The disease burden of Multiple Sclerosis from the individual and population perspective: Which symptoms matter most?

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Abstract: BACKGROUND MS symptoms affect many functional domains. Knowing the specific impact of symptoms on health-related quality of life (HRQoL) is vital for successful disease and symptom management in MS. We aimed at investigating how specific MS symptoms contribute to the disease burden in individuals and from a population perspective. METHODS We included 855 Swiss Multiple Sclerosis Registry participants with a relapsing-remitting form (RRMS) or a progressive form (PMS). HRQoL was measured with the EuroQol 5-Dimension EQ-5D-index and EQ-Visual Analogue Scale (EQ-VAS) on 0-100% scales. Their associations with 20 symptoms, socio-demographic and clinical information were explored in median regression models, stratified by RRMS and PMS. RESULTS We included 611 participants with RRMS and 244 with PMS. In RRMS, gait (-6.5%) and balance problems (-5.1%) had the largest EQ-5D-index reductions, and were also important at the population level (frequencies 45% and 52%). Fatigue, depression, and spasticity (frequencies 74.1%, 31%, 38%) also contributed to the population disease burden. In PMS, spasticity, paralysis, and bowel problems had the largest impact on EQ-5D-index, both at the individual and population levels. The largest impact on EQ-VAS at population level was associated in RRMS with balance problems, depression, dizziness, and spasticity, while in PMS with weakness, pain, and paralysis. CONCLUSIONS While HRQoL at population level is most affected by balance problems, spasticity, and depression in RRMS, the biggest HRQoL losses in PMS are caused by spasticity, paralysis, weakness, and pain. Many symptoms with the largest effects in individuals substantially contribute to the population disease burden.

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The disease burden of Multiple Sclerosis from the individual and population perspective: which symptoms matter most?

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Abstract

Background: MS symptoms affect many functional domains. Knowing the specific impact of symptoms on health-related quality of life (HRQoL) is vital for successful disease and symptom management in MS. We aimed at investigating how specific MS symptoms contribute to the disease burden in individuals and from a population perspective.

Methods: We included 855 Swiss Multiple Sclerosis Registry participants with a relapsing-remitting form (RRMS) or a progressive form (PMS). HRQoL was measured with the EuroQol 5-Dimension EQ-5D-index and EQ-Visual Analogue Scale (EQ-VAS) on 0-100% scales. Their associations with 20 symptoms, socio-demographic and clinical information were explored in median regression models, stratified by RRMS and PMS.

Results: We included 611 participants with RRMS and 244 with PMS. In RRMS, gait (-6.5%) and balance problems (-5.1%) had the largest EQ-5D-index reductions, and were also important at the population level (frequencies 45% and 52%). Fatigue, depression, and spasticity (frequencies 74.1%, 31%, 38%) also contributed to the population disease burden. In PMS, spasticity, paralysis, and bowel problems had the largest impact on EQ-5D-index, both at the individual and population levels. The largest impact on EQ-VAS at population level was associated in RRMS with balance problems, depression, dizziness, and spasticity, while in PMS with weakness, pain, and paralysis.

Conclusions: While HRQoL at population level is most affected by balance problems, spasticity, and depression in RRMS, the biggest HRQoL losses in PMS are caused by spasticity, paralysis, weakness, and pain. Many symptoms with the largest effects in individuals substantially contribute to the population disease burden.

Key-words

Quality of Life, Patient Care Management, Patient Reported Outcomes, EQ5D, Registries, Regression analysis

Abbreviations: AIC = Aikake's Information Criterion, CIS = Clinically Isolated Syndrome, DMT = Disease-modifying Therapy, EDSS = Expanded Disability Status Scale, EQ-5D-5L = European Quality of Life 5-Dimension 5 Level version, EQ-5D-index = European Quality of Life 5-Dimension Index, EQ-VAS = European Quality of Life Visual Analogue Scale, HRQoL = health-related quality of life, MICE = Multivariate Imputation by Chained Equations, RRMS = relapsing remitting multiple sclerosis, PwMS = persons with multiple sclerosis, PMS = progressive multiple sclerosis, SMSR = Swiss Multiple Sclerosis Registry

1. Introduction

The focus of MS research (including clinical studies) and the definition of relevant outcomes are increasingly shifting towards patient-reported outcomes, such as health-related quality of life (HRQoL).
It is well documented that MS can severely impact HRQoL, and impose high levels of psychological stress and financial strains on affected persons (Calabrese et al., 2017; Kobelt et al., 2017). Loss of HRQoL in MS is multifactorial, being potentially driven by fatigue, depression, pain, reduced mobility, or sexual and sphincter dysfunction (Vickrey et al., 1995; Wang et al., 2018). In addition, persons with MS (PwMS) suffer from secondary consequences of symptoms, such as job loss or increasing isolation (Campbell et al., 2014).

Not surprisingly, this multifaceted nature of HRQoL also introduces analytical complexity when studying the individual contribution of symptoms and other factors on HRQoL, which were not always adequately addressed in previous research (Arroyo et al., 2013; Benito-Leon et al., 2002; Fernández et al., 2011; Lobentanz et al., 2004). For example, several studies have only looked for univariate associations between certain symptoms and HRQoL, thereby disregarding important confounders such as age, disease duration, disease severity, and socioeconomic status (Arroyo et al., 2013). Similarly, multivariable regression was sometimes employed to adjust associations by such confounding factors, but with separate regression models fitted for each symptom (Benito-Leon et al., 2002; Lobentanz et al., 2004). This strategy is possibly inappropriate since multiple symptoms influence HRQoL simultaneously and confounding between symptoms is not controlled for. Moreover, non-clinical factors such as the living situation, socioeconomic status, lifestyle factors (Jelinek et al., 2016), or family history of MS have been largely neglected so far (Arroyo et al., 2013; Benito-Leon et al., 2002; Lobentanz et al., 2004).
Therefore, there is a need for studies that simultaneously consider influences of multiple symptoms on HRQoL, as well as demographic and socioeconomic variables. From a symptom management perspective, assessing the relative importance among the different symptoms could aid health care decisions. Moreover, population level data on the MS symptom burden may guide efficient allocation of health care resources.

