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Antonios Bayas, K. Schuh, Monika Christ

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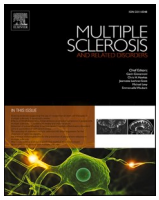

Original article

Self-assessment of people with relapsing-remitting and progressive multiple sclerosis towards burden of disease, progression, and treatment utilization—Results of a large-scale cross-sectional online survey (MS Perspectives)

A Bayas [a,*], K Schuh [b], M Christ [a]

[a] Department of Neurology, Faculty of Medicine, University of Augsburg, Augsburg, Germany
[b] Novartis Pharma GmbH, Nuremberg, Germany

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ABSTRACT

Background: Assessment of the disease course by people with multiple sclerosis (pwMS) themselves is important for a better understanding of the complex disease, patient counseling and treatment decisions. This may also facilitate identifying the often-unnoticed transition from relapsing-remitting (RRMS) to secondary progressive multiple sclerosis (SPMS).
Objective: MS Perspectives was designed to collect data on patients' self-assessment of multiple sclerosis (MS) symptoms, relapse-independent progression, and impact on everyday life.
Methods: MS Perspectives is a cross-sectional online survey conducted among adult pwMS in Germany. The questionnaire included 36 items on sociodemographic and clinical characteristics as well as pharmacological and non-pharmacological treatment.
Results: In total, 4555 pwMS completed the survey between December 2021 and February 2022, 69.2% had RRMS, 15.1% had SPMS. Relapse-independent worsening of symptoms was reported by 88.9% of RRMS patients with marked to severe and by 61.8% with no or mild to moderate disability. Problems with walking were most frequently (32.1%) mentioned as most bothersome by RRMS patients with marked to severe disability, fatigue, and cognitive impairment by RRMS patients with no or mild to moderate disability.
Conclusion: MS Perspectives gives an important insight in the self-assessed disease course and impact on daily life in a large-scale cohort of pwMS.

1. Introduction

Multiple sclerosis (MS) is a chronic immune-mediated disease of the central nervous system that involves inflammation, demyelination, and axonal or neuronal damage, potentially resulting in severe disability (Giovannoni et al., 2022; Hemmer et al., 2015). Approximately 85% of patients have relapsing-remitting MS (RRMS) at the beginning of the disease. Relapses are the main driver of disability progression in this phase (Katz Sand, 2015). RRMS may progress to secondary progressive MS (SPMS), which is characterized by a relapse-independent progression of disability. Without disease-modifying therapy (DMT) half of patients have progressed after 15 years and two third of patients after 30 years (Inojosa et al., 2021). Superimposed relapses can occur and are usually more frequent in the early SPMS phase and become less frequent over time (Casanova et al., 2002).

The most common MS symptoms include fatigue and walking difficulties, which, according to an analysis of the German MS Registry occur in about half of patients. One third reported spasticity and bladder disorders, and a quarter suffered from ataxia, tremor, cognitive disorders and pain (Flachenecker et al., 2020). These symptoms represent an enormous burden, leading to reduced quality of life and working ability (Flachenecker et al., 2020; Kobelt et al., 2017).

Discordant perception of the presence and severity of MS symptoms between healthcare professionals and people with multiple sclerosis (pwMS) may lead to an underestimation of symptom prevalence and relevance. Therefore, determining patients' perspectives is highly relevant for patient counseling and treatment decisions.

The present large cross-sectional survey "MS Perspectives" was

* Corresponding author.
E-mail address: antonios.bayas@uk-augsburg.de (A. Bayas).

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designed to collect data on patients' self-assessment of symptoms, the burden of the disease, disease progression, as well as the impact on daily activities. These data should help to better understand this complex disease adding to information by clinical routine examinations and patient reported outcomes (D'Amico et al., 2019; Filippi et al., 2020).

2. Patients and methods

2.1. Data collection

MS Perspectives is an online survey conducted in Germany between December 2021 and February 2022 through an online data collection tool hosted by Clinlife from Clariness. The survey included pwMS in Germany from the age of 18 years up. Participants were identified by the service provider Clariness through newsletters and targeted social media advertising in Germany. Details on social media targeting are available in the supplement.

The 36-item structured questionnaire is presented in Supplementary Table S1. Eligibility (age ≥18 years, living in Germany, MS diagnosis) was screened via opening questions, and eligible patients were offered to complete the full survey online. Data were handled confidentially, and anonymity of participants was secured throughout the study. The ethics committee of the Bavarian State Chamber of Medicine confirmed that due to the design of the survey with anonymity warranted an approval was not required.

In the current work, we focus on RRMS and SPMS subtypes and treatment use. Survey questions regarding magnetic resonance imaging (MRI), usage of devices to self-monitor health functions as well as the communication between pwMS and healthcare professionals will be analyzed and reported separately.

2.2. Statistics

Only patients answering all questions were included in the analysis. All data were analyzed descriptively. No formal statistical testing for group comparisons was performed. Categorical variables were summarized using frequency counts and percentages. Continuous variables were summarized as means including standard deviations (SD). Subgroup analyses involved comparisons by MS subtype as well as by disability status determined by Expanded Disability Status Scale (EDSS) and self-assessed disability status (no or mild to moderate disability: EDSS 0-3.5 *or* no / minimal / moderate disability [unrestricted walking distance]; marked to severe disability: EDSS 4-9.5 *or* walking distance restricted, but able to walk 500 m without assistance / able to walk 200 m without assistance / unilateral assistance required for 100 m / walking distance restricted up to 5 m, predominantly restricted to wheelchair / predominantly restricted to wheelchair, chair, or bed).

3. Results

In total, 4555 pwMS living in Germany completed the survey. Of these, 3151 (69.2%) reported to have RRMS, 690 (15.1%) reported to have SPMS, 330 (7.2%) reported to have primary progressive MS (PPMS). We are not aware, if participants reported their clinical phenotype based on their self-assessment (the question contained an explanation of the different phenotype characteristics) or on the assessment of their physician. 384 participants (8.4%) did not know their MS subtype.

Basic demographic characteristics and disease history of the total population as well as the RRMS and SPMS subgroups are shown in Table 1. Briefly, most patients in the total population (82.0%) and in the RRMS subpopulation (85.8%) were between 26 and 55 years of age. Age distribution shifted towards higher age in the SPMS population with the majority (88.1%) being between 36 and 65 years of age (Table 1). In the total population, 85.2% of patients were female, with a higher proportion in the RRMS (88.3%) than in the SPMS subgroup (78.0%) (Table 1).

Table 1
Basic characteristics for the total population and by MS subtype.

