THERAPEUTIC ADVANCES in
Neurological Disorders

Original Research

Real-world data on the prevalence and therapy of symptomatic bladder dysfunction in people with multiple sclerosis

Ther Adv Neurol Disord

2026, Vol. 19: 1–20

DOI: 10.1177/17562864261456559

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Abstract

Background: Bladder dysfunctions (BL-D) are common in people with multiple sclerosis (pwMS), significantly affecting daily life, infection risk, and survival. Nonetheless, BL-D are frequently stigmatized and inadequately addressed in clinical practice. To date, no comprehensive analysis of BL-D has been conducted in Germany.

Objective: To assess the prevalence of BL-D and its subtypes in a German cohort and identify associated factors and treatment patterns.

Methods: Data were analyzed from individuals enrolled in the German MS Register, aged ⩾18 with definite MS. Inclusion required ⩾3 visits and complete data on MS onset, diagnosis date, and BL-D status. BL-D were subclassified into urinary urgency, voiding dysfunction, bladder incontinence, and other BL-D. PwMS with different subtypes were compared regarding clinical, sociodemographic, and therapeutic characteristics and associated factors were identified using logistic regression.

Results: The study cohort included 10,572 pwMS (71.7% female) with a mean age of 48.2 years, disease duration of 16.0 years, and median Expanded Disability Status Scale score of 2.0. BL-D was present in 38.0% of pwMS, with urinary urgency being the leading subtype (41.0%). Associations included older age, longer disease duration, progressive disease course, polysymptomatic onset, and receiving disease-modifying therapy. Interestingly, 37.1% of pwMS with BL-D received no bladder treatment, while 36.9% received pharmaceutical and 36.4% non-pharmaceutical bladder treatment.

Conclusion: The results highlight the clinical relevance and burden of BL-D in MS and provide first insights into subtype-specific differences in the German MS population. Providing appropriate BL-D care requires investigation into causal factors and a deeper understanding of the underlying reasons of the treatment gap.

Design: Retrospective, cross-sectional study.

Plain language summary

Understanding bladder problems in multiple sclerosis: how common they are, who is affected and how they are treated

Bladder problems are common in people with multiple sclerosis (MS) and can strongly affect daily life, independence and overall health. Despite this, these symptoms are often overlooked, stigmatized or not treated accordingly in clinical practice. To better

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understand how common bladder dysfunctions are, which subtypes occur and which factors are associated with them, data from more than 10,000 people with MS enrolled in the German MS Register were analyzed. Overall, 38% of people with MS had bladder dysfunctions. The most common problem was a sudden and urgent need to urinate. Bladder problems were more likely in people who were older, had lived with MS for a longer time or had a progressive form of the disease. Importantly, we also observed clear differences between the various subtypes of bladder dysfunctions. A key finding was that over one-third of people with bladder problems were not receiving any symptom-related treatment. Pharmaceutical and non-pharmaceutical treatments were used at similar rates among those who did receive treatment. These results show that bladder problems are a major but often unmet need in MS care. Understanding how common these symptoms are, how they differ between subtypes and how they are currently treated can help improve care pathways and ensure that people with MS receive the support and therapies they need.

Keywords: bladder dysfunction, multiple sclerosis, neurogenic bladder, real-world evidence

Received: 7 January 2026; revised manuscript accepted: 18 May 2026.

Introduction

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system, characterized by the body's immune system attacking and damaging nerve cells of the brain and spinal cord. The resulting axonal damage, demyelination, synaptic pathology, and reactive astrocytes can lead to a range of symptoms that can significantly impact quality of life, physical and emotional well-being as well as work-related abilities and survival of those affected.[1]

As of 2023, approximately 2.9 million people are living with MS worldwide.[2] MS typically begins in early adulthood and is characterized by a variety of symptoms, including depression, fatigue, spasticity, cognitive impairments, and bladder dysfunctions (BL-D).[3–6] The latter is often perceived as particularly distressing, with high impact on the quality of life in people with MS (pwMS).[7] BL-D further raises the risk of urinary tract infections, which often lead to frequent hospitalizations and increased mortality.[8] The reported prevalence of BL-D ranges from 29.4% to 92.3%, reflecting differences in cohort characteristics, including factors such as age and disease duration.[4,6,9–14] A longitudinal study from 2017 reported an increase in the prevalence of BL-D from 48.1% (at baseline) to 71.4% (at follow-up after 6 years) in females and from 45.5% to 66.7% in male.[10] A meta-analysis of 12 studies revealed a pooled prevalence of 68.4% in pwMS.[5] A recent analysis of German data showed a significant age-dependent increase in prevalence, with 29.6% of pwMS under 55 years old, 49.2% of those aged 55–64, and 60.2% of those older than 65 years having BL-Ds.[6]

The sub-categorization of BL-Ds remains challenging due to the lack of internationally standardized definitions. BL-Ds can be distinguished based on pathophysiological mechanisms (focuses on the underlying cause) and clinical manifestations (how symptoms are perceived and reported by patients). According to the German Society for Neurology (DGN), subtypes can be classified pathophysiologically (neurogenic detrusor overactivity, neurogenic detrusor underactivity, neurogenic acontractile detrusor, and detrusor-sphincter dyssynergia) and clinically (voiding dysfunction, urinary urgency, and bladder incontinence).[15] Under clinical classification, the International Continence Society defines the subtypes as follows: Voiding dysfunction is a condition characterized by impaired bladder emptying due to a lack of muscle coordination during the emptying process, resulting from either the muscle's inability to contract properly or failure to relax during urination.[16] Urinary urgency can be defined as an unpleasant sensation of needing to urinate urgently, often triggered by a sudden intense desire to void, which can be accompanied by an overwhelming pain.[16] Bladder incontinence can

be described as an involuntary loss of urine due to failure of muscle control of the bladder.[16] This can result in an inability to handle a sudden urge to urinate or pressure on the bladder (e.g., during physical activity or coughing).[17]

There is a tendency of BL-D to be underdiagnosed[18] either due to underreporting driven by a lack of communication between patients and medical professionals to patients' shame and embarrassment, social stigma or inadequate or missing diagnosis techniques, and poor medical training. Moreover, the wide range of BL-D symptoms (such as bladder incontinence and voiding problems) can make diagnosis quite challenging.[19]

Given that previous studies are limited by small single-center cohorts and lack subtype differentiation, this study sought to (i) address this gap by examining the prevalence of BL-Ds and their subtypes within a large cohort from the German MS Register (GMSR), (ii) characterize pwMS with and without BL-D in terms of sociodemographic and clinical variables, (iii) analyze different BL-D subtypes across different patients' characteristics, and (iv) identify associations between the presence of BL-D and various clinical, sociodemographic, as well as therapeutic variables.

Materials and methods

Selection of study cohort

The present study utilized data from the GMSR, which was established by the German MS Society (DMSG) in 2001 with the objective of collecting and analyzing data on pwMS in Germany.[20] Data were collected during routine practice and entered in a nationwide database by MS centers distinguished by the DMSG. The GMSR includes longitudinal data on sociodemographic and clinical characteristics (such as disease course, level of disability, and MS-related symptoms), disease-modifying therapy (DMT), and symptomatic treatment. The database is under continuous development and expansion, which led to dataset revisions in July 2022 that resulted in the collection of data on BL-D subtypes. The present analysis was based on data from the most recent patient visit to the MS center at which a BL-D was reported, with a cut-off date of June 3, 2025. Patients fulfilling the following criteria were included: at least three visits in a MS center where data on the presence or absence of BL-Ds was available with at least one visit being after July 2022, a confirmed diagnosis of MS, minimum age of 18 years, and complete data on the MS onset or diagnosis date. Patients with missing or unknown data were removed from the analysis data set. This also included pwMS who had a documented BL-D but were missing information on the subtype of BL-D. To minimize potential misclassification bias, only patients with a "verified" BL-D status (presence or absence) were included. The presence of BL-D was considered "verified" if it was reported on two consecutive visits or if a patient with at least four visits had the following combination of the last four visits: presence of BL-Ds at the last visit, absence of BL-Ds or missing data at the second last visit, and presence BL-Ds at the third and fourth last visit. Patients with the presence of BL-Ds only at the last visit or who exhibited inconsistent reporting patterns, except the previously mentioned pattern, were not considered to have a verified presence of BL-Ds. Patients without BL-D at the last visit were required to have a consistent absence of bladder symptoms documented by the MS center in all prior visits as well at clinical onset. The inclusion criteria were met by 10,572 out of 47,650 living patients included in the GMSR since 2014 at the cut-off date (Figure 1).

Variable selection and categorization

The analysis of BL-Ds was conducted using two different categorizations: (i) the presence or absence of any BL-D and (ii) subtypes of BL-Ds. Subtypes were classified according to the GMSR documentation, which is based on the guideline for the diagnosis and treatment of MS, neuromyelitis optica spectrum disorders, and Myelin Oligodendrocyte Glycoprotein Immunoglobulin G-associated diseases, published by the DGN.[15] The categories included voiding dysfunction, urinary urgency, bladder incontinence, and other BL-Ds.