By making use of the comprehensive data collection of the Swiss Multiple Sclerosis Registry (SMSR), we aimed at investigating to which extent MS-specific symptoms affect the burden of disease in individual PwMS as well as at the population level, after adjusting for a multitude of additional clinical, demographic and socio-economic factors with possible effects on HRQoL.

2. Methods

2.1 The Swiss Multiple Sclerosis Registry

The SMSR is an ongoing, prospective, longitudinal, patient-centered survey study based in Switzerland funded by the Swiss MS Society. The primary objectives of the SMSR are to assess the epidemiology of MS in Switzerland and to study PwMS circumstances of living. The study was approved by the Ethics Committee Zurich (Study number PB-2016-00894) and all participants have provided informed consent (Puhan et al., 2018).

The SMSR was launched in June 2016 and enrolls persons with a suspected or confirmed MS diagnosis who are at least 18 years old and living or receiving care in Switzerland. Participants can contribute to a single questionnaire to the MS epidemiology ("entry questionnaire"), or to longitudinal surveys, consisting of a baseline survey and semi-annual follow-ups. The surveys are offered both on a web platform and on paper. After completion of the entry questionnaire, the participant must provide a diagnosis confirmation signed by their treating physician. All data are collected and analyzed by the Epidemiology, Biostatistics and Prevention Institute of the University of Zurich.

2.2 The variables

This study makes use of all entry and baseline surveys completed up to the September 20, 2017. Data on sex and region of residence (German-, French-, and Italian-speaking regions of Switzerland) stem from the participants' contact information. The entry survey collects information on HRQoL, frequency of symptoms (never/once/recurrent/permanent), age, disease duration (years since MS diagnosis), MS form, use of disease-modifying treatment (DMT), health professionals visited in the previous year, confirmed MS

diagnosis in parents, siblings or offspring, mobility (Ferchichi and van der Maas, 2015; van der Maas, 2017), lifestyle factors, and socioeconomic status. As Expanded Disability Status Scale (EDSS) was rarely reported, a proxy measure was derived from available mobility data (Appendix) (Ferchichi and van der Maas, 2015; van der Maas, 2017). The symptoms were categorized as follows: problems with balance, bladder, and bowel, dizziness, depression, dysarthria, dysphagia, epileptic seizures, fatigue, gait problems, memory problems, pain, paralysis, paresthesia, sexual dysfunction, spasticity, tics, tremor, visual problems, and general weakness. The actual terminology used is available in table A2 of the Appendix.

HRQoL was assessed by use of the European Quality of Life 5-Dimension 5-Level version (EQ-5D-5L) instrument, which covers the dimensions of mobility, self-care, usual activities, pain/discomfort and anxiety/depression (EuroQoL Group, 1990; Herdman et al., 2011). These factors were used to estimate a single utility figure (called EQ-5D-index) using the French value set (Matter-Walstra et al., 2014; Perneger et al., 2010). We then rescaled the index from 0 (worst health) to 100 (best health). The instrument is accompanied by a visual analogue scale (EQ-VAS) assessing the overall health status on the current day on a 0 to 100 scale, from the worst to the best imaginable health. Therefore, while EQ-VAS tends to be a reflection of more immediate health-related circumstances, the more comprehensive EQ-5D-index covers different domains in a more detailed, but less responsive manner.

2.3 Statistical analysis

Data were analyzed using regression models with the EQ-5D-index or EQ-VAS as dependent and the individual symptoms as main independent variables. We characterized each symptom as “currently present” if it was “recurrent” or “permanent”, and as “absent” otherwise. If occurring in less than 5% of the sample, a symptom was excluded from the analysis. Due to the skewed distribution of the dependent variables, we used median regression instead of linear regression. Moreover, to account for possible effect-modification of symptoms with MS disease stage, we stratified all analyses into two subgroups: the relapsing remitting form (RRMS) and the progressive forms (PMS). Patients with other MS forms (i.e. CIS or unspecified transition forms) or with missing dependent variables were excluded. The primary and the secondary

progressive form were analyzed jointly after ascertainment of the absence of statistical differences in symptoms frequencies with the 2-sample z-test (using p-value threshold of $\alpha=0.05/20=0.0025$).

Known confounders, namely age, sex, and disease duration, were always included in regression models. Other potential confounders were selected if they improved the model's goodness of fit (see Appendix). Potential confounders were recent DMT use (previous 6 months), recent relapse (previous 3 months), living situation, education level, socioeconomic status, region of residence, overweight (i.e. BMI>25), presence of comorbidities, presence of social network, family doctor/neurologist visited in the previous year, confirmed MS diagnosis in the family, ever smoker, and alcohol consumption. For analyses on participants with PMS, recent DMT intake and recent relapse were excluded. Indeed the first drug approved for PMS is very recent (Montalban et al., 2017), and only patients with active MS were eligible to the hitherto available DMTs; additionally relapses rarely occur in PMS. A possible interdependence of the various symptoms was assessed with Spearman correlation for each pair of symptoms, stratified by RRMS and PMS.

We performed univariable median regression for each of the four models and then also included all other symptoms and confounders in the model. Complete case analysis was explored. However, although the proportion of missing data was small (ranging between 0.1% and 10% for individual variables), the cumulative loss of data points was not negligible. Therefore, we imputed the missing confounders by means of the MICE (multivariate imputation by chained equations) algorithm, creating 120 different imputed datasets. The portion of missing information and the imputation method for each confounder are shown in the Appendix (table A3).