	Total *N*=4555	RRMS *N*=3151	SPMS *N*=690
Age, n (%)			
18-25	266 (5.8)	230 (7.3)	8 (1.2)
26-35	1,215 (26.7)	1,021 (32.4)	60 (8.7)
36-45	1,405 (30.8)	1,053 (33.4)	174 (25.2)
46-55	1,114 (24.5)	629 (20.0)	269 (39.0)
56-65	496 (10.9)	200 (6.3)	165 (23.9)
65+	59 (1.3)	18 (0.6)	14 (2.0)
Gender, n (%)			
Female	3,880 (85.2)	2,783 (88.3)	538 (78.0)
Male	669 (14.7)	363 (11.5)	152 (22.0)
Diverse	6 (0.1)	5 (0.2)	0 (0.0)
How long ago did your first MS symptoms start? n (%)			
<1 year	141 (3.1)	111 (3.5)	4 (0.6)
1-2 years	334 (7.3)	268 (8.5)	10 (1.4)
2-5 years	718 (15.8)	557 (17.7)	38 (5.5)
5-10 years	965 (21.2)	736 (23.4)	86 (12.5)
10-15 years	935 (20.5)	665 (21.1)	138 (20.0)
15-20 years	620 (13.6)	398 (12.6)	131 (19.0)
>20 years	842 (18.5)	416 (13.2)	283 (41.0)
How long ago was your MS diagnosed? n (%)			
<1 year	309 (6.8)	236 (7.5)	11 (1.6)
1-2 years	487 (10.7)	381 (12.1)	26 (3.8)
2-5 years	856 (18.8)	662 (21.0)	58 (8.4)
5-10 years	1,020 (22.4)	747 (23.7)	117 (17.0)
10-15 years	848 (18.6)	565 (17.9)	160 (23.2)
15-20 years	491 (10.8)	297 (9.4)	123 (17.8)
>20 years	544 (11.9)	263 (8.3)	195 (28.3)
How long have you had a diagnosis of secondary progressive MS (SPMS)? n (%)			
<1 year			99 (14.3)
1-2 years			113 (16.4)
2-5 years			180 (26.1)
5-10 years			138 (20.0)
10-15 years			88 (12.8)
15-20 years			40 (5.8)
>20 years			32 (4.6)

MS: multiple sclerosis; N: total number of patients in the population; n: number of patients in the category; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis.

3.1. Disability, symptom prevalence and severity

28.5% of pwMS were aware of EDSS being assessed during the last appointment with the neurologist, 26.3% in the RRMS subgroup, and 43.0% in the SPMS subgroup. About half of patients of each group remembered their EDSS score (Table 2). Mean (SD) EDSS was 3.8 (2.2) in the total population, 2.8 (1.8) in the RRMS population, and 5.7 (1.6) in the SPMS population. Participants who could not report their EDSS score were asked to self-assess their disability status instead (Table 2 and Fig. 1). According to either EDSS score or self-assessment, 72.3% of patients of the total population were classified as having no or mild to moderate disability, and 27.7% of patients were classified as having marked to severe disability (Table 2). The distribution in the RRMS subgroup was quite similar (85.4% vs. 14.6%), whereas in the SPMS subgroup, most patients had marked to severe disability (30.0% vs. 70.0%) (Table 2).

We found a two-fold higher impact of the disease on impairment in daily activities in SPMS patients compared to RRMS. While 8.1% to 38.0% of RRMS patients reported moderate to severe impairment or complete loss of independence in daily activities assessed, in SPMS patients this was more prevalent with 45.7% to 77.7%. Marked differences regarding moderate and severe impairment or complete loss of independence were observed e.g., in mobility (28.3% in RRMS vs. 77.7% in SPMS), work ability (34.8% vs. 68.3%), and hobbies or leisure activities (32.8% vs. 69.1%), which are the most strongly impaired activities among SPMS patients (Fig. 2). The pattern of impaired areas was rather similar in RRMS and SPMS patients with the same disability status (**Supplementary Fig. 1**). 22.5% of the total population reported to have

Table 2
Disability status in the total population and by MS subtype.

	Total N=4555	RRMS N=3151	SPMS N=690
Was the EDSS score assessed during your last visit? n (%)			
No	3,257 (71.5)	2,323 (73.7)	393 (57.0)
Yes	1,298 (28.5)	828 (26.3)	297 (43.0)
Do you know what the EDSS score was at your last visit? n (%)			
My doctor told me, but I cannot remember	403 (8.8)	248 (7.9)	94 (13.6)
My doctor did not tell me	282 (6.2)	188 (6.0)	51 (7.4)
Yes, I know my score	613 (13.5)	392 (12.4)	152 (22.0)
Please indicate what the EDSS score was at your last visit[a] n (%)			
0-3.5	313 (6.9)	277 (8.8)	21 (3.0)
4-9.5	300 (6.6)	115 (3.6)	131 (19.0)
How would you yourself describe the severity of your MS? n (%)			
Self-assessed no or mild to moderate disability	**2,980 (65.4)**	**2,413 (76.6)**	**186 (27.0)**
No disability	1,012 (25.7)	858 (27.2)	19 (2.8)
Minimal disability	972 (24.7)	811 (25.7)	48 (7.0)
Moderate disability (unrestricted walking distance)	996 (25.3)	744 (23.6)	119 (17.2)
Self-assessed marked to severe disability	**962 (21.1)**	**346 (11.0)**	**352 (51.0)**
Walking distance restricted, but able to walk 500 m without assistance	329 (8.3)	179 (5.7)	85 (12.3)
Walking distance restricted, but able to walk 200 m without assistance	162 (4.1)	70 (2.2)	60 (8.7)
Unilateral assistance required for 100 m	232 (5.9)	57 (1.8)	96 (13.9)
Walking distance restricted up to 5 m, predominantly restricted to wheelchair	148 (3.8)	27 (0.9)	72 (10.4)
Predominantly restricted to wheelchair, chair, or bed	91 (2.3)	13 (0.4)	39 (5.7)
Disability status by EDSS and self-assessment.			
No or mild to moderate disability[b]	3,293 (72.3)	2,690 (85.4)	207 (30.0)
Marked to severe disability[c]	1,262 (27.7)	461 (14.6)	483 (70.0)

EDSS: Expanded Disability Status Scale; MS: multiple sclerosis; N: total number of patients in the population; n: number of patients in the category; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis.

[a] Patients reported exact EDSS scores; results are presented by category.

[b] Patients with EDSS 0-3.5 AND patients with self-assessed no or mild to moderate disability.

[c] Patients with EDSS 4-9.5 AND patients with self-assessed marked to severe disability

retired prematurely, with differences in proportions by MS subtype and disability status (RRMS with no or mild to moderate disability vs. marked to severe disability: 9.5% vs. 46.4%; SPMS with no or mild to moderate disability vs. marked to severe disability: 30.0% vs. 58.8%) (**Supplementary Fig. 2**).

The most bothersome symptoms in both RRMS and SPMS patients with marked to severe disability were problems with walking and moving. They were less pronounced in patients with lower disability status, but in this subgroup more than twice as frequent in SPMS (17.9%) than in RRMS (6.8%). In contrast, fatigue, cognitive impairment (problems with concentration and remembering), vision impairment, as well as numbness or tingling were more frequent in RRMS and SPMS patients with lower disability status compared to higher disability status. Among these symptoms, fatigue (31.4% vs. 21.7%), vision impairment (13.9% vs. 8.7%) and numbness or tingling (9.7% vs. 5.3%) were more bothersome for RRMS than SPMS patients (Fig. 3).

3.2. Relapses and disability progression

Active MS, here defined as the presence of relapse activity in the past 6 months, was reported by 26.9% of the total population, 25.6% of RRMS patients, and 35.9% of SPMS patients. Relapse activity was lower in RRMS patients with no or mild to moderate disability compared to patients with marked to severe disability (24.1% vs. 34.9%). In SPMS patients, relapse activity did not differ substantially between patients with no or mild to moderate disability and marked to severe disability (36.7% vs. 35.6%) (**Supplementary Fig. 3**).