Sociodemographic, clinical, and therapeutic data were compiled. Sociodemographic characteristics included, sex (female, male), school level (no school-leaving certificate/certificate of secondary education (NSCE/CSE), general CSE (GCSE), A level/advanced technical college entrance qualification/advanced level (ATCEQ)), educational level (completed vocational training, completed

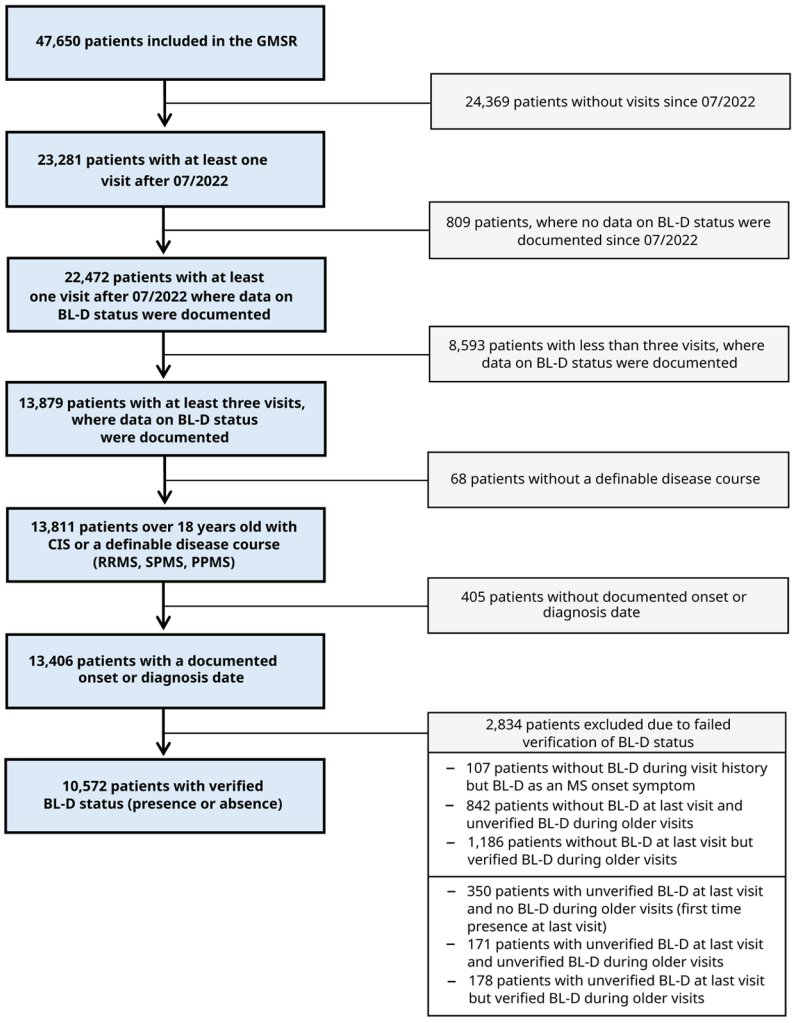

Figure 1. Selection of the study population. At the date of patient selection (June 3, 2025), the GMSR contained data on 10,572 patients who met the following inclusion criteria: alive with CIS or a definable MS type, minimum age of 18 years, at least three visits with at least one visit since July 2022, complete data on the MS onset (date where the first MS symptoms appeared) or diagnosis date and verified BL-D status with data on the subtype (if BL-D was present).
BL-D, bladder dysfunction; CIS, clinically isolated syndrome; GMSR, German MS Register; MS, multiple sclerosis; PPMS, primary progressive MS; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS.

university education, no completed/ongoing training), and employment status (employed—full-time, employed—part-time, retired—disability, other (including retired due to age, in training and unemployed)).

Clinical characteristics included age (in years), the course and duration of disease (in years), the time to clinically isolated syndrome (CIS) or MS diagnosis (in years), degree of disability, number of diagnosed comorbidities, specific comorbidities, and MS symptoms. The disease duration was measured from the date of clinical onset to the last visit of the patient. In cases where the onset date was missing but the diagnosis date was reported, the onset date was imputed by setting it to 6 months prior to the diagnosis date. Time to MS diagnosis was defined as the time between the clinical onset and diagnosis. The degree of disability was assessed using the Expanded Disability Status Scale (EDSS).[21] Comorbidities were coded using the International Classification of Diseases (ICD) system (10th Revision German modification (ICD-10-GM)). Additional information about the availability of comorbidity data is provided in Figure S1, as the coverage of this

variable is limited in the GMSR. MS symptoms included sexual dysfunction, bowel dysfunction, spasticity, movement disorder, fatigue, pain, cognitive dysfunction, depression, ocular motor disorder, dysarthria, dysphagia, epileptic seizure, sensory dysfunction, paresthesia, restless legs syndrome, Uhthoff's phenomenon, mobility impairment/paresis, fine motor dysfunction, balance disorder, sleep disorder, and visual dysfunction in accordance with the DGN guideline.[15] For pwMS with BL-Ds, the occurrence of BL-Ds at MS onset was also included. The other clinical variables were grouped as follows: age (mean ± standard deviation (SD)) and age categories (18–29, 30–39, 40–49, 50–59, ⩾60 years), disease course (CIS/relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS)), disease duration (0–1, 2–9, 10–19, 20–29, 30–39, ⩾40 years), EDSS score (mild (0.0–2.5), moderate (3.0–5.5), severe (⩾6.0)), and number of comorbidities (0, 1, 2–4, ⩾5). For age at MS onset the categorization also included the category <18 years old.

Therapeutic characteristics were assessed based on the prescription of a DMT at the last visit, which was categorized into the following groups: receiving a DMT and not receiving a DMT. Additionally, the type of symptomatic treatment for BL-Ds was gathered while distinguishing between four groups: pharmaceutical treatment, non-pharmaceutical treatment, a combination of both treatments, and no or refusal of treatment. Pharmaceutical treatments included all pharmacological interventions classified according to the Anatomical Therapeutic Chemical system for the management of BL-D (e.g., anticholinergics, beta-3 adrenergic agonists, or botulinum toxin). Non-pharmaceutical treatment included provision of aids (such as incontinence pads or urinary catheters), physiotherapy (such as pelvic floor training), and psychotherapy.

Statistical analysis

Descriptive statistics included frequencies, means, SDs, medians, and quartiles. Categorical variables were compared between pwMS with and without BL-Ds using Chi-square tests or Fisher's exact tests (when more than 20% of expected cell frequencies were below 5%). Continuous variables were analyzed using the Mann–Whitney *U* test for non-normally distributed variables and Student's *t*-test for normally distributed variables. Due to the explorative design of this study, *p*-values smaller than 0.05 were considered to indicate statistically significant differences without adjustment for multiple testing.

Variables associated with the occurrence of BL-Ds were identified using univariable logistic regression models with complete cases and presented as odds ratios (OR) with 95% confidence intervals (CI) along with the area under the curve as a measure for the importance of each variable. Next, significant associations identified in the univariable analyses were included in the multivariable logistic regression model.

Variables with a missing data rate exceeding 20% were excluded to minimize sample size reduction and preserve statistical power. To assess the potential impact of multicollinearity, variance inflation factors (VIF) were computed for each independent variable. Multicollinearity was considered substantial when VIF values were ⩾5, however, no variable reached this threshold. As the calculation of the EDSS score incorporates certain criteria directly associated with bladder function, the score was excluded in the multivariable logistic regression analysis.[21] Given the small number of CIS patients (0.6%, $n = 60$), cases with CIS and RRMS were combined into a single group. Further combinations due to unbalanced sample sizes concern the school level with ATCEQ/A level and NSCE/CSE. Forest plots with ORs were used for visualization. The *x*-axis of the plots was scaled logarithmically. Following the collection of data on subgroups of BL-Ds, frequency analyses with bar chart visualizations and the calculation of 95% Clopper–Pearson CIs for those frequencies were performed. Selection of variables was based on the results of the univariable logistic regression models. Graphical displays, data wrangling, data transformation, and data management were performed in R 4.4.2 (R Foundation, Vienna, Austria) using the tidyverse package.[22]

Results

Characterization of the study population

Overall study population. The overall study population (N_o) consisted of 22,472 pwMS with ⩾1 visit after July 2022, for whom data on the occurrence of BL-Ds at their last visit has been

documented. BL-D was classified based solely on information of the last visit: pwMS with documented dysfunction were classified as affected; those without were classified as unaffected. Of these 22,472 pwMS, 71.7% (n = 16,104) were female with a mean age of 48.6 years, mean disease duration of 15.3 years, and median EDSS score of 2.5 at the last visit. The most common disease course was RRMS (78.2%, n = 17,437). BL-Ds were present in 8671 of 22,472 patients (38.6%).

"Verified" study population. The final study population with "verified" BL-D status (N_v) consisted of 10,572 pwMS, of whom 71.7% (n = 7584) were female, with a mean age of 48.2 years, mean disease duration of 16.0 years, and a median EDSS score of 2.0 at the last visit. The majority of the pwMS had a relapsing-remitting disease course (81.5%, n = 8611), were in a partnership (78.8%, n = 7591), had completed vocational training (70.0%, n = 6450), and at least one comorbidity (62.5%, n = 2406). The most common comorbidities classified according to ICD-10-GM categories were essential (primary) hypertension (I10; 13.0%, n = 500), depressive episodes (F32; 10.8%, n = 414), and other disorders of thyroid (E07; 6.2%, n = 238). The prevalence of a verified presence of BL-D at the last visit was at 38.0% (n = 4014), which is nearly identical to the prevalence of the overall study population (N_o). Both the verified and the overall study population were compared to investigate if there were any differences between both cohorts (Table S1). No significant differences between the pwMS with a verified BL-D status (N_v) and those who were excluded from the overall study population (N_o) due to failed verification were found, except for the higher prevalence of polysymptomatic courses at MS onset in the excluded group compared to the verified study population.

The pwMS with verified BL-D status were significantly older (mean age at MS onset: 33.5 vs 31.5 years, OR = 1.19 (1.15; 1.23) and mean age at last visit: 53.8 vs 44.8 years, OR = 1.86 (1.79; 1.93)), had a longer time to MS diagnosis (1.8 vs 1.0 years, OR = 1.07 (1.05; 1.09)), and had significantly more frequently multiple symptoms at the onset of MS (47.4% vs 41.7%, OR = 1.26 (1.17; 1.36)) than pwMS without BL-Ds. Moreover, the prevalence of a progressive-onset MS disease course was significantly higher among pwMS with BL-Ds than in pwMS without BL-Ds (8.0% vs 2.0%, OR = 3.91 (3.20; 4.81)). The pwMS with BL-Ds had a longer disease duration (mean at last visit: 20.3 vs 13.3 years, OR = 2.13 (2.03; 2.23)) and exhibited higher degree of disability (median EDSS score at last visit 4.5 vs 1.5, OR = 2.14 (2.07; 2.20)) compared to those without BL-Ds. They also were more often retired due to disability (44.8% vs 10.8%, OR = 10.94 (8.74; 13.87)) and more often received a high-efficacy DMT (74.9% vs 57.4%, OR = 2.21 (1.96; 2.50)). While ATCEQ or A level was the most common school-leaving qualification for pwMS with no BL-Ds (45.5%), GCSE was more prevalent in pwMS with BL-Ds (45.1%; Tables 1 and 2).