An automatic variable selection procedure based on Akaike's information criterion (table A3 in Appendix) was performed separately for each of the four models (EQ-VAS or EQ-5D-index as outcomes, stratified by RRMS or PMS). We assessed the absolute performance of the final model with the calibration slope through observed versus predicted outcome values, computed on 1000 imputed datasets and pooled. The model is said to be well-calibrated if the calibration slope is approximately 1.

To reflect the relevance of a particular symptom at the population level, individual regression coefficients for symptoms were multiplied by the frequency of their occurrence in the sample, yielding an "importance

score". These importance scores, which reflect the population burden, were analyzed graphically and contrasted with the individual symptom burden. All analyses were performed using R, version 3.4.0 (R Core Team, 2017).

3. Results

3.1 Description of participants

Of 971 participants who completed the entry and baseline surveys by September 20, 2017, 37 did not provide information on the MS form, 36 had a clinically isolated syndrome (CIS) and 31 were transitioning from RRMS to PMS and were therefore excluded. Twelve additional participants had missing values for EQ-5D-index (11) or EQ-VAS (2). Of the remaining 855 PwMS 611 had RRMS and 244 had PMS. Table 1 shows their demographic and clinical information. The distribution of the dependent variables (EQ-5D-index and EQ-VAS) is illustrated in the Appendix, stratified by subgroup (figures A1-A6).

Table 1. Demographic and clinical information of the included sample.

Variables	All	RRMS	PMS
N	855	611	244
Age	48 (38;57)	44 (35;51)	59 (53;65)
Sex-female	622 (72.7%)	482 (78.9%)	140 (57.4%)
Disease duration (years)	9 (3.5;16)	7 (3;12)	16 (8;21)
MS form			
RRMS	611 (71.5%)	611 (100%)	-
PPMS	97 (11.3%)	-	97 (39.8%)
SPMS	147 (17.2%)	-	147 (60.2%)
Confirmation of diagnosis received	699 (81.8%)	502 (82.2%)	197 (80.7%)
EDSS*			
0-3.5	640 (74.9%)	556 (91%)	84 (34.4%)
4-6.5	140 (16.4%)	49 (8%)	91 (37.3%)
7-10	75 (8.8%)	6 (1%)	69 (28.3%)
Recent DMT use (last 6 months)	524 (61.3%)	438 (71.7%)	86 (35.2%)
Recent relapse (last 3 months)	83 (10.7%)	72 (12.7%)	11 (5.3%)
EQ-5D-index	77.6 (62.5;89.9)	83.5 (71.6;94.1)	59 (46;73.2)
EQ-VAS	78 (50.5;90)	80 (68.5;94)	60 (40;80)

Results are shown as median (interquartile range) or number (percentage). RRMS = relapsing remitting multiple sclerosis, PPMS = primary progressive multiple sclerosis, SPMS = secondary progressive multiple sclerosis, *derived from mobility-related questions, DMT = disease-modifying therapy.