Complete recovery from their last relapse was achieved in 23.0% of all patients with active MS, in 31.1% of patients with active RRMS, and in 4.8% of patients with active SPMS. Higher disability was associated with higher frequency of residual symptoms after the last relapse (**Supplementary Fig. 4**). Of interest, of 638 RRMS patients with continuous relapse-independent progression in the last 12 months and relapse activity in the past 6 months, only 157 patients (24.6%) reported complete recovery from their last relapse. Complete, or almost complete recovery from last relapse was much higher in active RRMS with relapse-independent progression than in active SPMS (62.7% vs. 28.2%) (**Supplementary Fig. 4**).

2,073 RRMS patients (65.8%) reported continuous worsening of symptoms independent of relapses in the previous 12 months, 88.9% of RRMS patients with marked to severe disability, and 61.8% of RRMS patients with no or mild to moderate disability (Fig. 4). Among all SPMS patients, continuous relapse-independent progression within the previous 12 months was reported by 92.9% irrespective of the extent of disability (Fig. 4).

The most common symptoms affected by relapse-independent worsening within the last 12 months in RRMS with marked to severe disability were problems with walking in 54.4% of patients, and fatigue in 49.7%. In RRMS with no or mild to moderate disability, fatigue prevailed in 33.9% and cognitive deficits in 21.3% of pwMS. In SPMS with marked to severe disability the most common symptoms worsening independently of relapses were problems with walking (73.5%), and problems with coordination and balance (44.5%) (Fig. 5). For subgroups, most bothersome symptoms are shown in **Supplementary Fig. 5**.

3.3. Treatment

3.3.1. Immunotherapy

24.4% of RRMS and 43.5% of SPMS patients did not receive any DMT (Fig. 6) with the proportion of patients without DMT being slightly higher in active SPMS (defined by relapse activity in the past 6 months) than in non-active SPMS patients (active SPMS 47.2%, non-active SPMS 41.4%) (Fig. 7). The reasons for which patients remained without DMT were not queried. Among patients with continuous relapse-independent progression within the last 12 months, the proportions of patients receiving DMTs did not differ by presence or absence of relapse activity in the previous 6 months **(Supplementary Fig. 6).** Oral medications were the more frequent DMTs used in RRMS and SPMS patients, being more common in RRMS patients (Fig. 6). Oral DMTs were most prevalent in both active and non-active SPMS (Fig. 7). Most of the patients who received immunotherapy had been taking the current medication for one year or longer (Table 3). Steroid use was not part of the survey.

3.3.2. Symptomatic treatment

Overall, 36.9% of patients received pharmacological treatment to ease MS symptoms (30.5% of RRMS patients and 61.7% of SPMS patients), details are described in **Supplementary Table 2**. Of note, pwMS receiving DMT also had more often symptomatic pharmacological therapy than pwMS without DMT, irrespective of MS subtype and disability status (**Supplementary Fig. 7**). Non-pharmacological symptomatic treatment was more common in patients with marked to severe disability than in patients with no or mild to moderate disability (57.3% vs. 28.7%), details are shown in **Supplementary Fig. 8.**

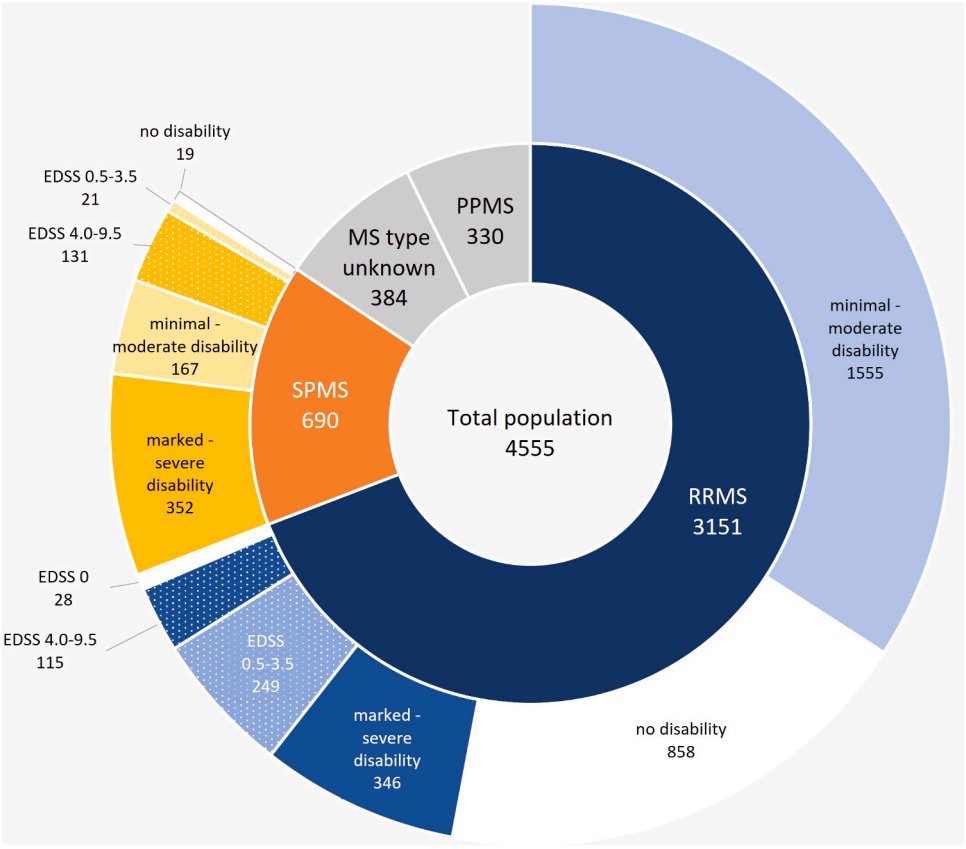

Fig. 1. MS subtypes and EDSS / disability status; figures in segments represent absolute patient numbers. Disability not indicated for unknown MS type and PPMS.