The prevalence of MS symptoms at the last visit was stratified by the BL-D status (Figure 2). Among pwMS with BL-Ds, the most frequently reported MS symptoms—each affecting more than half of those individuals—included mobility impairment/paresis, fatigue, balance disorders, spasticity, movement disorders, and sensory dysfunctions. The leading symptom was mobility impairment/paresis with 77.9% of pwMS with BL-Ds being affected, whereas fatigue was the most common symptom reported by pwMS with no BL-Ds (35.7%). Significant differences between the two groups were observed for all symptoms, as indicated by 95% Clopper–Pearson CIs. PwMS without BL-Ds exhibited a significantly lower prevalence of all MS symptoms compared to those with BL-Ds.

Multivariable analysis of factors associated with BL-Ds. Variables associated with the presence of BL-Ds were identified using a multivariable logistic regression model (Figure 3). After excluding variables with either a high proportion of missing data or no statistically significant difference in the univariable analyses, the following variables were included in the multivariable logistic regression model: sex, age at last visit, disease duration, disease course at last visit, employment status, school and educational level, partnership status, polysymptomatic onset of MS, and DMT. The analysis revealed that older age (OR = 1.19 (1.12; 1.27)), longer disease duration (OR = 1.40 (1.30; 1.51)), progressive disease courses such as SPMS and PPMS (OR = 5.01 (4.06; 6.21) and OR = 4.70 (3.57; 6.21)), having more than one MS symptom at MS onset (OR = 1.37 (1.22; 1.54)) and currently receiving DMT (OR = 1.23 (1.04; 1.46)) were all statistically significantly associated with the presence of BL-D. Moreover, BL-Ds

Table 1. Characterization of the pwMS (study population N_v) at MS onset stratified by the occurrence of verified BL-Ds at the last visit in pwMS.

Variables	Total (N_v = 10,572)	BL-Ds (n = 4014)	No BL-Ds (n = 6558)	p	OR (95% CI)	AUC
Sociodemographics						
Sex, *n* (%)				**0.001**[Chi]		0.515
Female	7584 (71.7)	2952 (73.5)	4632 (70.6)		1.16 (1.06; 1.26)	
Male	2988 (28.3)	1062 (26.5)	1926 (29.4)		Reference	
Clinical variables						
Age at MS onset (years), mean (SD)[a]	32.3 (10.6)	33.5 (11.1)	31.5 (10.2)	<**0.001**[t]	1.19 (1.15; 1.23)	0.550
<18, *n* (%)	608 (5.8)	222 (5.5)	386 (5.9)	<**0.001**[Fi]	1.13 (0.95; 1.35)	0.551
18–29, *n* (%)	4429 (41.9)	1495 (37.2)	2934 (44.7)		Reference	
30–39, *n* (%)	3029 (28.7)	1165 (29.0)	1864 (28.4)		1.23 (1.11; 1.35)	
40–49, *n* (%)	1810 (17.1)	798 (19.9)	1012 (15.4)		1.55 (1.38; 1.73)	
50–59, *n* (%)	603 (5.7)	287 (7.2)	316 (4.8)		1.78 (1.50; 2.12)	
⩾60, *n* (%)	93 (0.9)	47 (1.2)	46 (0.7)		2.01 (1.33; 3.03)	
Disease course at MS onset, *n* (%)[b]				<**0.001**[Fi]		0.530
ROMS	9853 (95.6)	3570 (92.0)	6283 (97.8)		Reference	
POMS	451 (4.4)	311 (8.0)	140 (2.2)		3.91 (3.20; 4.81)	
Time to diagnosis (years), mean (SD)[b]	1.24 (3.22)	1.80 (4.07)	1.00 (2.75)	<**0.001**[t]	1.07 (1.05; 1.09)	0.567
Polysymptomatic at MS onset, *n* (%)[c]	4634 (43.8)	1902 (47.4)	2732 (41.7)	<**0.001**[Chi]	1.26 (1.17; 1.36)	0.529
Bladder dysfunction at MS onset, *n* (%)[b,c]	489 (5.9)	489 (15.9)	–	–	–	–

Bold font indicates statistical significance.
[a]ORs are presented in 10-year/score-point units.
[b]Sample size may vary due to missing values.
[c]Reference category is absence of symptom(s).
AUC, area under the curve; BL-D, bladder dysfunction; Chi, Chi-square-test; CI, confidence interval; Fi, Fisher's exact test; MS, multiple sclerosis; *N*, number of patients; OR, odds ratio; *p*, *p*-value; POMS, progressive-onset MS; pwMS, people with MS; Q1, first quartile (25%); Q3, Third quartile (75%); ROMS, predominantly relapse-onset MS (RRMS, SPMS); RRMS, relapsing-remitting MS; SD, standard deviation; SPMS, secondary progressive MS; *t*, Student's *t* test; *U*, Mann–Whitney *U* test.

were significantly more likely to occur in female pwMS (OR = 1.18 (1.03; 1.36)). Other sociodemographic variables associated with BL-Ds were part-time employment (OR = 1.54 (1.31; 1.82)), early retirement due to disability (OR = 5.81 (4.93; 6.84)), and no completed or ongoing training (OR = 1.38 (1.06; 1.79)). In contrast, no statistically significant associations were observed for school level or partnership status. A second multivariable logistic model was used to examine whether specific MS symptoms are associated with the occurrence of BL-Ds (Figure S2). Among all the MS symptoms reported in the GMSR, bowel dysfunctions (OR 6.94 (5.12; 9.51)) and sexual dysfunctions (OR 2.99 (2.25; 4.01)) were most strongly associated with the occurrence of BL-Ds.

Prevalence of BL-D subtypes. Urinary urgency was the most prevalent subtype, affecting 41.0% (n = 1644) of pwMS with BL-Ds, followed by bladder incontinence (31.0%, n = 1243), voiding

Table 2. Characterization of pwMS (study population N_v) at last visit stratified by the occurrence of verified BL-Ds at the last visit in pwMS.

Variables	Total (N_v = 10,572)	BL-Ds (n = 4014)	No BL-Ds (n = 6558)	p	OR (95% CI)	AUC
Sociodemographics						
Age at last visit (years), mean (SD)[a]	48.2 (12.6)	53.8 (11.6)	44.8 (12.0)	<**0.001**[t]	1.86 (1.79; 1.93)	0.705
18–29, *n* (%)	774 (7.3)	97 (2.4)	677 (10.3)	<**0.001**[Chi]	Reference	0.694
30–39, *n* (%)	2343 (22.2)	442 (11.0)	1901 (29.0)		1.62 (1.29; 2.07)	
40–49, *n* (%)	2643 (25.0)	891 (22.2)	1752 (26.7)		3.55 (2.84; 4.48)	
50–59, *n* (%)	2761 (26.1)	1331 (33.2)	1430 (21.8)		6.50 (5.21; 8.18)	
⩾60, *n* (%)	2051 (19.4)	1253 (31.2)	798 (12.2)		10.96 (8.74; 13.87)	
School level at last visit, *n* (%)[b]				<**0.001**[Chi]		0.558
NSCE/CSE	1470 (16.5)	664 (19.7)	806 (14.5)		1.20 (1.06; 1.35)	
GCSE	3736 (41.9)	1523 (45.1)	2213 (39.9)		Reference	
ATCEQ/A level	3710 (41.6)	1188 (35.2)	2522 (45.5)		0.68 (0.62–0.75)	
Educational level at last visit, *n* (%)[b]				<**0.001**[Chi]		0.528
Completed vocational training	6450 (70.0)	2566 (73.2)	3884 (68.0)		Reference	
Completed university education	2115 (22.9)	698 (19.9)	1417 (24.8)		0.75 (0.67; 0.83)	
No completed/ongoing training	651 (7.1)	240 (6.9)	411 (7.2)		0.88 (0.75; 1.04)	
Employment status at last visit, *n* (%)[b]				<**0.001**[Chi]		0.738
Employed—full-time	3653 (40.5)	694 (20.1)	2959 (53.1)		Reference	
Employed—part-time	1710 (19.0)	514 (14.9)	1196 (21.5)		1.83 (1.60; 2.09)	
Retired—disability	2146 (23.8)	1544 (44.8)	602 (10.8)		10.94 (9.65; 12.40)	
Other	1511 (16.8)	696 (20.2)	815 (14.6)		3.64 (3.20; 4.15)	
Partnership status at last visit, *n* (%)[b]				**0.007**[Chi]		0.512
Single	2045 (21.2)	838 (22.6)	1207 (20.3)		Reference	
Any partnership	7591 (78.8)	2862 (77.4)	4729 (79.7)		0.87 (0.79; 0.96)	
Clinical variables						
Disease course at last visit, *n* (%)				<**0.001**[Fi]		0.658
CIS/RRMS	8671 (82.0)	2512 (62.6)	6159 (93.9)		Reference	
SPMS	1359 (12.9)	1118 (27.9)	241 (3.7)		11.37 (9.84; 13.20)	
PPMS	542 (5.1)	384 (9.6)	158 (2.4)		5.96 (4.93; 7.23)	
Disease duration from MS onset to last visit (years), mean (SD)[a]	16.0 (10.0)	20.3 (10.6)	13.3 (8.59)	<**0.001**[t]	2.13 (2.03; 2.23)	0.701
0–1, *n* (%)	121 (1.1)	14 (0.4)	107 (1.6)	<**0.001**[Fi]	Reference	0.682

(Continued)

Table 2. (Continued)

