zhao:** Software, Data curation. **Mariann Polgar-Turcsanyi:** Project administration. **Taylor J. Saraceno:** Project administration. **Refujia Gomez:** Project administration. **Adam Santaniello:** . **SUMMIT Consortium:** Project administration, Funding acquisition. **Nabil El Ayoubi:** Project administration. **Bruce A.C. Cree:** Supervision, Project administration. **Stephen L. Hauser:** Supervision, Project administration. **Howard Weiner:** Project administration. **Tanuja Chitnis:** Project administration. **Samia Khoury:** Project administration. **Riley Bove:** Conceptualization, Methodology, Validation, Writing – original draft, Writing – review & editing, Supervision.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was funded by the National Multiple Sclerosis Society (SUMMIT Consortium), NIH Grant 5R35NS111644, and the Valhalla Foundation.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: T. Kaplan has received consulting and advisory board fees from Biogen, Genzyme-Sanofi, Roche-Genentech/Roche, Novartis, and Bristol Myers Squibb. A. Gopal has no conflict of interest to declare; V. Block has no conflict of interest to declare; C. Zhao has no conflict of interest to declare; N. El Ayoubi has received consulting fees from Biogen, Sanofi_Genzyme, Roche, Merck, and Novartis Pharmaceuticals; M. Polgar-Turcsanyl, T. Saraceno, R. Gomez and A. Santaniello have no conflicts of interest to declare; B. Cree has received personal compensation for consulting from Alexion, Atara, Autobahn, EMD Serono, Novartis, Sanofi, Therini and TG Therapeutics and received research support from Genentech. SL. Hauser serves on the board of trustees for Neurona and on scientific advisory boards for Alector, Annexon, Bionure and Molecular Stethoscope, and has received travel reimbursement and writing assistance from F. Hoffmann-La Roche Ltd and Novartis for CD20-related meetings and presentations. T. Chitnis has received compensation for consulting from Biogen, Novartis Pharmaceuticals, Roche Genentech, and Sanofi Genzyme, and she has received research support from the National Institutes of Health, National MS Society, US Department of Defense, EMD Serono, I-Mab Biopharma, Mallinckrodt ARD, Novartis Pharmaceuticals, Octave Bioscience, Roche Genentech, and Tiziana Life Sciences. S. Khoury received personal compensation for participation in the Roche MaeStro Exchange Program and for participation in Merck-Serono medical advisory board; R. Bove is funded by the NMSS Harry Weaver Award. She has received consulting and advisory board fees from Alexion, Biogen, EMD-Serono, Genzyme-Sanofi, Novartis, and Roche-Genentech. She has received research support from Akili Therapeutics, Biogen and Roche Genentech.

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