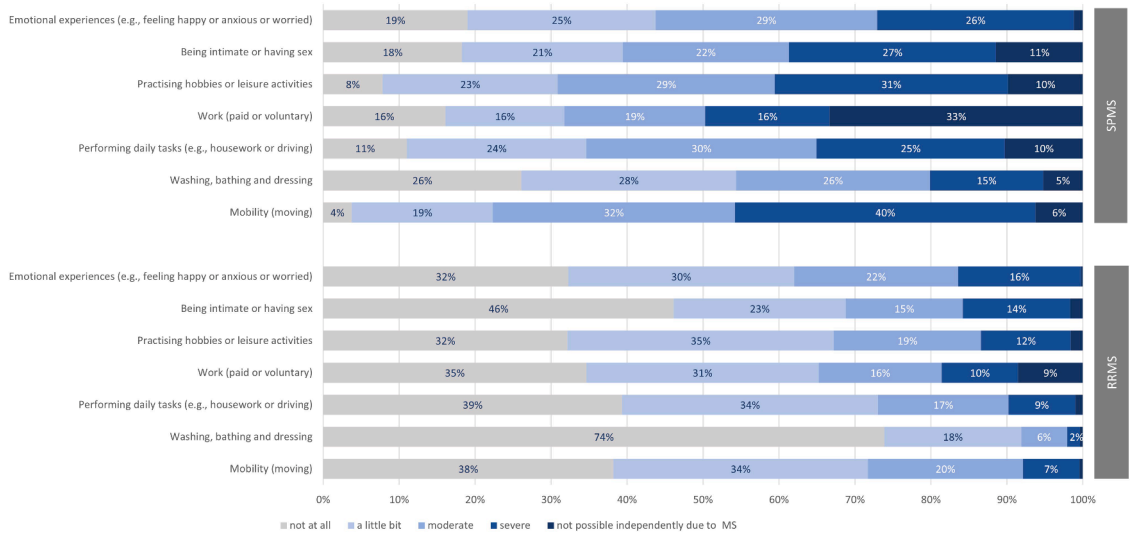

Fig. 2. Impairment in activities of daily living by MS type.

4. Discussion

MS Perspectives represents a large-scale cross-sectional study, here we report patient perceived symptoms, disease activity, burden of disease and treatment utilization.

Regarding participants' characteristics, 69.2% had an RRMS and 15.1% reported an SPMS disease course. Of all pwMS, 85.2% were female, 82% were in the age range of 26 to 55 years with the majority between 36 and 45 years of age. Disease duration between 5 and 15 years was reported by 41.7% of patients. Where reported, mean EDSS was 3.8 in the total population, 2.8 in the RRMS population, and 5.7 in the SPMS population. In an updated analysis of the German MS Registry (years 2014–2018) with data of 18,030 pwMS, 74.2% had a relapsing and 16.1% an SPMS disease course. Mean age was 46.3 (± 12.2, SD) with most patients between the age of 31 and 61 years, 72% were female. Mean disease duration was 10.6 (± 8.7, SD) years, median EDSS in this cohort was 3.0 (Flachenecker et al., 2020). According to statutory health insurance data (in the year 2010) in Germany, with data of 199, 505 pwMS (for analysis of disease type 125,453 pwMS with clear diagnosis assessed), 70.5% had a relapsing and 14% an SPMS disease

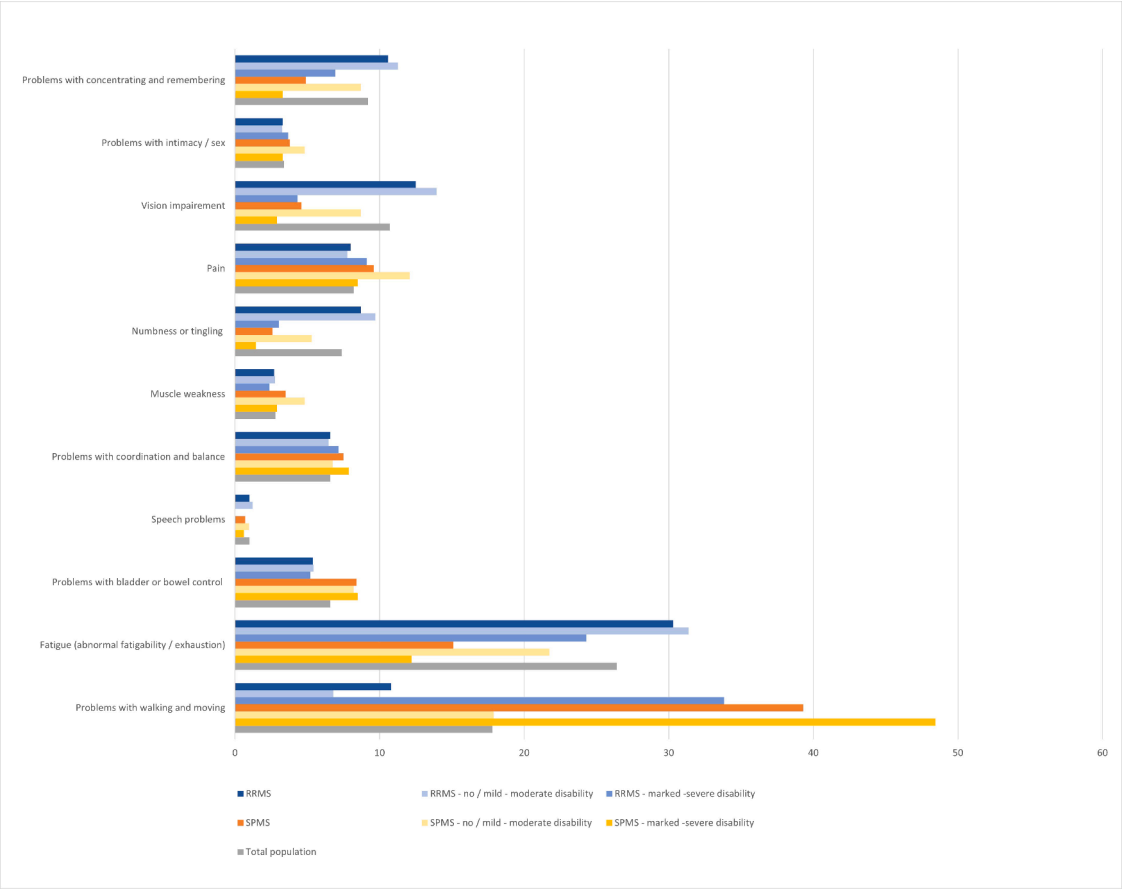

Fig. 3. Most bothersome symptom by MS type and disability status.

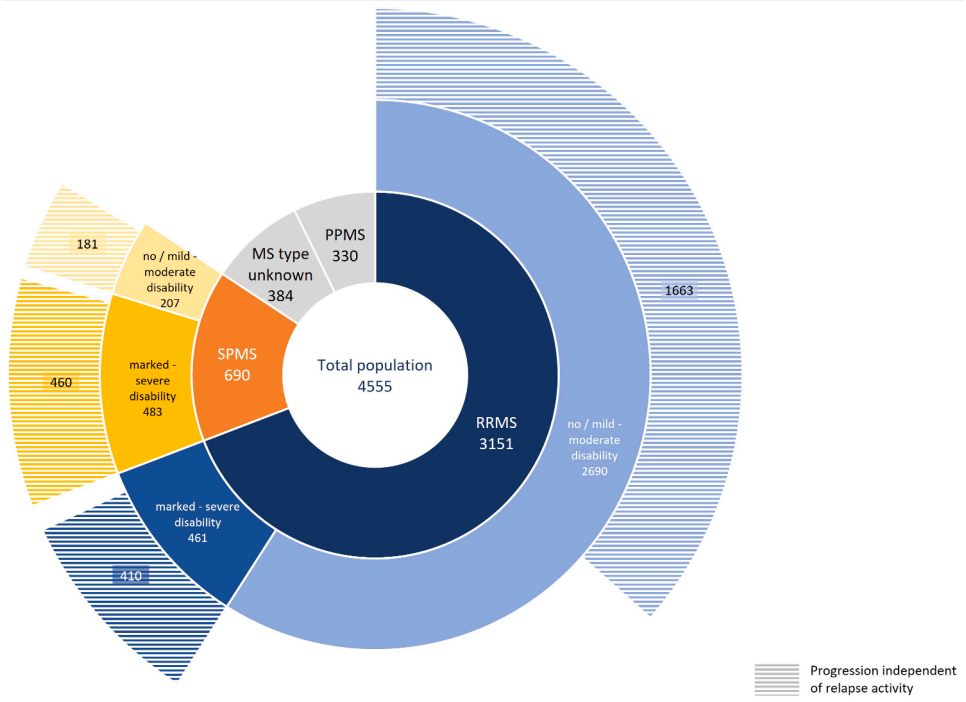

Fig. 4. Presence of progression independent of relapse activity in last 12 months by MS type and disability status; figures in segments represent absolute patient numbers. Disability not indicated for unknown MS type and PPMS.