Variables	Total (N_v = 10,572)	BL-Ds (n = 4014)	No BL-Ds (n = 6558)	p	OR (95% CI)	AUC
2–9, *n* (%)	3076 (29.1)	638 (15.9)	2438 (37.2)		2.00 (1.18; 3.67)	
10–19, *n* (%)	4032 (38.1)	1411 (35.2)	2621 (40.0)		4.11 (2.43; 7.53)	
20–29, *n* (%)	2249 (21.3)	1181 (29.4)	1068 (16.3)		8.45 (4.98; 15.50)	
30–39, *n* (%)	820 (7.8)	563 (14.0)	257 (3.9)		16.74 (9.73; 31.06)	
⩾40, *n* (%)	274 (2.6)	207 (5.2)	67 (1.0)		23.61 (13.07; 45.63)	
EDSS score at last visit, median (*Q*1; *Q*3)[b]	2.0 (1.5; 4.0)	4.5 (3.0; 6.5)	1.5 (1.0; 2.5)	**<0.001**[U]	2.14 (2.07; 2.20)	0.860
Mild (0–2.5), *n* (%)	5839 (56.8)	825 (21.4)	5014 (78.0)	**<0.001**[Chi]	Reference	0.810
Moderate (3.0–5.5), *n* (%)	2703 (26.3)	1541 (40.0)	1162 (18.1)		8.06 (7.25; 8.96)	
Severe (⩾6.0), *n* (%)	1738 (16.9)	1484 (38.5)	254 (4.0)		35.51 (30.55; 41.42)	
Number of comorbidities, mean (SD)[b,c]	1.69 (2.11)	2.53 (2.46)	1.20 (1.69)	**<0.001**[Chi]	1.38 (1.33; 1.43)	0.683
0, *n* (%)	1444 (37.5)	304 (21.4)	1140 (47.0)		Reference	0.676
1	884 (23.0)	304 (21.4)	580 (23.9)		1.97 (1.63; 2.37)	
2–4	1137 (29.5)	558 (39.2)	579 (23.8)		3.61 (3.05; 4.30)	
⩾5	385 (10.0)	256 (18.0)	129 (5.31)		7.44 (5.83; 9.55)	
Disease-modifying therapy, *n* (%)[b,c]	8644 (82.4)	3035 (76.4)	5609 (86.1)	**<0.001**[Chi]	0.52 (0.47; 0.58)	0.548
Non-high efficacy	2084 (36.7)	475 (25.1)	1609 (42.6)	**<0.001**[Chi]	Reference	0.587
High efficacy	3587 (63.3)	1416 (74.9)	2171 (57.4)		2.21 (1.96; 2.50)	

Bold font indicates statistical significance. High efficacy disease-modifying therapies included cladribine, fingolimod, ozanimod, ponesimod, Siponimod, alemtuzumab, natalizumab, ocrelizumab, ofatumumab, rituximab, and ublituximab, while non-high efficacy disease-modifying therapies included dimethyl fumarate, diroximel fumarate, glatiramer acetate, interferons, teriflunomide, azathioprine, mitoxantrone, methotrexate, and cyclophosphamide.
[a]ORs are presented in 10-year/score-point units.
[b]Sample size may vary due to missing values.
[c]Reference category is absence of therapy.
ATCEQ, advanced technical college entrance qualification; AUC, area under the curve; Chi, Chi-square-test; CI, confidence interval; CIS, clinically isolated syndrome; CSE/GCSE, certificate of secondary education/general CSE; EDSS, Expanded Disability Status Scale; Fi, Fisher's exact test; MS, multiple sclerosis; *n*, number of patients; NSCE, no school-leaving certificate); OR, odds ratio; *p*, *p*-value; PPMS, primary progressive MS; *Q*1, first quartile (25%); *Q*3, third quartile (75%); RRMS, relapsing-remitting MS; school levels (A level, advanced level; SD, standard deviation; SPMS, secondary progressive MS; *t*, Student's *t*-test; *U*, Mann–Whitney-*U*-test.

dysfunction (29.6%, n = 1190), and other BL-Ds (21.9%, n = 880). The prevalence of BL-D subtypes was further stratified by the variables most strongly associated with BL-Ds in the univariable analyses (Figure 4). A total of 29.0% of the patients with CIS/RRMS had at least one type of BL-D, while over three quarters (82.3%) of the patients with secondary progressive and 70.8% with a primary progressive disease course had at least one BL-D subtype (Figure 4(a)). The most prevalent subtype in patients with CIS/RRMS was urinary urgency with 12.4% of those affected, followed by voiding dysfunction (8.3%) and bladder incontinence (7.7%). Meanwhile, bladder incontinence was the most prevalent subtype in patients with SPMS (33.3%), whereas patients with PPMS were also most frequently affected by urinary urgency (31.2%). An analysis based on the disease duration revealed that the prevalence of having any BL-D was significantly higher in pwMS with a disease longer than 40 years than in pwMS having BL-D in the first disease year (75.5% vs 11.6%). While urinary urgency was the most prevalent subtype in the first 40 years of the

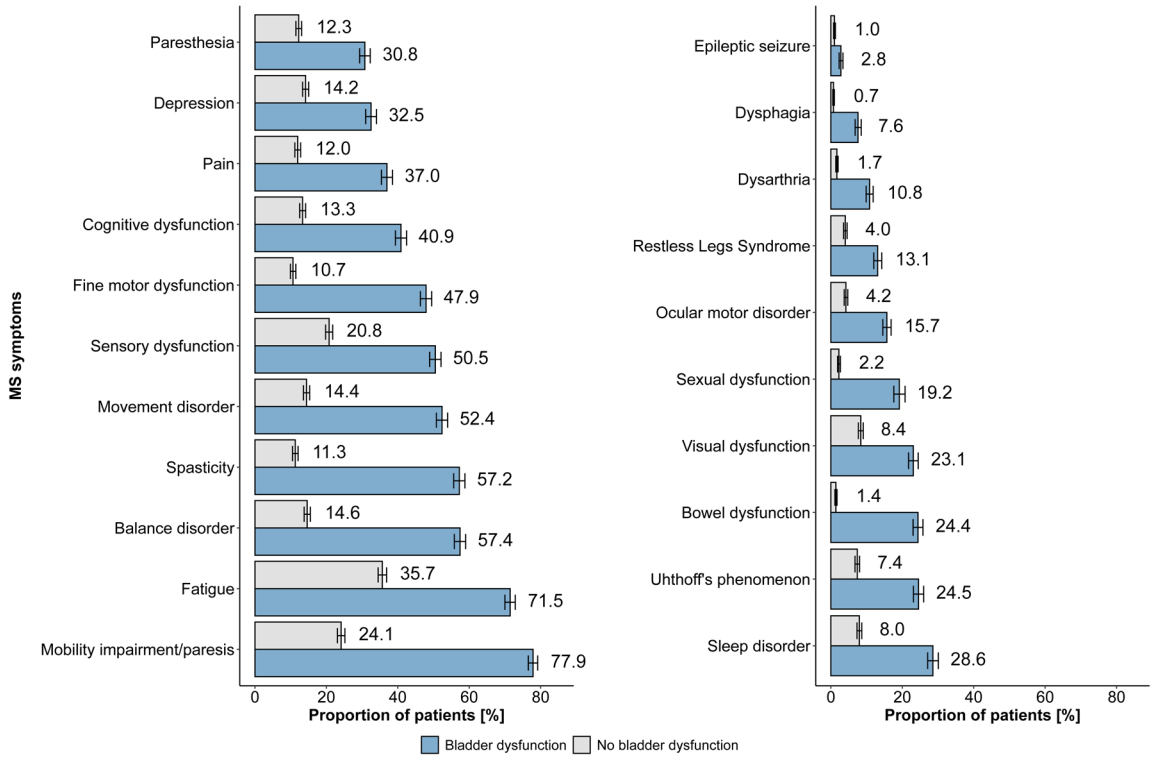

Figure 2. Prevalence of MS symptoms stratified by the occurrence of verified BL-Ds (N_v = 10,572). Sample sizes for individual symptoms may vary due to missing values. The blue bars show the proportion of pwMS with a specific MS symptom among pwMS with BL-Ds, while the gray bars show the proportion of pwMS with a specific MS symptom among pwMS without BL-Ds (in descending order of prevalence). Error bars at the end of the bars indicate the 95% Clopper–Pearson interval for the proportion of patients with a specific MS symptom. The most prevalent symptoms among pwMS with BL-Ds with a prevalence of over 50% included mobility impairment/paresis, fatigue, balance disorders, spasticity, movement disorders, and sensory dysfunctions. PwMS without BL-Ds exhibited a significantly lower prevalence of all additional MS symptoms assessed.
BL-D, bladder dysfunction; MS, multiple sclerosis; pwMS, people with MS.

disease, bladder incontinence was seen more often in pwMS after 40 years of living with MS (Figure 4(b)). Age- and sex-specific differences in the occurrence of BL-Ds are visualized in Figure 4(c). Overall, female pwMS were more likely to develop a BL-D compared to male pwMS. Significant differences in the prevalence of any BL-D between male and female pwMS were observed in the age groups 18–29 (5.1% vs 15.4%) and 40–49 (29.3% vs 35.5%) years old. Bladder incontinence was significantly more prevalent in female pwMS over 50 years old (16.4% vs 9.7% in age group 50–59 and 25.3% vs 17.4% in age group ⩾60) than in male pwMS. Male pwMS over 60 years old reported significantly more frequently other BL-Ds than female pwMS (16.3% vs 11.2%). Across all age groups, men most frequently reported urinary urgency. Among women, urinary urgency was also the most common subtype in all age groups except the oldest (⩾60 years), in which bladder incontinence was the most prevalent subtype (25.3%).