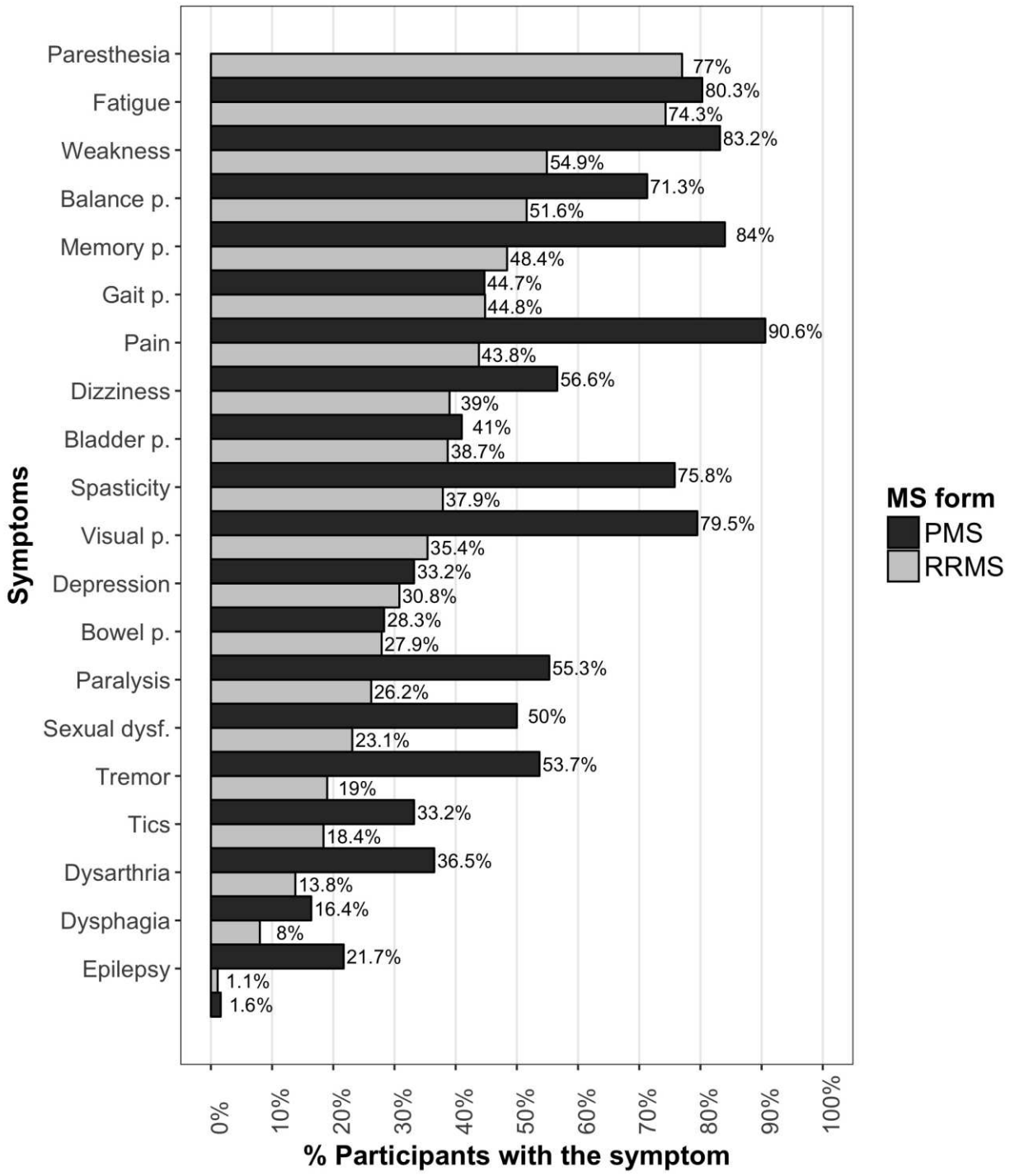
3.2 Frequency of symptom occurrence

The frequency of symptoms is reported in figure 1, stratified by MS form. Among participants with RRMS the most frequent symptoms were paresthesia (77.1%), fatigue (74.1%), and weakness (54.8%), whereas among participants with PMS gait problems (90.6%), balance problems (84.0%), and fatigue (83.2%) were most common. Most symptoms were more frequent in the PMS subgroup. We excluded epileptic seizures from further analyses, due to its low occurrence in both subgroups.

For participants with RRMS, the assessment of interdependence between different symptoms reached a maximum value of 0.54 between balance problems and gait problems. The second and third highest observed correlations were between fatigue and weakness (0.48), as well as between gait problems and spasticity (0.48). Among participants with PMS the only correlation above 0.4 was between dysarthria and dysphagia (0.49). All correlations are listed - stratified by subgroup - in the Appendix (figures A7-A8).

Figure 1. Frequency of reported symptoms in participants with RRMS and PMS.

(1 column)



RRMS = relapsing remitting MS, PMS = progressive MS, dysf. = dysfunction, p. = problems.

3.3 Regression analyses for RRMS

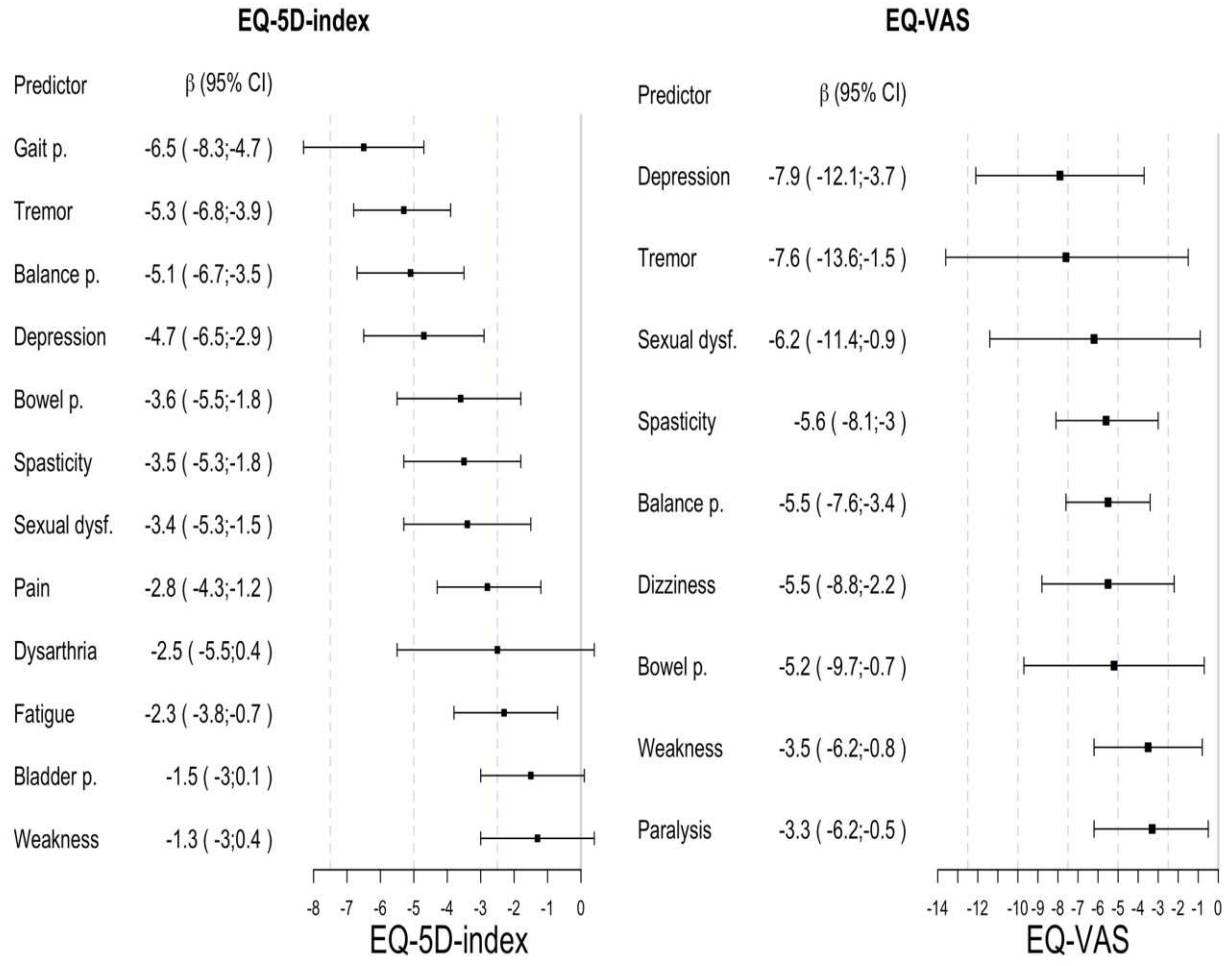
The final multivariable model for RRMS with EQ-5D-index as outcome was adjusted for age, sex, disease duration, overweight, and alcohol consumption. For each symptom, regression coefficients and their 95% confidence intervals (CI) are illustrated in Figure 2 (left-hand side). The symptoms most strongly associated with EQ-5D-index were gait problems, balance problems, and tremor. The model was well-calibrated, as the mean calibration slope among the imputed datasets was 0.93 (0.89-0.97 95% CI).