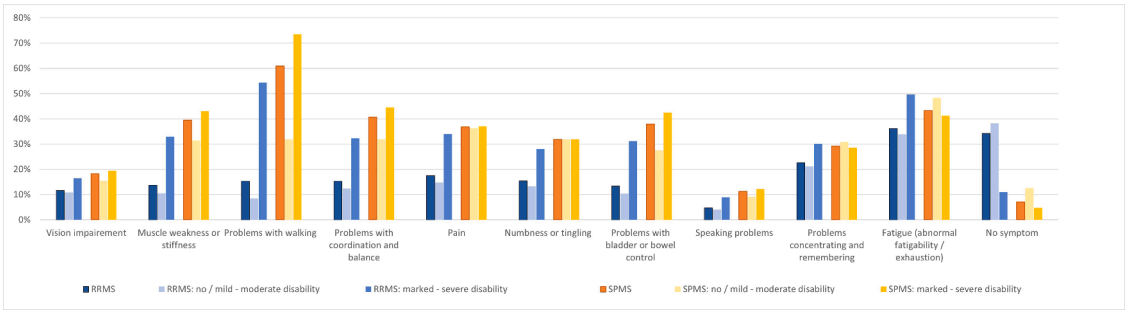

Fig. 5. Symptom progression independent of relapse activity in the past 12 months by MS type and disability status.

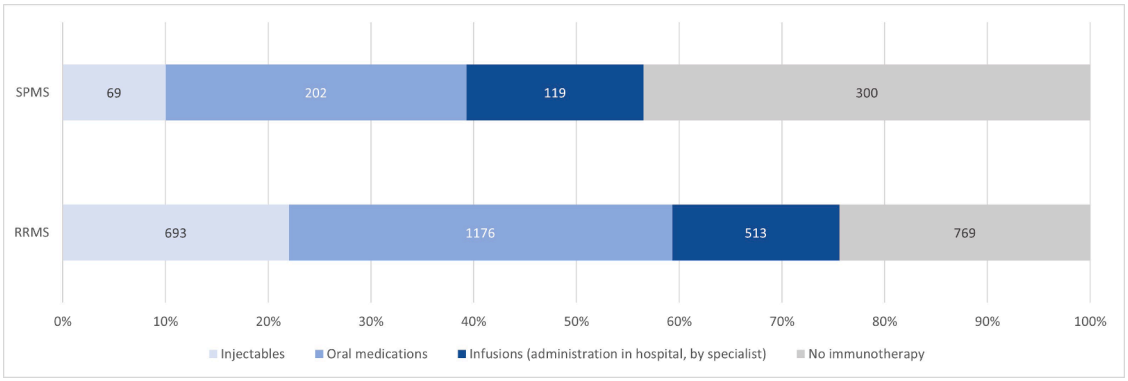

Fig. 6. Immunotherapy by MS type; figures in bars represent absolute patient numbers.

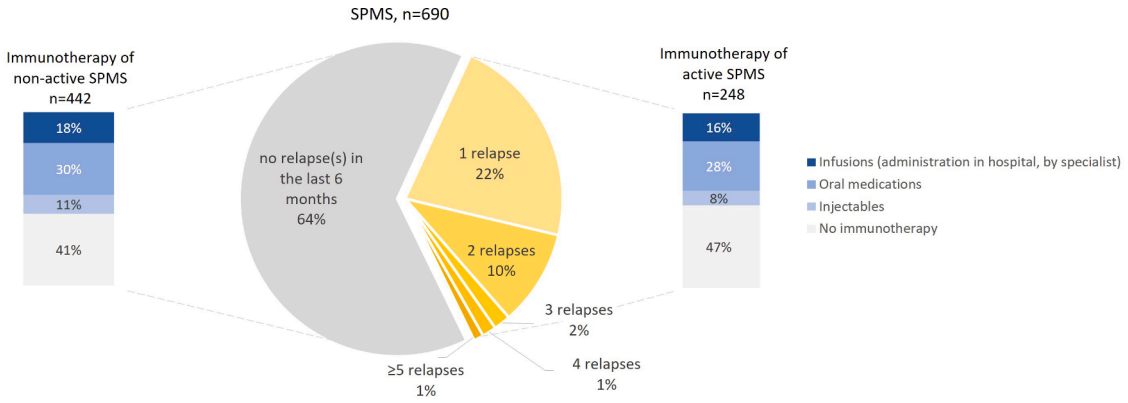

Fig. 7. Immunotherapy in active (relapse in the last 6 months) versus non-active SPMS.

course (Flachenecker et al., 2020; Petersen et al., 2014). Mean age was 49.4 years (Petersen et al., 2014). Thus, comparing patient characteristics in our online survey herewith shows that in our study baseline characteristics seem to be highly representative for the MS population in Germany strengthening the findings in our study. This also makes obvious that an online survey as presented has not only the potential to gather representative, but also large-scale data, in our study from 4555 pwMS. Thus, an online survey as used in our study may serve as an additional source of important information assessed by patients themselves making a tool like this appropriate also for other research questions in different disorders.

Overall, patients with RRMS were younger, had less disability, and shorter disease duration than SPMS patients. This is as expected, as it is consistent with the natural history of the disease (Inojosa et al., 2021). However, a relevant proportion of RRMS patients also showed longer disease duration and accumulated disability. In the nationwide MS registry in Germany, fatigue was the most frequently reported symptom (57.6%) in RRMS patients, while in SPMS this was spasticity (81.9%) (Rommer et al., 2019). In our survey we did not investigate symptom prevalence, but occurrence in the last 6 months and most bothersome symptoms, what we regard as a strength in our study. In the total RRMS subgroup, 50.5% of participants reported fatigue occurring within the last 6 months, similar to the study by Rommer et al. (Rommer et al., 2019), and fatigue was the most frequently occurring, most bothersome symptom in 30.3% of RRMS patients (15.1% in SPMS) clearly indicating the burden of this symptom. Spasticity was not separately evaluated, however, in SPMS, gait problems occurred in 56.2% of pwMS within the last 6 months, and motor weakness and stiffness in 52.6%. Symptoms affecting mobility were judged as most bothersome and were the most frequently reported symptoms in 39.3% in the total SPMS cohort compared to 10.8% in the RRMS cohort. As expected, impairment in daily activities was approximately two-fold higher in SPMS patients compared to RRMS. Mobility, hobbies or leisure activities, and work ability were the most strongly impaired activities (moderate / severe /

Table 3
Treatment (total and by MS subtype).