Further frequency analyses for the symptomatic treatment of BL-Ds were conducted in 3287 pwMS, who had complete data on symptomatic treatment. Regardless of specific subtypes of BL-Ds, 37.1% of pwMS most frequently remained untreated (Figure 5). The proportion of pharmaceutical treatment and non-pharmaceutical treatment was comparable at 36.9% and 36.4%, respectively, while combination therapy was reported less frequently (10.4%). Non-pharmaceutical treatment was the most prevalent treatment option for pwMS with urinary urgency, bladder incontinence, and other BL-Ds, with between 38.7% and 53.6% of pwMS receiving this type of treatment. Among pwMS with

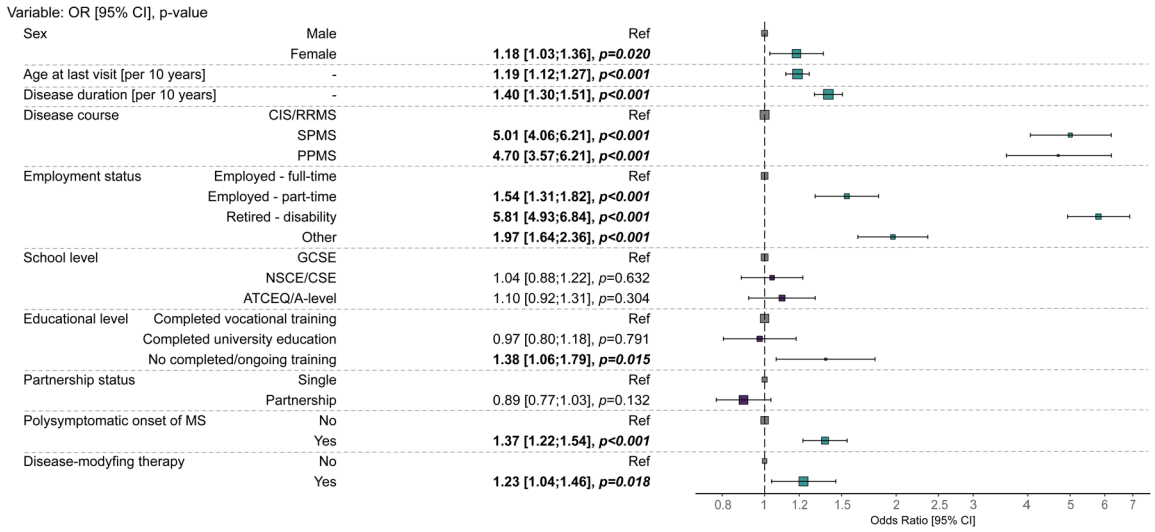

Figure 3. Factors associated with the occurrence of BL-Ds were analyzed among 7781 pwMS with complete data using a multivariable logistic regression model. The forest plot contains colored boxes indicating the ORs of the variables analyzed for the occurrence of BL-D. Green boxes and bold fonts indicate statistical significance. Boxes with no indication of statistical significance are purple colored, and reference boxes are colored in gray. Box size is proportional to the number of patients included. ORs >1 favor the presence of BL-Ds. Whiskers represent 95% CIs of the ORs. Female sex, older age, longer disease duration, progressive disease courses, part-time employment and early retirement, no completed/ongoing educational training, polysymptomatic onset of MS, and currently receiving DMT were statistically significantly associated with the presence of BL-Ds.

A-level/ATCEQ, advanced technical college entrance qualification; CI, confidence interval; CIS, clinically isolated syndrome; CSE/GCSE, certificate of secondary education/ general CSE; DMT, disease-modifying therapy; MS, multiple sclerosis; NSCE, no school-leaving certificate; OR, odds ratio; *p*, *p*-value; PPMS, primary progressive MS; pwMS, people with MS; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS.

voiding dysfunction, no or refusal of treatment was reported the most, with nearly half (45.1%) remaining untreated.

Discussion

Comparison with previous research

With 38.0%, the prevalence of BL-Ds in pwMS included in the GMSR was consistent with previously reported rates from international studies ranging from 29.4% to 92.3%, although the prevalence observed here lies at the lower end of this range.[6,10–12,14,23,24] Variations in BL-D prevalence rates may be attributed to differences in sample selection and size as well as divergent definitions of BL-D. Given that BL-D is often underreported in clinical settings due to patients' embarrassment and insufficient symptom screening, the use of physician-documented data in the GMSR may also contribute to a lower observed prevalence compared to other studies relying on self-reported symptoms. Previous studies on symptomatic treatment in MS in the German population were conducted by Skierlo et al. (initial study[25]) and Rommer et al. (follow-up study[4]). Both studies aimed to analyze the prevalence of MS symptoms, including BL-D and to identify symptomatic treatment patterns. The analyses showed that BL-D was among the most frequently reported MS symptoms. Both studies reported a comparable prevalence of BL-D, with 51.7% of 5113 patients affected in 2016 and 44.0% of 14,835 patients affected in 2018.[4,25] Although those two studies and the present study were based on the same source of data, differences in criteria for study population selection may have contributed to the slight differences in reported prevalence rates.

The present study revealed that the occurrence of a BL-D is associated with multiple factors, including sex, age, MS course type, and MS disease duration. Khalaf et al.[14] assessed the prevalence of BL-Ds among 1047 pwMS residing in the United States and found significant differences in

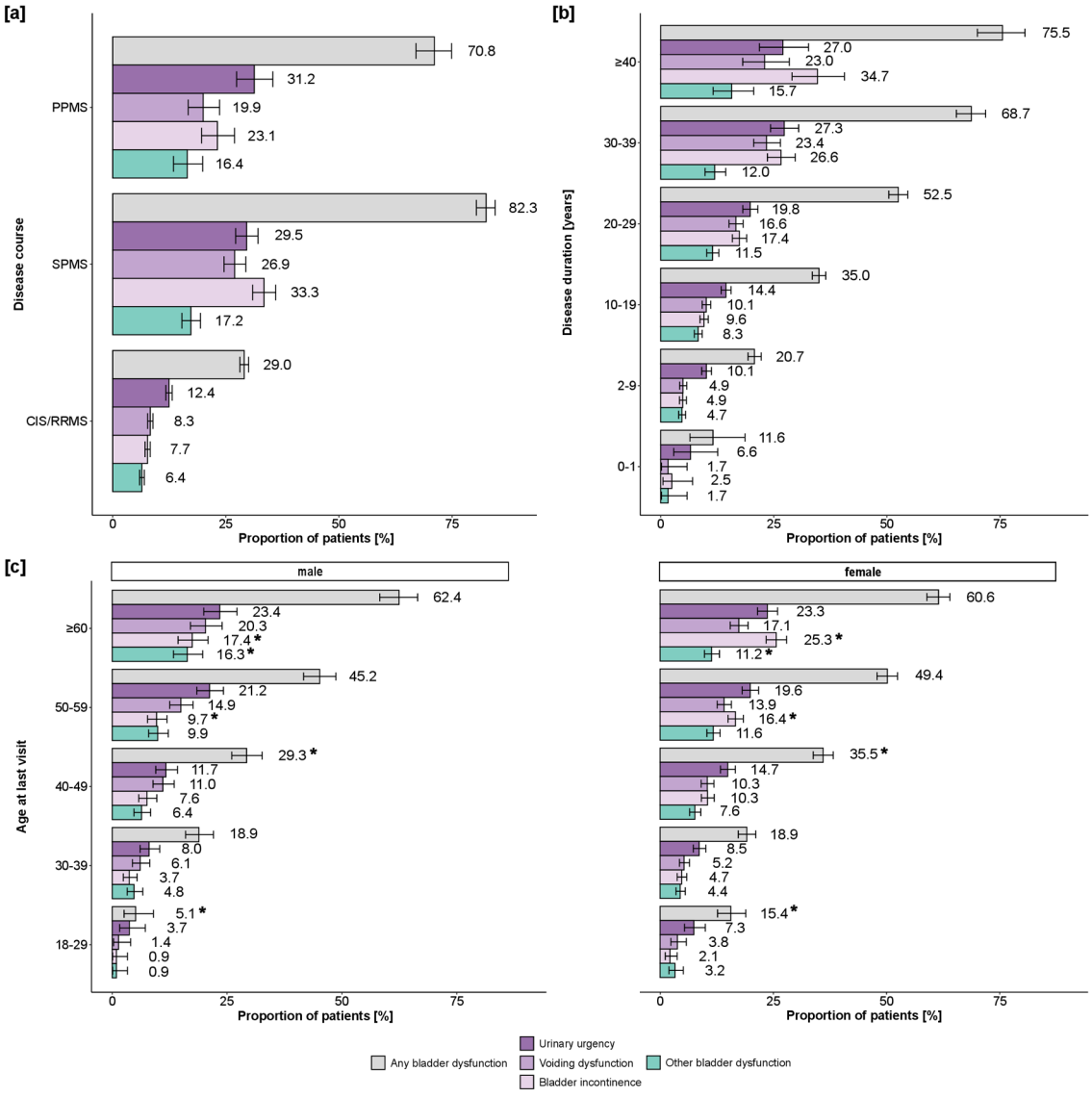

Figure 4. Prevalence of the subtypes of BL-D stratified by (a) MS disease course, (b) MS disease duration, and (c) age (in years) stratified by sex. Subtypes are categorized into urinary urgency (dark purple), voiding dysfunction (purple), bladder incontinence (light purple), and other BL-Ds (green). The proportion of pwMS with any BL-D independently from the subtype is shown in gray. Error bars at the end of the bars indicate the 95% Clopper–Pearson interval for the proportion of patients with BL-D.
*Indicate statistically significant differences between the sexes. Patients could be assigned to more than one BL-D subtype due to symptoms overlap; therefore, percentages are not mutually exclusive and represent individual symptom frequencies within the cohort. Patients with progressive disease courses (Box (a)), with longer disease duration (Box (b)), and in older age groups (Box (c)) were more likely to experience BL-Ds. Urinary urgency was the most prevalent subtype in most patient subgroups, especially in younger patients with CIS/RRMS and shorter disease duration. However, the proportion of pwMS with bladder incontinence was relatively high in older, female pwMS with progressive disease courses, and longer disease duration, often becoming more prevalent than urinary urgency.
CIS, clinically isolated syndrome; MS, multiple sclerosis; PPMS, primary progressive MS; pwMS, people with MS; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS.

the occurrence of BL-D between age groups and between disease durations. More recently, Azadvari et al.[9] conducted a cross-sectional study in which the prevalence of BL-Ds was estimated using questionnaire responses from 228 Iranian pwMS. The observed prevalence of BL-Ds in this