The final model for RRMS with EQ-VAS as outcome was adjusted for age, sex, disease duration, recent relapse, and education level. Figure 2 (right-hand side) shows regression coefficients and 95% CI. The symptoms most strongly associated with EQ-VAS were –in order- depression, tremor, and sexual dysfunction. The mean calibration slope was 0.82 (0.71-0.94), indicating a good calibration.

The complete list of coefficients from the univariable and the multivariable models for RRMS are shown in the Appendix (table A4).

Figure 2. Impact of symptoms on HRQoL for persons with RRMS.

(2 columns)



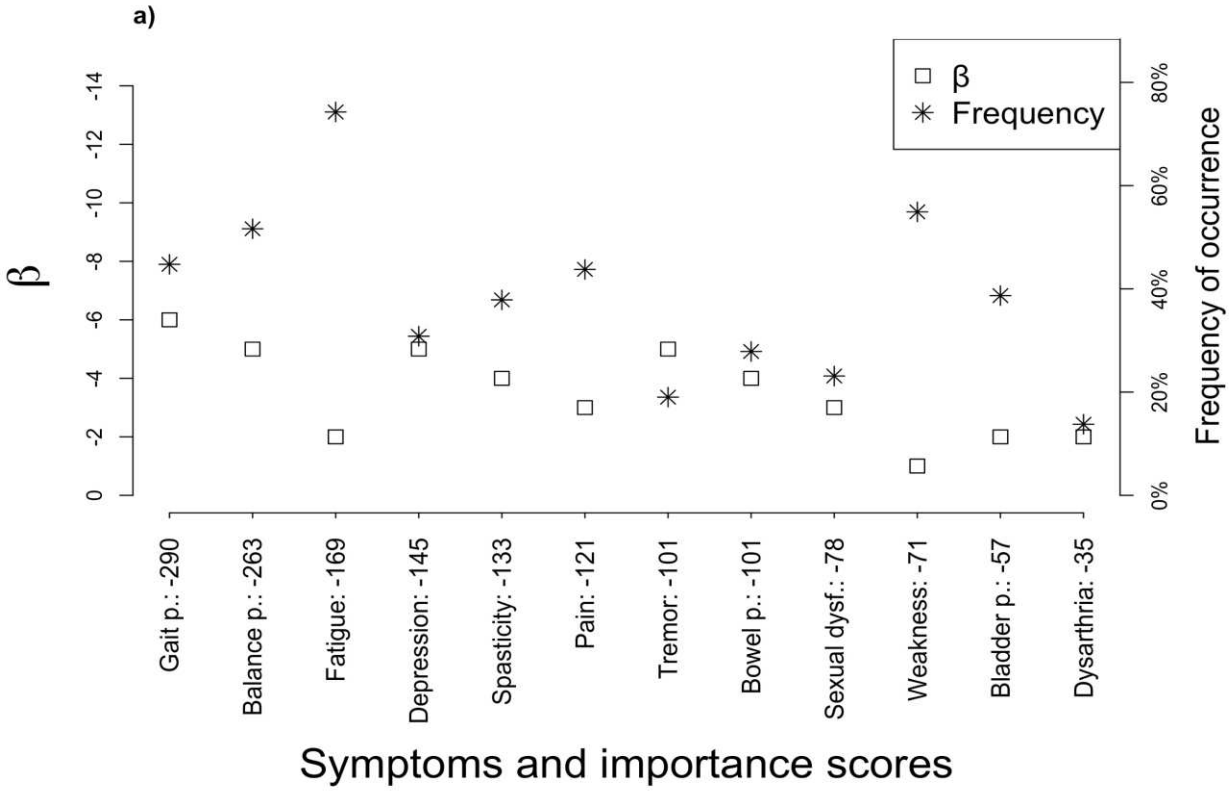
β = median regression coefficient, dysf. = dysfunction, p. = problems.