	Total *N*=4555	RRMS *N*=3151	SPMS *N*=690
How long have you been taking the current medication (immunotherapy)[a]? n (%)			
<6 months	422 (9.3)	324 (10.3)	51 (7.4)
6-12 months	442 (9.7)	353 (11.2)	52 (7.5)
1-2 years	640 (14.1)	486 (15.4)	66 (9.6)
2-5 years	904 (19.8)	685 (21.7)	113 (16.4)
>5 years	739 (16.2)	534 (16.9)	108 (15.7)

DMT: disease-modifying therapy; i.m.: intramuscular; N: total number of patients in the population; n: number of patients in the category; RRMS: relapsing-remitting multiple sclerosis; s.c.: subcutaneous; SPMS: secondary progressive multiple sclerosis.

[a] Approved DMTs at the time of the survey: alemtuzumab, cladribine, dimethyl fumarate, diroximel fumarate, fingolimod, glatiramer acetate, interferon-beta 1a s.c., interferon-beta 1a i.m., interferon-beta 1b s.c., mitoxantrone, natalizumab, ocrelizumab, ofatumumab, ozanimod, peginterferon-beta 1a s.c./i.m., ponesimod, siponimod, teriflunomide.

not possible independently) among SPMS patients. In RRMS these were emotional experiences, work ability and hobbies or leisure activities. In the study by Rommer et al. (2019), 24.7% of patients had prematurely retired from work due to MS, in our total population this was similar with 22.5%. RRMS patients with marked to severe disability showed a similar pattern regarding impairment in their daily activities like SPMS patients. The most bothersome symptoms in these subgroups were related to mobility.

Surprisingly, continuous worsening of symptoms independent of relapses in the previous 12 months was reported by the vast majority (88.9%) of RRMS patients with marked to severe disability and over half of patients with no or mild to moderate disability. In our survey, we selected a period of 12 months since this may fulfil the definition for SPMS (Hemmer, 2021; Plantone et al., 2016). The most common symptoms affected by relapse-independent worsening within the last 12 months in RRMS with marked to severe disability, were, in descending order, gait problems, fatigue, pain, vegetative dysfunction and cognitive deficits in one third to half of patients. In RRMS with no or mild to moderate disability, fatigue and cognitive deficits prevailed. Given that a deterioration over 12 months may indicate transition to SPMS, based on our data, non or less visible symptoms like fatigue, cognitive decline or vegetative function deserve closer monitoring in clinical practice. A higher degree of disability (EDSS $\geq$4.0) is part of the diagnostic criteria for SPMS proposed by Lorscheider et al. (2016)) and has been used as a proxy for SPMS in analyses of relapsing MS studies (Giovannoni et al., 2010; Kappos et al., 2020). Thus, the present data at least suggests that in a relevant proportion of RRMS patients, above all, but not only with marked to severe disability, a transition to SPMS may have already occurred but had not been recognized by the patient or healthcare professional. This may be related to the fact that SPMS is often diagnosed retrospectively and delayed by up to 3 years after a period of diagnostic uncertainty (Katz Sand et al., 2014).

The question, if participants reporting continuous worsening of symptoms, had progression independent of relapse activity (PIRA) or transitioned to SPMS remains open. PIRA rates have been reported to be as high as 27.6% in RRMS/clinically isolated syndrome to 50% in RRMS (Masanneck et al., 2022; Portaccio et al., 2022). In studies investigating PIRA, a definition has been provided for it (Kappos et al., 2020; Masanneck et al., 2022; Portaccio et al., 2022). Due to the nature of our study, no such criteria were applied in our survey and no follow-up assessments for the evaluation of confirmed disability accumulation were established. This also applies to the potential transition to SPMS. Nevertheless, the high proportion of patients reporting continuous worsening of symptoms over months should be acknowledged. In clinical practice, these patients deserve special attention, and it should regularly be assessed, whether they fulfil the criteria for PIRA or SPMS.

The difficulty distinguishing between relapse-independent progression and relapse-related deterioration may be one reason that SPMS transition is frequently underrecognized (Cree et al., 2021; Inojosa et al., 2021). Especially in the early phase, SPMS can present with superimposed relapses (Casanova et al., 2002). This is also seen in our cohort. In the present survey, relapses were defined as new or worsened symptoms in the last 6 months independent of infections or vaccinations. It is possible that deterioration in this period rather resulted from chronic progression than from relapse activity in several pwMS. It is surprising that the relapse rate was higher in SPMS (35.9%) than RRMS (25.6%). We cannot exclude that in addition to physician-confirmed relapses, symptom fluctuations were reported. Due to the higher symptom burden in SPMS patients this may have contributed to a higher rate of reported active SPMS than expected from a well characterized SPMS population (Kappos et al., 2018).

The results of the survey indicate that patients perceive relapse-independent worsening of symptoms, what we rate as a surrogate of chronic progression. The rates of symptom worsening independent of relapses has been impacted by the fact, that fatigue among others was included as a potential progression-determining symptom. However, fatigue alone should not determine relapse-independent progression. Due to the nature of the data and the multiple answers option to the question on relapse-independent symptom worsening, it is not possible to calculate worsening rates excluding fatigue. However, fatigue was reported to have worsened independently of relapses by 36.2% of RRMS and 43.3% of SPMS patients and therefore has contributed relevantly. To which extent it has effectively been contributing to the progression rate as single symptom cannot be assessed. Nevertheless, it may be hypothesized that diagnosing SPMS too late might rather be attributable to insufficient attention towards transition to SPMS with superimposed relapses. However, these subtle changes experienced by patients are often difficult to communicate or to assess during neurological examination. Special education for patients and health care providers might help to overcome these issues (O'Loughlin et al., 2017). The RRMS classification of those patients eventually already transitioned to SPMS may however also be related to the fact that many neurologists hesitate to diagnose SPMS due to the limited number of approved DMTs for this disease course despite recent advances.

Diagnosis of transition to SPMS is a prerequisite to adapt DMTs accordingly. Surprisingly, around half of SPMS patients were not receiving DMTs with active SPMS patients prevailing (total SPMS 43.5%; active SPMS 47.2%, non-active SPMS 41.4%; in comparison: RRMS 24.4%). Overall, the results of MS Perspectives on treatment rates are well within the line of published literature data. Accordingly, data from a Swiss MS Registry and a German National MS Cohort revealed that 20.8 to 32.2% of RRMS patients are untreated (Bossart et al., 2022; von Bismarck et al., 2018). Among SPMS patients in a German MS registry cohort, 48.1% were reported not to receive any DMT (Flachenecker et al., 2019). US claims data revealed an even higher proportion (63.6%) of pwMS without DMT (Zhu et al., 2022). Regarding the predominance of non-active SPMS patients receiving DMTs, it may be speculated that this is explained by the reduced relapse rate under immunotherapy. MS guidelines distinguish between active and non-active SPMS in their recommendations (Hemmer, 2021; Montalban et al., 2018), and nowadays, numerous DMTs are approved for active SPMS. The treatment landscape at least allows DMTs for the majority of active SPMS patients in contrast to non-active disease, with no MRI or relapse activity (Hemmer, 2021). Our data suggest that treatment was not initiated as required in a number of active SPMS cases.