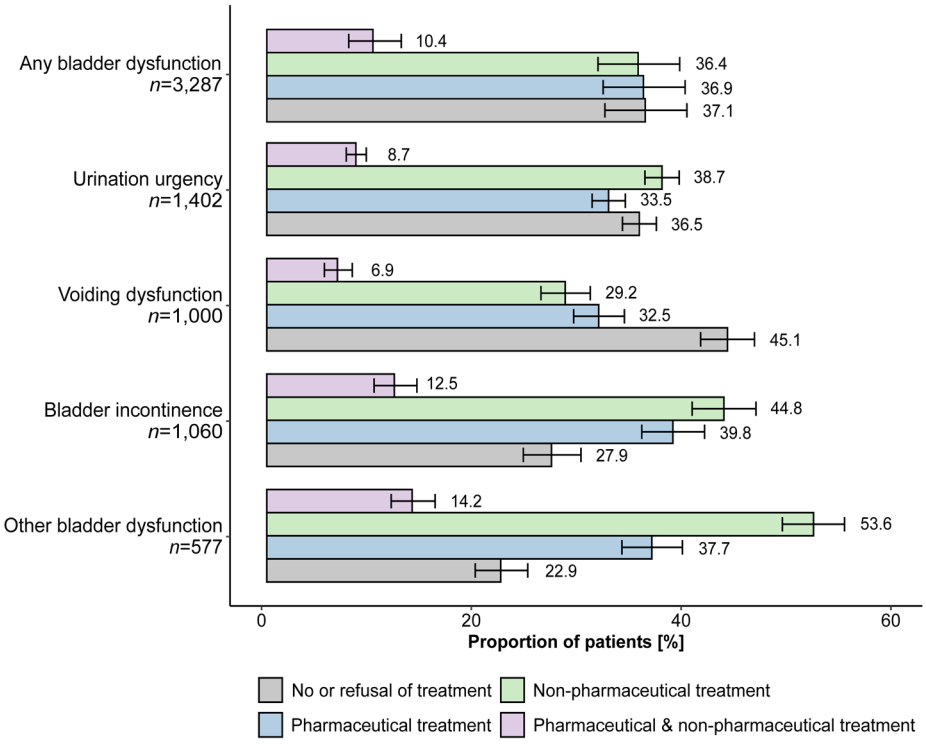

Figure 5. Prevalence of symptomatic treatment types stratified by BL-D subgroups. The gray bars show the proportion of patients who received no treatment or refused treatment of BL-D (with 43 out of 3287 pwMS refusing treatment, representing a small proportion of the study population). Symptomatic treatments were categorized into pharmaceutical treatment (blue) and non-pharmaceutical treatment such as physiotherapy, psychotherapy or provision of aids (green), and a combination of both (purple). Error bars indicate the 95% Clopper–Pearson interval for the proportion of patients receiving a specific type of symptomatic treatment. The sum of the percentages does not equal 100%, as the categories are not mutually exclusive. PwMS who received combination treatments are included in both the "pharmaceutical treatment" and the "non-pharmaceutical treatment" category. The figure shows that a high proportion of pwMS (ranging from 22.9% up to 45.1%) did not receive any form of symptomatic treatment. This trend is especially notable in patients with voiding dysfunction. Patients receiving treatment were most often treated either with medication alone or with no medication alone, while a combination therapy was documented less frequently. Bladder incontinence was treated more frequently than voiding dysfunction and urinary urgency.
MS, multiple sclerosis; *n*, number of patients; pwMS, people with MS.

study was higher in older pwMS and the disease duration was also found to be associated with the occurrence of BL-Ds. Subsequent analysis using data from the GMSR included a study from Goereci et al.[6] in 2024, who evaluated symptom burden, degree of disability, and therapy use among 40,428 pwMS. Findings revealed that BL-Ds were more frequently reported in pwMS aged 55 years or older, with rates of 49.2% in those aged between 55 and 64 years and 60.2% in those aged 65 years or older, compared to 29.6% in pwMS younger than 55 years old. BL-D was also one of the leading symptoms in the older age groups.[6] One of the few longitudinal studies conducted to assess the change in the prevalence of BL-Ds over time demonstrated an increase in the occurrence of BL-Ds from 48.1% for males and 45.5% for females up to 71.4% for males and 66.7% for females over a period of 6 years.[10] This is in line with the findings of the present study, according to which BL-Ds affected 11.6% of pwMS in their first year following MS diagnosis, whereas three out of four pwMS were affected after 40 years of disease duration. It should be taken into account that the observed age effect also occurs independently of MS, as aging itself significantly increases the risk and severity of BL-D. This is attributable to age-related decline in bladder control, pelvic floor weakness in older women, and the increased risk of developing

prostatic hyperplasia in older men leading to a higher prevalence of bladder symptoms.[26,27]

The literature on sex-related difference in pwMS with BL-D yielded conflicting results. Kisic Tepavcevic et al.[10] and Azadvari et al.[9] found no significant association between sex and the occurrence of BL-D. In contrast, Kaplan et al.[28] found significant differences with female pwMS showing worse bladder functional system scores when examining the impact of clinical and demographic factors (OR = 1.52 (1.10; 2.13)). The findings of the present study were comparable to these findings. The present study revealed sex differences in pwMS (OR = 1.18 (1.03; 1.36)), which were age-dependent, with female pwMS tending to exhibit higher overall prevalence rates in younger age groups than males, while no significant differences were found in the overall prevalence observed in pwMS over 50 years of age. Discrepancies between the studies may be attributable to differences in the age distribution of the studies. In the study by Azadvari et al., the mean age of the included pwMS was 36.7 years. Similarly, in the 30–39 age group of the present study, no sex related differences were observed. However, in the present study, the mean age was higher at 48.2 years and within the 40–49 age group sex-related differences became evident.

The MS disease course was also identified as a factor associated with BL-D, with a significantly higher prevalence of BL-D found in progressive MS types. This finding is consistent with the results of Kaplan et al.,[28] who found that a progressive MS type was associated with worse lower urinary tract symptoms. Mubaraki et al.[29] analyzed data from two questionnaires on urinary incontinence and overactive bladder, confirming that the severity was significantly higher in pwMS with progressive MS types compared to those with RRMS. These findings emphasize the importance of accounting for such factors when interpreting prevalence estimates and highlight the need for more context-dependent interpretations.

BL-D was more prevalent in pwMS, who retire early due to disability or were partially employed instead of being fully employed. Managing BL-Ds presents significant challenges not only in everyday life but also in professional settings. Many workplaces lack easily accessible restrooms or offer limited flexibility in work schedules. Frequent urination episodes during the night can disrupt sleep patterns, which can lead to sleep deprivation and fatigue.[30] Consequences may include a decline in concentration, a reduction in productivity and performance issues.[31] Moreover, frequent and sudden urges to urinate can disrupt concentration during work tasks or require sudden leave in work meetings. In such cases, maintaining a full-time job can be quite challenging and may subsequently lead to a reduction in working hours or early retirement.[32] While BL-D can contribute to the decision to retire early or reduce working hours, it should be taken into account that these decisions are often multifactorial rather than stemming from a single cause. Other factors such as other MS symptoms (e.g., mobility impairments or fatigue)[33] or high disease activity (e.g., high relapse rates) can affect the ability of pwMS to maintain employment.

The comprehensive analysis of symptoms occurring alongside BL-D revealed that mobility impairment was the most prevalent MS symptom in the present study. Similar to the results of the present study, Akkoç et al.[34] showed that a longer disease duration and walking difficulties were associated with more severe overactive bladder symptoms. Azadvari et al.[9] also confirmed this finding, reporting a higher prevalence of BL-D in pwMS with walking difficulties. Moreover, Grus conducted a single-center study to investigate the relationship between bladder symptoms and mobility impairments in female pwMS and showed that an increase in the severity of urinary incontinence and overactive bladder symptoms significantly impaired patient mobility.[35]

Interestingly, while the univariable logistic regression model suggested a protective effect of DMTs on BL-D (OR = 0.52 (0.47; 0.58)), this effect was reversed in the multivariable logistic regression model when controlling for factors such as age, disease duration, and disease course (OR = 1.23 (1.04; 1.46)), indicating that pwMS receiving DMTs are more likely to experience BL-D. DMTs are preferentially used in patients with highly inflammatory disease activity, reflecting a potential treatment indication bias.[15] Highly active MS is characterized by a higher relapse rate, which increases the likelihood of developing new or worsening MS symptoms, possibly explaining the reversed finding. Given the potential for residual confounding, indication bias, and

reverse causality, these observed association between DMT use and BL-Ds should be interpreted with caution.

Urinary urgency was identified as the most prevalent subtype of BL-D in the present study followed by bladder incontinence and voiding dysfunction. This finding was earlier reported by Akkoç et al.[34] and El Moudane et al.,[36] who both investigated the frequency and severity of overactive bladder symptoms in pwMS and found that urinary urgency was the most prevalent subtype, affecting over half of the pwMS in their study populations. These findings are also in line with the results of Seddone et al.,[12] who found urinary urgency to be the most prevalent subtype, following urge incontinence and voiding problems. However, given the inconsistency in how different BL-D subtypes were defined and how detailed categorized by different authors, a reliable comparison of subtype prevalence rates remains challenging. In addition, the analysis of the present study revealed that the prevalence of bladder incontinence increased with age and disease duration, indicating that incontinence is more relevant in the later stages of the disease. This could explain, why bladder incontinence was the most prevalent subtype in patients with a SPMS type, whereas patients with RRMS or PPMS tend to experience urinary urgency more frequently.[29] Further analyses revealed that the age-related prevalence of BL-D subtypes differs between female and male pwMS, with a more marked increase in the prevalence of bladder incontinence for women, making bladder incontinence the most prevalent subtype in older women. The age-dependent increase in the risk of experiencing bladder incontinence in women is also seen in the general population due to pelvic floor weakening and hormonal changes.[37] Thus, the general age-related risk and the disease-related risk both contribute to an increased prevalence of bladder incontinence in elder female pwMS.

The high proportion of pwMS without symptomatic treatment of BL-Ds found in the present study raises concerns as untreated BL-Ds can increase the risk of urinary tract infections, bladder damage, and other complications, reducing people's quality of life.[38] This finding is in line with the findings from Khalaf et al.[14] who reported no treatment of lower urinary tract symptoms in 29.4% of the study population. The present study revealed that this was a consistent issue across all BL-D subtypes, but especially common among pwMS experiencing voiding dysfunctions with nearly half of them not receiving treatment. Although 27.9% of pwMS experiencing bladder incontinence were often reported as untreated, they were more likely to receive treatment than those with urinary urgency and voiding dysfunctions. It may be hypothesized that the socially apparent nature of bladder incontinence—compared to less visible subtypes such as voiding dysfunction—may contribute to higher treatment rates. Given the widely known status of this symptom in the general population,[39] people's awareness and social acceptability might also differ compared to other subtypes, making it more likely to be reported, discussed, and treated. The high proportion of untreated BL-Ds is likely the result of multiple underlying barriers and factors such as the lack of communication between the patient and clinician, including inadequate guidance provided and not being taken seriously by the latter and patient's discomfort and shame reporting symptoms, the belief that symptoms were not severe enough to warrant treatment or that treatment would not provide any relief, insurance barriers, or no access to specialized physicians.[14]

Strengths and limitations

While the present study provides important insights into BL-Ds in pwMS, several limitations must be acknowledged. Compared to other studies, this registry-based study included a large number of pwMS with BL-Ds. Nevertheless, the generalizability of the findings may be limited, as participation in the GMSR is voluntary and restricted to distinguished MS centers, potentially introducing selection bias. Given the observational, cross-sectional design, identified associations cannot be interpreted as evidence of causality, and temporal relationships cannot be assessed.