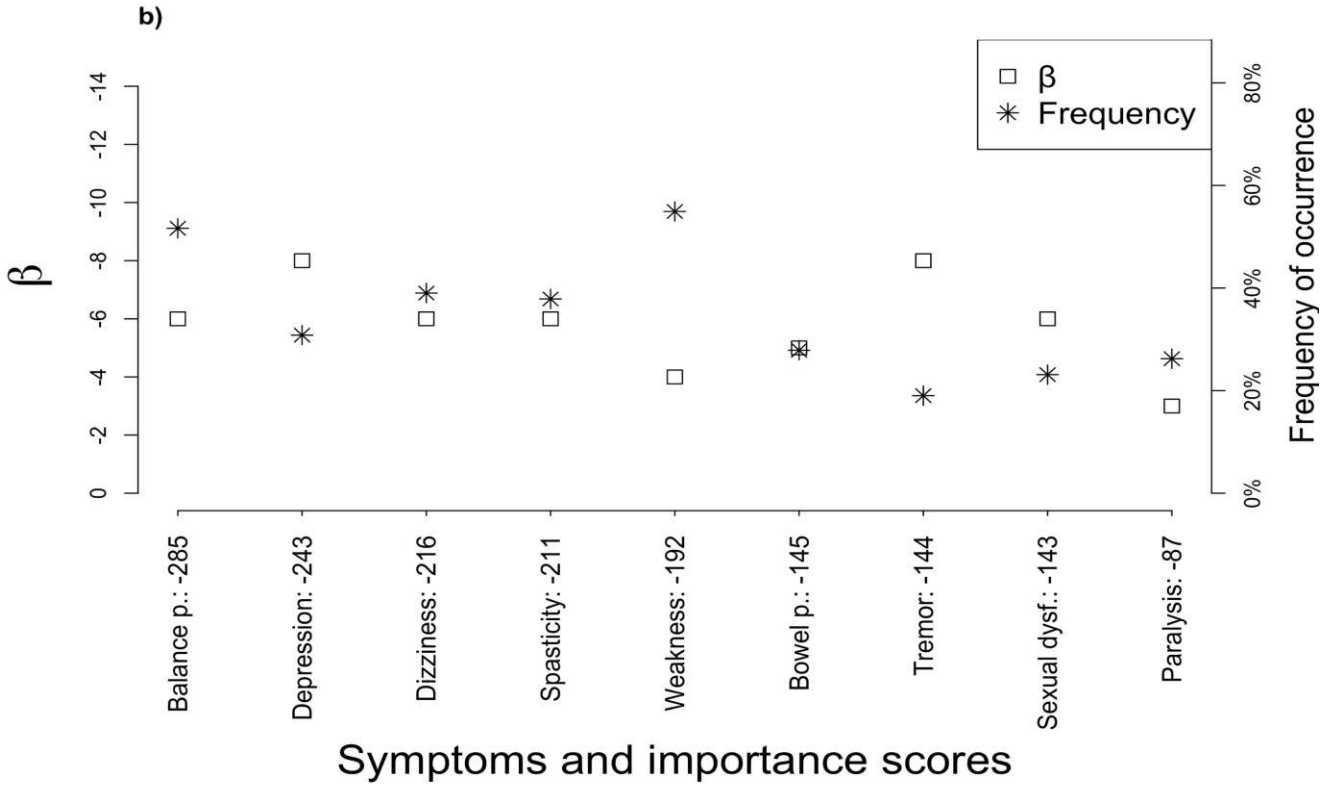
The median regression coefficients (β) are to be interpreted as follows: among persons with RRMS, those who experience –for instance- gait problems will have a median EQ-5D-index 6.5 points lower than those not experiencing that impairment. Furthermore, if some symptoms co-exist, their effects add up: those who

experience tremor (β =-5.3) and balance problems (β =-5.1) will have a median -10.4 points lower than those who experience neither of these symptoms.

Figure 3 shows the combined information from regression coefficients and the frequency of occurrence of each symptom. On the horizontal axis all symptoms are listed together with their importance scores. Since regression coefficients have negative values and are multiplied by positive frequencies, lower importance scores correspond to higher impact of the symptom on the outcome at the population level. The symptoms of largest impact at the population level were gait problems, balance problems and fatigue on EQ-5D-index, and balance problems, depression, and dizziness on EQ-VAS. Tremor and sexual dysfunction had less impact on both outcomes at the population level due to their low frequency.

Figure 3. HRQoL-reduction, occurrence frequencies, and importance scores for specific symptoms in persons with RRMS.





a) Model on EQ-5D-index, b) Model on EQ-VAS; β = median regression coefficient, dysf. = dysfunction, p. = problems.

3.4 Regression analyses for PMS

The final multivariable model for PMS with EQ-5D-index as outcome was adjusted for age, sex, disease duration, socioeconomic status, and alcohol consumption. Figure 4 (left-hand side) shows the regression coefficients of this model. Spasticity, paralysis, and bowel problems were, in this order, negatively associated with EQ-5D-index. The mean calibration slope was 0.77 (0.58-0.97), indicating a good calibration.

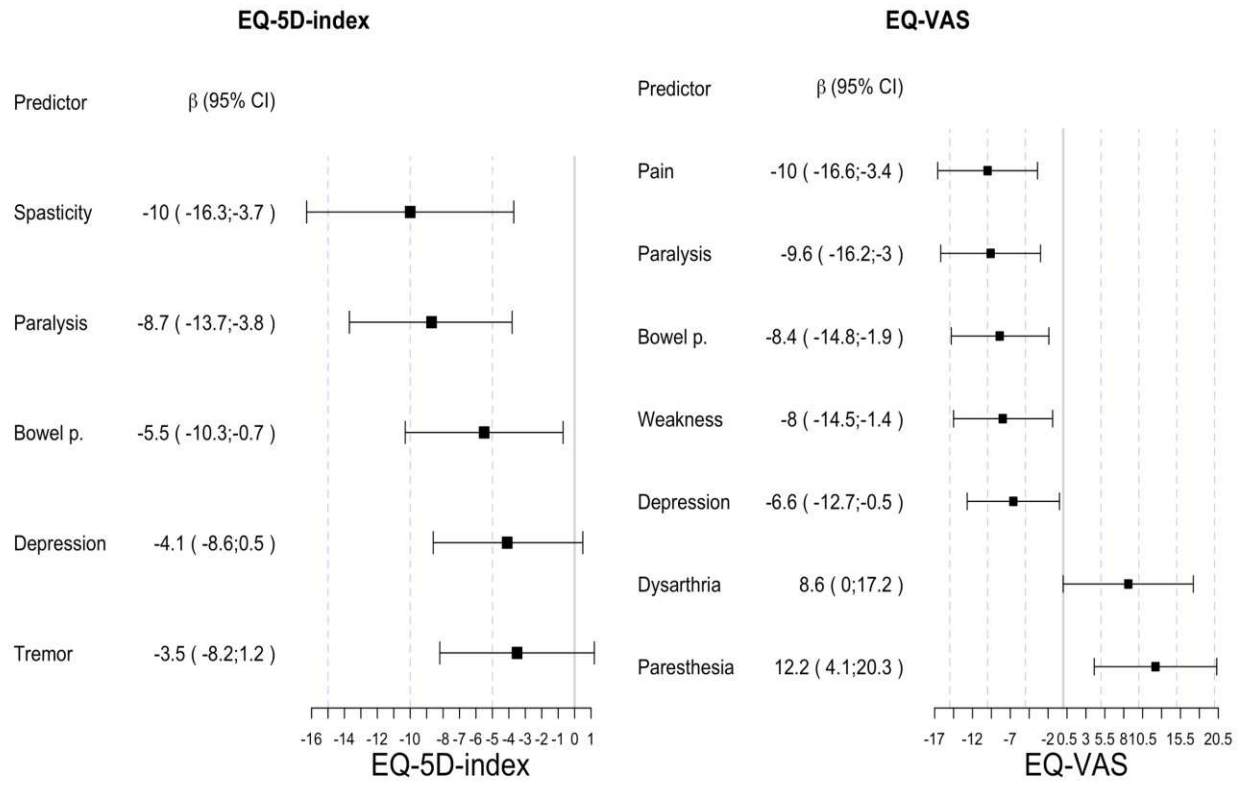
The final multivariable model for PMS with EQ-VAS as outcome was adjusted for age, sex, disease duration, and alcohol consumption. Figure 4 (right-hand side) illustrates its regression coefficients. Pain, paralysis, and bowel problems were the most strongly associated symptoms with EQ-VAS. Some included symptoms, namely dysarthria and paresthesia, showed a statistically significant positive effect on EQ-VAS,