Furthermore, our study showed that patients without DMT were less likely to receive pharmacological symptomatic therapy regardless of the disease course and severity of disability. Based on this, it may be hypothesized that some patients generally lack adequate therapeutic care, either based on patient's decision or inadequate or limited access to neurological care. According to a French population-based study, a visit to a neurologist increased the probability of being treated (Leblanc et al.,

2021). Furthermore, assessing the need for non-pharmacological treatment by evaluation of (potential) MS symptoms could significantly facilitate the early identification of chronic progression (Penner et al., 2021).

Despite analyzing data from a large and representative MS cohort in Germany, the present survey has some limitations. First, no validated questionnaire was used, and second, no formal hypothesis testing was applied. The results therefore need to be interpreted with caution and need to be considered rather hypothesis-generating than confirming. Third, web-based medical surveys are prone to a participation bias with higher level of education and better health state among the respondents compared to non-respondents (Arafa et al., 2019). Participants with higher disease awareness might be overrepresented as only responders who answered all questions were included. Survey participation of patients was not encouraged by incentives. Finally, another limitation of the study is that findings, e.g., the extent of progression, were not correlated with history taking or clinical testing by neurologists and that no MRI data were available. These aspects, however, were incompatible with the anonymous nature of the survey.

The present data show that an online survey in a representative MS cohort is an appropriate tool to gain valuable insights into the patient perceived disease course. In the present cohort with over 4,500 pwMS, which is a representative MS cohort, it became obvious that in RRMS patients with less disability, fatigue and vision impairment were the most frequent bothersome symptoms, whereas SPMS patients reported pain, walking difficulties and fatigue as most frequent. We suggest that especially the presence and severity of these frequent bothersome symptoms should be queried in daily clinical practice to identify potential therapeutic needs. With 65.8% of patients with RRMS reporting relapse-independent deterioration according to our survey, the challenge in clinical practice will be to confirm progression and, if so, to identify SPMS in order to make appropriate treatment decisions. As symptomatic pharmacological therapy was more prevalent in immunotherapy users, the indication of symptomatic therapies should also be monitored in patients who are not or no longer receiving immunotherapy.

CRediT authorship contribution statement

A Bayas: Conceptualization, Methodology, Data curation, Formal analysis, Visualization, Writing – original draft. **K Schuh:** Conceptualization, Methodology, Data curation, Funding acquisition, Project administration, Writing – review & editing. **M Christ:** Conceptualization, Formal analysis, Data curation, Visualization, Writing – review & editing.

Declaration of Competing Interest

Antonios Bayas received personal compensation from Merck Serono, Biogen, Novartis, TEVA, Roche, Sanofi/Genzyme and Celgene/Bristol Myers Squibb, Janssen, Sandoz/HEXAL. He received grants for congress travel and participation from Biogen, TEVA, Novartis, Sanofi/Genzyme, Merck Serono, and Celgene. None related to this manuscript.

Katrin Schuh is employee of Novartis Pharma GmbH.

Monika Christ declares that there is no conflict of interest.

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Supplementary materials

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References

Arafa, A.E., Anzengruber, F., Mostafa, A.M., Navarini, A.A., 2019. Perspectives of online surveys in dermatology. J. Eur. Acad. Dermatol. Venereol. 33 (3), 511–520.

Bossart, J., Kamm, C.P., Kaufmann, M., Stanikic, M., Puhan, M.A., Kesselring, J., Zecca, C., Gobbi, C., Rapold, I., Kurmann, R., Ammann, S., von Wyl, V., Swiss Multiple Sclerosis, R., 2022. Real-world disease-modifying therapy usage in persons with relapsing-remitting multiple sclerosis: cross-sectional data from the Swiss Multiple Sclerosis Registry. Mult. Scler. Relat. Disord. 60, 103706.

Casanova, B., Coret, F., Valero, C., Landete, L., Pascual, A., Vilchez, J.J., 2002. High clinical inflammatory activity prior to the development of secondary progression: a prospective 5-year follow-up study. Mult. Scler. 8 (1), 59–63.

Cree, B.A.C., Arnold, D.L., Chataway, J., Chitnis, T., Fox, R.J., Pozo Ramajo, A., Murphy, N., Lassmann, H., 2021. Secondary progressive multiple sclerosis: new insights. Neurology 97 (8), 378–388.

D'Amico, E., Haase, R., Ziemssen, T., 2019. Review: Patient-reported outcomes in multiple sclerosis care. Mult. Scler. Relat. Disord. 33, 61–66.

Filippi, M., Preziosa, P., Langdon, D., Lassmann, H., Paul, F., Rovira, A., Schoonheim, M. M., Solari, A., Stankoff, B., Rocca, M.A., 2020. Identifying progression in multiple sclerosis: new Perspectives. Ann. Neurol. Sep;88(3), 438–452. https://doi.org/10.1002/ana.25808.

Flachenecker, P., Eichstadt, K., Berger, K., Ellenberger, D., Friede, T., Haas, J., Kleinschnitz, C., Pohlau, D., Rienhoff, O., Stahmann, A., Zettl, U.K., 2020. Multiple sclerosis in Germany: updated analysis of the German MS Registry 2014-2018. Fortschr. Neurol. Psychiatr. 88 (7), 436–450.

Flachenecker, P., Eichstadt, K., Berger, K., Ellenberger, D., Friede, T., Kleinschnitz, C., Poehlau, D., Rienhoff, O., Stahmann, A., Zettl, U.K., 2019. Progrediente multiple Sklerose: aktuelle Erkenntnisse aus dem MS-Register der DMSG. Neuro Aktuell 2019 (4), 7–11.

Giovannoni, G., Comi, G., Cook, S., Rammohan, K., Rieckmann, P., Soelberg Sorensen, P., Vermersch, P., Chang, P., Hamlett, A., Musch, B., Greenberg, S.J., Group, C.S., 2010. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. N. Engl. J. Med. 362 (5), 416–426.

Giovannoni, G., Popescu, V., Wuerfel, J., Hellwig, K., Iacobeus, E., Jensen, M.B., Garcia-Dominguez, J.M., Sousa, L., De Rossi, N., Hupperts, R., Fenu, G., Bodini, B., Kuusisto, H.M., Stankoff, B., Lycke, J., Airas, L., Granziera, C., Scalfari, A., 2022. Smouldering multiple sclerosis: the 'real MS'. Ther. Adv. Neurol. Disord. 15, 17562864211066751.

Hemmer, B., 2021. Diagnose und Therapie der Multiplen Sklerose, Neuromyelitis-optica-spektrum-Erkrankungen und MOG-IgG-assoziierten Erkrankungen, S2k-Leitlinie. www.dgn.org/leitlinien. (Accessed 05 February 2022).

Hemmer, B., Kerschensteiner, M., Korn, T., 2015. Role of the innate and adaptive immune responses in the course of multiple sclerosis. Lancet Neurol. 14 (4), 406–419.

Inojosa, H., Proschmann, U., Akgun, K., Ziemssen, T., 2021. A focus on secondary progressive multiple sclerosis (SPMS): challenges in diagnosis and definition. J. Neurol. 268 (4), 1210–1221.