The classification of BL-D into voiding dysfunction, bladder incontinence, and urinary urgency is consistent with the current DGN guideline,[15] but may not fully capture the underlying pathophysiological complexity. Incomplete bladder emptying due to voiding dysfunction can result in an increased residual volume, which can subsequently increase the risk of overflow incontinence and associated involuntary leakage,[40] indicating a clear classification into said subgroups can become challenging.

A key limitation of this study is the lack of standardized diagnostic procedures for BL-D, as the GMSR captures only final clinical documentation without access to the clinical decision-making process, diagnostic criteria, or objective assessments such as uroflowmetry. This limitation is compounded by the fact that relying on routine clinical documentation can lead to inconsistent reporting, underreporting of symptoms, and variability in data quality across MS centers. This is particularly relevant in the context of BL-D, where patient-reported symptoms may not be fully captured in physician-assessed measures. Misclassification bias is likely, with expected false positives and negatives, mainly due to underreporting. To minimize misclassification, only cases with a verified BL-D status (consistent across prior and last visits) were included.

The retrospective, registry-based design further limited the analysis to data already documented in the GMSR, rather than data that could be systematically collected to address specific research questions. Clinical topics not routinely documented in practice are often recorded with limited detail or only optionally in the GMSR. This applies to clinically relevant information in the assessment and management of BL-D such as pregnancy,[41] menopause status,[42] comorbidities, access to healthcare, the differentiation of specific symptomatic treatments (e.g., catheters or specific medications), and detailed functional assessments, especially bladder and bowel function as part of the EDSS score calculation. These restrictions introduced the potential for unmeasured confounding and may have affected the reliability of the results.

Given the multifactorial nature of BL-D, the observed prevalence may not be fully attributable to MS alone. Age is known to be a significant independent risk factor for BL-D, with prevalence increasing substantially in older adults.[26] Although age was accounted for in the analysis, a potential overestimation of the observed prevalence cannot be entirely ruled out. This limitation is further compounded by the fact that several other relevant factors were excluded from the multivariable analysis because of limited data availability. Conditions such as diabetes or benign prostatic hyperplasia can disrupt normal bladder function.[27,43] The lack of adjustment for comorbidities introduces the potential for residual confounding. Another critical consideration, often underrecognized as contributors to BL-D, is the presence of polypharmacy and medication-related side effects. Patients frequently require multiple medications to manage comorbidities and MS-related symptoms.[44] Medications such as alpha-blockers for the treatment of benign prostatic hyperplasia, oral estrogens for menopausal symptom management, and angiotensin-converting enzyme inhibitors for treating hypertension can increase the risk of BL-D.[45] The data presented in this study represent the most reliable and current evidence available on BL-Ds in the German MS population and are intended to provide a comprehensive understanding about associated factors and differences between subtypes. The large study population provides high statistical power and greater precision in estimates, increasing confidence in the findings.

Conclusion

The present study comprises one of the largest study populations of pwMS with BL-Ds. It also represents the first analysis of BL-D subtypes in Germany providing important insights for practical application and for overcoming barriers and knowledge gaps in this topic. Results showed that 38.0% of the pwMS studied experience BL-D. The most prevalent BL-D subtype was urinary urgency, although differences could be observed in relation to sex, age groups, and disease duration. The occurrence of BL-Ds in pwMS was associated with multiple clinical and sociodemographic factors such as female sex, older age, longer disease duration, progressive MS types, early retirement due to disability, part-time employment, no completed/ongoing educational training, more than one symptom at MS onset, and receiving DMT. Despite the apparent relevance of symptomatic BL-D in pwMS, the high proportion of patients (37.1%) not receiving a dedicated treatment for this condition raises concerns about the reasons behind this treatment gap. These findings highlight the need for a more differentiated understanding of BL-D in pwMS in order to bridge existing knowledge gaps, provide better and more personalized care, develop strategies to prevent stigma, and enable more transparent communication between physicians and patients. Longitudinal analyses and further research are recommended to clarify causality and explore unmeasured factors—such as the impact of pregnancy in women, quality of life, and the severity of BL-Ds or reasons for untreated

bladder symptoms in German pwMS. A key challenge for future research lies in addressing the discordance between patient-reported and physician-assessed disability. A patient may experience significant impairment due to BL-D, yet still have a low EDSS score, which reflects only the physician's clinical assessment and may lead to underestimation of symptom burden and treatment gaps in clinical practice.

Declarations

Ethics approval and consent to participate

The GMSR is registered in the German Register for Clinical Trials (Deutsches Register Klinischer Studien (DRKS); Number DRKS00011257). The initial ethics vote was approved by the Institutional Review Board of the University of Würzburg (Permit Number 142/12; approval date July 11, 2012). All participants provided written consent for the utilization of their anonymized data for research purposes. This study was conducted in accordance with the ethical standards and guidelines issued by the ethics committee listed above, the principles of the Helsinki Declaration of 1964 and its later amendments and the International Council for Harmonisation Good Clinical Practice (ICH-GCP) guidelines.

Consent for publication

Not applicable.

Author contributions

Mathia Kirstein: Conceptualization; Formal analysis; Methodology; Visualization; Writing – original draft; Writing – review & editing.

Niklas Frahm: Conceptualization; Methodology; Writing – review & editing.

David Ellenberger: Conceptualization; Formal analysis; Methodology; Writing – review & editing.

Alexander Stahmann: Conceptualization; Methodology; Supervision; Writing – review & editing.

Firas Fneish: Conceptualization; Formal analysis; Writing – review & editing.

Melanie Peters: Conceptualization; Writing – review & editing.

Friedemann Paul: Conceptualization; Writing – review & editing.

Clemens Warnke: Conceptualization; Writing – review & editing.

Kerstin Hellwig: Conceptualization; Writing – review & editing.

Peter Flachenecker: Conceptualization; Writing – review & editing.

Klaus Berger: Conceptualization; Writing – review & editing.

Michaela Mai: Conceptualization; Writing – review & editing.

Michael Hecker: Conceptualization; Formal analysis; Methodology; Writing – review & editing.

Uwe K. Zettl: Conceptualization; Methodology; Supervision; Writing – review & editing.

Acknowledgments

We would like to thank all the patients who gave their informed consent to the use of their data. Furthermore, this study would not have been possible without the efforts of the staff working at the centers participating in the GMSR.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The GMSR was established in 2001 by the German Multiple Sclerosis Society and the German Multiple Sclerosis Foundation and operated by the non-profit company MSFP. The MSFP receives funding from public and private sponsors, including the German MS Society, the German MS Foundation, the Innovation Fund of the German Federal Joint Committee, and the German Retirement Insurance. In 2025, Bristol Myers Squibb, Merck Healthcare Germany GmbH, Novartis Pharma GmbH, Roche Pharma AG, and TG Therapeutics/Neuraxpharm were participating in the multi-stakeholder funding approach to support the GMSR's operation and to allow the collection and reporting of (pharmacovigilance) data required as part of the EMA minimal data set. Industry funding does not result in restrictions to publishing data, nor do the funders have access to raw data or have any influence over the scientific conduct of the GMSR.

Competing interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: M.K., D.E., F.F., and M.P. had no personal financial interests to disclose other than being an employee of the GMSR. N.F. had no personal financial interests to disclose other than being an employee of the GMSR and of Rostock's University Medical Center. A.S. has no personal pecuniary interests to disclose, other than being the lead of the GMSR, which receives (project) funding from a range of public and corporate sponsors. F.P. received speaking fees, travel support, honoraria from advisory boards, and/or financial support for research activities from Bayer, Novartis, Biogen, Bristol Myers Squibb, Teva, Sanofi-Aventis/Genzyme, Merck Healthcare, Alexion, Chugai, MedImmune, Shire, German Research Council, Werth Stiftung of the City of Cologne, German Ministry of Education and Research, EU FP7 Framework Program, Arthur Arnstein Foundation Berlin, Guthy Jackson Charitable Foundation, and National Multiple Sclerosis of the USA. He serves as academic editor for *PLoS One* and associate editor for *Neurology, Neuroimmunology and Neuroinflammation*. C.W. received institutional support from Novartis, Alexion, Sanofi Genzyme, Biogen, Merck Healthcare, Janssen, Bayer, and Roche. He received personal honoraria for teaching lectures from Biontech, Medpoint Medizinkommunikations, F&U confirm, Privatinstitut für Klinikmanagement, The Royal College of Physicians, and for consulting from Wuesthoff + Wuesthoff and Bristows LLP. K.H. received speaking fees and/or institutional grant support from Bayer, Biogen, BMS, Merck Healthcare, Novartis, Roche, Sanofi-Genzyme, and Teva. P.F. received speaker's fees and honoraria for advisory boards from Almirall, Bayer, Biogen Idec, BMS-Celgene, Coloplast, Genzyme, GW Pharma, Hexal, Janssen-Cilag, Novartis, Merck Healthcare, Roche, Sanofi, Stadapharm, and Teva. K.B. received a grant from the German Ministry of Education and Research (within the German Competence Net Multiple Sclerosis) plus additional funds from Biogen, all to the University of Muenster for an investigator initiated adverse events register for patients with multiple sclerosis. M.M. is an employee of the German MS Society, federal association, which receives funding from a range of public and corporate sponsors, recently including BMG, BfArM, G-BA, The German MS Trust, BMS, Neuraxpharm, Merck, Novartis, Roche, Sandoz and Viatris. M.H. received speaking fees and travel funds from Bayer HealthCare, Biogen, Merck Healthcare, Novartis, and Teva. U.K.Z. received research support, speaking fees, and travel funds from Alexion, Almirall, Bayer HealthCare, Biogen, Bristol Myers Squibb, Janssen, Merck Healthcare, Novartis, Roche, Sanofi Genzyme, and Teva as well as the European Union, BMBF, BMWi, and DFG. None resulted in a conflict of interest.