that was absent in the univariable analysis. The mean calibration slope was 0.65 (0.48-0.81), indicating a moderate calibration.

Table A5 in the Appendix shows the complete list of coefficients from the univariable and the multivariable models on PMS.

Figure 4. Impact of symptoms on HRQoL for persons with PMS.

(2 columns)



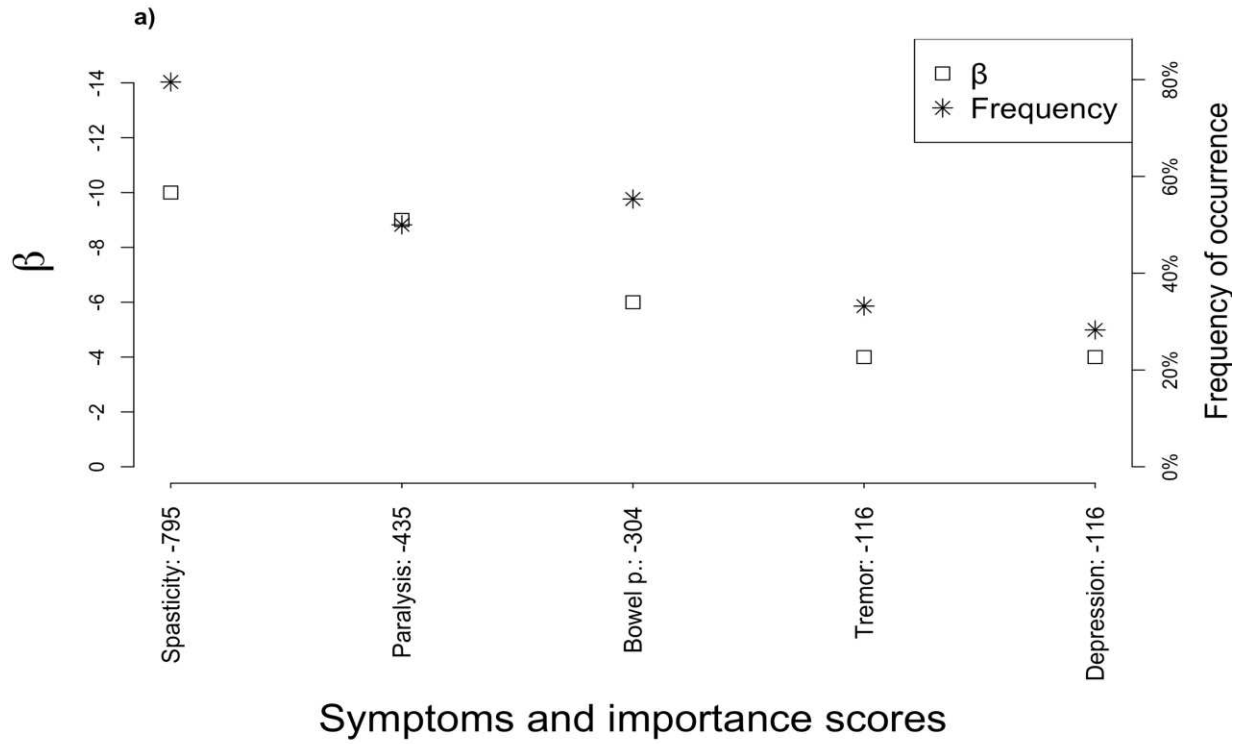
β = median regression coefficient, p. = problems.