Kappos, L., Bar-Or, A., Cree, B.A.C., Fox, R.J., Giovannoni, G., Gold, R., Vermersch, P., Arnold, D.L., Arnould, S., Scherz, T., Wolf, C., Wallstrom, E., Dahlke, F., Investigators, E.C., 2018. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. Erratum Lancet 392, 2170.

Kappos, L., Wolinsky, J.S., Giovannoni, G., Arnold, D.L., Wang, Q., Bernasconi, C., Model, F., Koendgen, H., Manfrini, M., Belachew, S., Hauser, S.L., 2020. Contribution of relapse-independent progression vs relapse-associated worsening to overall confirmed disability accumulation in typical relapsing multiple sclerosis in a pooled analysis of 2 randomized clinical trials. JAMA Neurol. 77 (9), 1132–1140.

Katz Sand, I., 2015. Classification, diagnosis, and differential diagnosis of multiple sclerosis. Curr. Opin. Neurol. 28 (3), 193–205.

Katz Sand, I., Krieger, S., Farrell, C., Miller, A.E., 2014. Diagnostic uncertainty during the transition to secondary progressive multiple sclerosis. Mult. Scler. 20 (12), 1654–1657.

Kobelt, G., Thompson, A., Berg, J., Gannedahl, M., Eriksson, J., MSCOI Study Group, European Multiple Sclerosis Platform, 2017. New insights into the burden and costs of multiple sclerosis in Europe. Mult. Scler. 23 (8), 1123–1136.

Leblanc, S., Roux, J., Tillaut, H., Le Page, E., Leray, E., 2021. Disease-modifying therapy usage in patients with multiple sclerosis in France: a 6-year population-based study. Rev. Neurol. 177 (10), 1250–1261. Paris.

Lorscheider, J., Buzzard, K., Jokubaitis, V., Spelman, T., Havrdova, E., Horakova, D., Trojano, M., Izquierdo, G., Girard, M., Duquette, P., Prat, A., Lugaresi, A., Grand'Maison, F., Grammond, P., Hupperts, R., Alroughani, R., Sola, P., Boz, C., Pucci, E., Lechner-Scott, J., Bergamaschi, R., Oreja-Guevara, C., Iuliano, G., Van Pesch, V., Granella, F., Ramo-Tello, C., Spitaleri, D., Petersen, T., Slee, M., Verheul, F., Ampapa, R., Amato, M.P., McCombe, P., Vucic, S., Sanchez Menoyo, J. L., Cristiano, E., Barnett, M.H., Hodgkinson, S., Olascoaga, J., Saladino, M.L., Gray, O., Shaw, C., Moore, F., Butzkueven, H., Kalincik, T., Group, M.S.S., 2016. Defining secondary progressive multiple sclerosis. Brain J. Neurol. 139 (Pt 9), 2395–2405.

Masanneck, L., Rolfes, L., Regner-Nelke, L., Willison, A., Rauber, S., Steffen, F., Bittner, S., Zipp, F., Albrecht, P., Ruck, T., Hartung, H.P., Meuth, S.G., Pawlitzki, M., 2022. Detecting ongoing disease activity in mildly affected multiple sclerosis patients under first-line therapies. Mult. Scler. Relat. Disord. 63, 103927.

Montalban, X., Gold, R., Thompson, A.J., Otero-Romero, S., Amato, M.P., Chandraratna, D., Clanet, M., Comi, G., Derfuss, T., Fazekas, F., Hartung, H.P., Havrdova, E., Hemmer, B., Kappos, L., Liblau, R., Lubetzki, C., Marcus, E., Miller, D. H., Olsson, T., Pilling, S., Selmaj, K., Siva, A., Sorensen, P.S., Sormani, M.P., Thalheim, C., Wiendl, H., Zipp, F., 2018. ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. Eur. J. Neurol. 25 (2), 215–237.

O'Loughlin, E., Hourihan, S., Chataway, J., Playford, E.D., Riazi, A., 2017. The experience of transitioning from relapsing remitting to secondary progressive multiple sclerosis: views of patients and health professionals. Disabil. Rehabil. 39 (18), 1821–1828.

Penner, I.K., Gass, A., Schreiber, H., Wattjes, M.P., 2021. Neuropsychological and MRI diagnostics in secondary progressive multiple sclerosis. Nervenarzt 92 (12), 1293–1301.

Petersen, G., Wittmann, R., Arndt, V., Göpffarth, D., 2014. Epidemiologie der multiplen sklerose in Deutschland. Nervenarzt 85 (8), 990–998.

Plantone, D., De Angelis, F., Doshi, A., Chataway, J., 2016. Secondary progressive multiple sclerosis: definition and measurement. CNS Drugs 30 (6), 517–526.

Portaccio, E., Bellinvia, A., Fonderico, M., Pasto, L., Razzolini, L., Totaro, R., Spitaleri, D., Lugaresi, A., Cocco, E., Onofrj, M., Di Palma, F., Patti, F., Maimone, D., Valentino, P., Confalonieri, P., Protti, A., Sola, P., Lus, G., Maniscalco, G.T., Brescia Morra, V., Salemi, G., Granella, F., Pesci, I., Bergamaschi, R., Aguglia, U., Vianello, M., Simone, M., Lepore, V., Iaffaldano, P., Filippi, M., Trojano, M., Amato, M.P., Italian Multiple Sclerosis Register Centers, G., 2022. Progression is independent of relapse activity in early multiple sclerosis: a real-life cohort study. Brain. 2022 Aug 27;145(8):2796-2805. doi:10.1093/brain/awac111.

von Bismarck, O., Dankowski, T., Ambrosius, B., Hessler, N., Antony, G., Ziegler, A., Hoshi, M.M., Aly, L., Luessi, F., Groppa, S., Klotz, L., Meuth, S.G., Tackenberg, B., Stoppe, M., Then Bergh, F., Tumani, H., Kumpfel, T., Stangel, M., Heesen, C., Wildemann, B., Paul, F., Bayas, A., Warnke, C., Weber, F., Linker, R.A., Ziemann, U., Zettl, U.K., Zipp, F., Wiendl, H., Hemmer, B., Gold, R., Salmen, A., 2018. Treatment choices and neuropsychological symptoms of a large cohort of early MS. Neurol. Neuroimmunol. Neuroinflamm. 5 (3), e446.

Zhu, W., Tang, X., Heyman, R.A., Cai, T., Suh, K., Seeger, J.D., Xia, Z., 2022. Patterns of Utilization and expenditure across multiple sclerosis disease-modifying therapies: a retrospective cohort study using claims data from a commercially insured population in the United States, 2010-2019. Neurol. Ther. 11 (3), 1147–1165.

Rommer, P.S., Eichstadt, K., Ellenberger, D., Flachenecker, P., Friede, T., Haas, J., Kleinschnitz, C., Pohlau, D., Rienhoff, O., Stahmann, A., Zettl, U.K., 2019. Symptomatology and symptomatic treatment in multiple sclerosis: Results from a nationwide MS registry. Mult. Scler., 2019 Oct;25(12):1641-1652. doi:10.1177/1352458518799580.