Availability of data and materials

Anonymized data will be provided to qualified researchers under the GMSR's access policy, subject to patient consent and ethical review.

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Supplemental material

Supplemental material for this article is available online.

References

1. Lee Mortensen G and Rasmussen PV. The impact of quality of life on treatment preferences in multiple sclerosis patients. *Patient Prefer Adherence* 2017; 11: 1789–1796.
2. The Multiple Sclerosis International Federation (MSIF). *Atlas of MS*. 3rd ed., www.atlasofms.org (2020, accessed 25 August 2025).
3. Fox RJ, Bacon TE, Chamot E, et al. Prevalence of multiple sclerosis symptoms across lifespan: data from the NARCOMS Registry. *Neurodegener Dis Manag* 2015; 5: 3–10.
4. Rommer PS, Eichstädt K, Ellenberger D, et al. Symptomatology and symptomatic treatment in multiple sclerosis: results from a nationwide MS registry. *Mult Scler* 2019; 25: 1641–1652.
5. Al Dandan HB, Coote S and McClurg D. Prevalence of lower urinary tract symptoms in people with multiple sclerosis: a systematic review and meta-analysis. *Int J MS Care* 2020; 22: 91–99.
6. Goereci Y, Ellenberger D, Rommer P, et al. Persons with multiple sclerosis older than

55 years: an analysis from the German MS registry. *J Neurol* 2024; 271: 3409–3416.

7. Khalaf KM, Coyne KS, Globe DR, et al. The impact of lower urinary tract symptoms on health-related quality of life among patients with multiple sclerosis. *Neurourol Urodyn* 2016; 35: 48–54.
8. Medeiros Junior WLGD, Demore CC, Mazaro LP, et al. Urinary tract infection in patients with multiple sclerosis: an overview. *Mult Scler Relat Disord* 2020; 46: 102462.
9. Azadvari M, Emami Razavi SZ, Shahrooei M, et al. Bladder dysfunction in iranian patients with multiple sclerosis. *J Multidiscip Healthc* 2020; 13: 345–349.
10. Kisic Tepavcevic D, Pekmezovic T, Dujmovic Basuroski I, et al. Bladder dysfunction in multiple sclerosis: a 6-year follow-up study. *Acta Neurol Belg* 2017; 117: 83–90.
11. Rzepka M, Chmiela T, Kaczmarczyk A, et al. Insomnia, fatigue, bladder disorders and mood disorders among polish patients with multiple sclerosis: cross-sectional study. *J Clin Med* 2024; 13: 1043.
12. Seddone S, Marturano M, Bientinesi R, et al. Lower urinary tract disorders in multiple sclerosis patients: prevalence, clinical features, and response to treatments. *Neurourol Urodyn* 2021; 40: 1500–1508.
13. Nazari F, Shaygannejad V, Mohammadi Sichani M, et al. The prevalence of lower urinary tract symptoms based on individual and clinical parameters in patients with multiple sclerosis. *BMC Neurol* 2020; 20: 24.
14. Khalaf KM, Coyne KS, Globe DR, et al. Lower urinary tract symptom prevalence and management among patients with multiple sclerosis. *Int J MS Care* 2015; 17: 14–25.
15. Hemmer B. Diagnose und therapie der multiplen sklerose, neuromyelitis-optica-spektrum-erkrankungen und MOG-IgG-assoziierten Erkrankungen, S2k-Leitlinie, https://register.awmf.org/assets/guidelines/030-050l_S2k_Diagnose-Therapie-Multiple-Sklerose-Neuromyelitis-Optica-Spektrum-MOG-IgG-assoziierte-Erkrankungen_2024-01.pdf (2024, accessed 19 September 2025).
16. D'Ancona C, Haylen B, Oelke M, et al. The International Continence Society (ICS) report on the terminology for adult male lower urinary tract and pelvic floor symptoms and dysfunction. *Neurourol Urodyn* 2019; 38: 433–477.
17. Moris L, Heesakkers J, Nitti V, et al. Prevalence, diagnosis, and management of stress urinary incontinence in women: a collaborative review. *Eur Urol* 2025; 87: 292–301.
18. Rivera KC, Rickard M, Varghese A, et al. Bladder and bowel dysfunction: an updated guide for the pediatrician and pediatric nephrologist. *Curr Pediatr Rep* 2024; 12: 199–209.
19. Domurath B, Kurze I, Kirschner-Hermanns R, et al. Neurourological assessment in people with multiple sclerosis (MS): a new evaluated algorithm. *Mult Scler Relat Disord* 2020; 44: 102248.
20. Ohle L-M, Ellenberger D, Flachenecker P, et al. Chances and challenges of a long-term data repository in multiple sclerosis: 20th birthday of the German MS registry. *Sci Rep* 2021; 11: 13340.
21. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983; 33: 1444–1452.
22. Wickham H, Averick M, Bryan J, et al. Welcome to the Tidyverse. *J Open Source Softw* 2019; 4: 1686.
23. Carotenuto A, Costabile T, Moccia M, et al. Interplay between cognitive and bowel/bladder function in multiple sclerosis. *Int Neurourol J* 2021; 25: 310–318.
24. Lin SD, Butler JE, Boswell-Ruys CL, et al. The frequency of bowel and bladder problems in multiple sclerosis and its relation to fatigue: a single centre experience. *PLoS One* 2019; 14: e0222731.
25. Skierlo S, Rommer PS and Zettl UK. Symptomatic treatment in multiple sclerosis—interim analysis of a nationwide registry. *Acta Neurol Scand* 2017; 135: 394–399.
26. Hardy CC and Korstanje R. Aging and urinary control: alterations in the brain–bladder axis. *Aging Cell* 2023; 22: e13990.
27. Calogero AE, Burgio G, Condorelli RA, et al. Epidemiology and risk factors of lower urinary tract symptoms/benign prostatic hyperplasia and erectile dysfunction. *Aging Male* 2019; 22: 12–19.
28. Kaplan TB, Gopal A, Block VJ, et al. Challenges to longitudinal characterization of lower urinary tract dysfunction in multiple sclerosis. *Mult Scler Relat Disord* 2022; 62: 103793.
29. Mubaraki AA, Alnemari MA, Aljuaid SO, et al. The prevalence and impact of urinary incontinence on multiple sclerosis patients in Taif City, Saudi Arabia. *Cureus* 2024; 16: e57010.
30. Veauthier C, Radbruch H, Gaede G, et al. Fatigue in multiple sclerosis is closely related

to sleep disorders: a polysomnographic cross-sectional study. *Mult Scler* 2011; 17: 613–622.

31. Bhattarai JJ, Patel KS, Dunn KM, et al. Sleep disturbance and fatigue in multiple sclerosis: a systematic review and meta-analysis. *Mult Scler J Exp Transl Clin* 2023; 9: 20552173231194352.
32. Pokryszko-Dragan A, Nowakowska-Kotas M, Ciastoń R, et al. Vocational activity for patients with multiple sclerosis. *Neurol Neurochir Pol* 2022; 56: 435–440.
33. Salter A, Thomas N, Tyry T, et al. Employment and absenteeism in working-age persons with multiple sclerosis. *J Med Econ* 2017; 20: 493–502.
34. Akkoç Y, Ersöz M, Yüceyar N, et al. Overactive bladder symptoms in patients with multiple sclerosis: frequency, severity, diagnosis and treatment. *J Spinal Cord Med* 2016; 39: 229–233.
35. Grus C. Monitoring the relationship between overactive bladder and mobility disorders in women with multiple sclerosis. *Česka Gynekol* 2023; 88: 353–358.
36. El Moudane A, Chhita K, Jdaini A, et al. Overactive bladder and multiple sclerosis in the University Hospital of Oujda. *Afr J Urol* 2023; 29: 23.
37. Patel UJ, Godecker AL, Giles DL, et al. Updated prevalence of urinary incontinence in women: 2015–2018 national population-based survey data. *Female Pelvic Med Reconstr Surg* 2022; 28: 181–187.
38. Campetella M, Filomena G, Marino F, et al. Etiology, presentation and management of urinary tract infections in multiple sclerosis patients: a review of the current literature. *Urol J* 2024; 91: 384–393.
39. Batmani S, Jalali R, Mohammadi M, et al. Prevalence and factors related to urinary incontinence in older adults women worldwide: a comprehensive systematic review and meta-analysis of observational studies. *BMC Geriatr* 2021; 21: 212.
40. Ingram CF, Lincoln JA and Khavari R. Voiding phase dysfunction in multiple sclerosis. *Urol Clin North Am* 2024; 51: 177–185.
41. Vukusic S, Carra-Dalliere C, Ciron J, et al. Pregnancy and multiple sclerosis: 2022 recommendations from the French multiple sclerosis society. *Mult Scler* 2023; 29: 11–36.
42. Johnson KA, DuBose LE, Shah AA, et al. The impact of menopause in women with multiple sclerosis: a survey study. *Mult Scler Relat Disord* 2025; 99: 106485.
43. Adrian AE, Boucher NJ, McVary KT, et al. Mitochondrial dysfunction in urologic disease. *Prostate Cancer Prostatic Dis* Epub ahead of print 24 March 2026. DOI: 10.1038/s41391-026-01097-5.
44. Frahm N, Hecker M and Zettl UK. Polypharmacy in chronic neurological diseases: multiple sclerosis, dementia and Parkinson's disease. *Curr Pharm Des* 2021; 27: 4008–4016.
45. Yoshizawa S, Tachi T, Takahashi Y, et al. Impact of polypharmacy and risk factors for exacerbation of lower urinary tract symptoms in patients with urological conditions: a retrospective study in a Japanese Municipal Hospital. *Biol Pharm Bull* 2024; 47: 818–826.