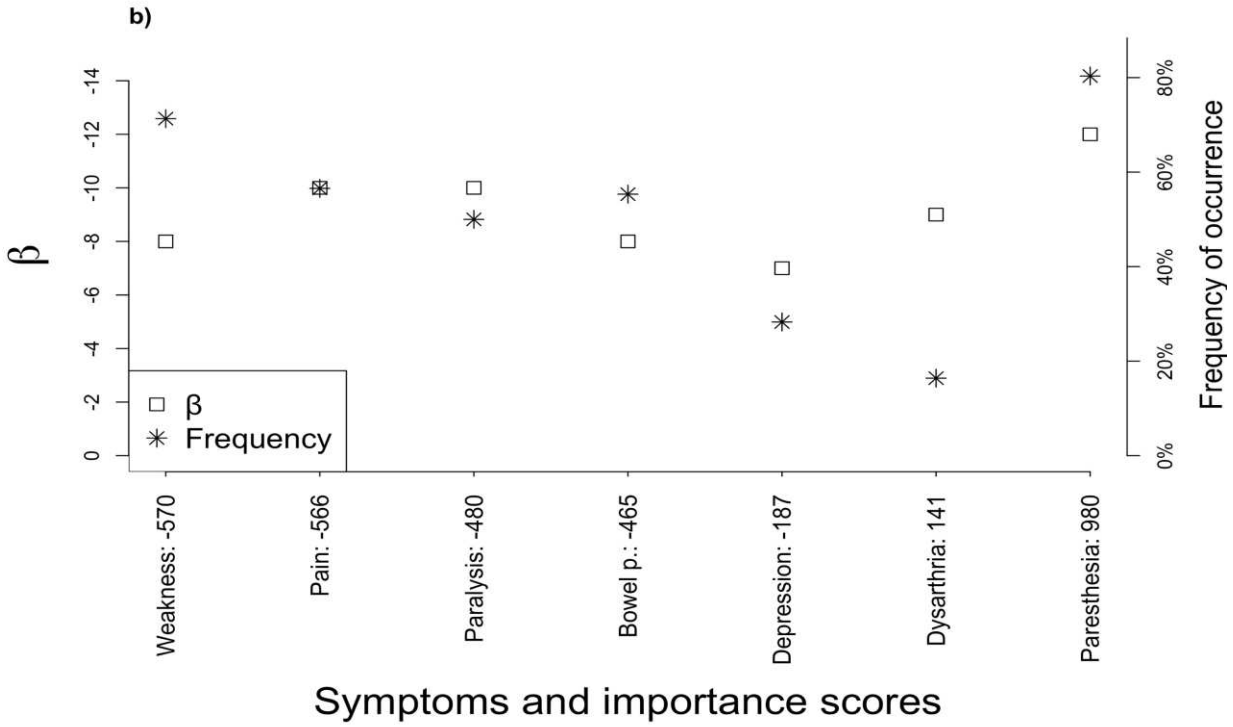
Figure 5 summarizes the importance scores at the population level for the PMS group. In the model with EQ-5D-index, the order of importance almost coincides with the order of magnitude.

In the EQ-VAS model, weakness reached a greater importance due to its high frequency (71%). Pain, paralysis, and bowel problems maintained their relative order (Figure 4).

Figure 5. HRQoL-reduction, occurrence frequencies, and importance scores for specific symptoms in persons with PMS.

(1.5 columns)





a) Model on EQ-5D-index, b) Model on EQ-VAS; β = median regression coefficient, p. = problems.

4. Discussion

We used cross-sectional patient-reported surveys from 855 PwMS included in the Swiss MS Registry, to assess the influence of specific MS symptoms on quality of life. The patient-centered design of the SMSR, promotion by the Swiss MS Society, plus the support of the medical community all helped improving the representativeness of the study population, as indicated by the inclusion of PwMS subgroups frequently absent in hospital-based studies (Puhan et al., 2018). Previous population-based studies in Switzerland have shown similar sample characteristics (Calabrese et al., 2017). Our analysis focused on both the individual and population levels of the disease burden, with the aim of improving MS care management and assessing the adequacy of resource allocations. Separate analyses were performed for RRMS and PMS, and multivariable models were used to limit the effect of confounding factors.

When measured by EQ-5D-index, the symptom with the largest effect on HRQoL in persons with RRMS, was gait problems, followed by balance problems, fatigue, and depression. Balance problems, depression , dizziness, and spasticity were most strongly associated with loss in self-perceived health (EQ-VAS). By contrast, the most important symptoms in persons with PMS were spasticity, paralysis, and bowel problems when assessed using EQ-5D-index, while associations with EQ-VAS were stronger for weakness, pain, and paralysis. The observed differences regarding the most influential symptoms between persons with RRMS and PMS may be explained by the differences in types of symptoms occurring at the different stages of the disease, as well as by the "response shift" phenomenon (Spuling et al., 2017), whereby priorities and evaluation of past health status tend to change as MS progresses.

Further differences were noted between the assessments of EQ-5D-index and EQ-VAS, which arise from the different domains these measures cover. The former is heavily weighted towards mobility (hence both gait and balance problems were included for RRMS), while the latter is based on a single domain. Therefore, this "lack of constraints" in EQ-VAS has led to the exclusion of certain symptoms that were deemed relevant in the EQ-5D index analysis.

The finding of certain symptoms with positive effects on HRQoL (Figure 4) can be regarded as accidental and most likely due to residual confounding.

When comparing our findings with existing literature, the majority of symptoms identified as relevant by this study have evidence supporting their negative influence on HRQoL. Among the most studied symptoms, physical disability (including gait problems) (Beiske et al., 2007; Buhse et al., 2014; Fernández et al., 2011; Janardhan and Bakshi, 2002; Miller et al., 2003), fatigue (Beiske et al., 2007; Janardhan and Bakshi, 2002; Lobentanz et al., 2004; Nogueira et al., 2009), and depression (Buhse et al., 2014; D'Alisa et al., 2006; Hopman et al., 2007; Janardhan and Bakshi, 2002; Lobentanz et al., 2004) were consistently found to affect HRQoL. Not surprisingly, pain was also reported to exert a major impact on HRQoL in some studies (Rafie and Young, 2013), but not in others (Hopman et al., 2007; Motl et al., 2009). Despite being a domain in EQ-5D, the role of pain was only limited in our analysis, possibly due to masking by other symptoms such as spasticity, gait and balance problems. Our analysis also covered symptoms that were less frequently considered by other studies, for example sexual dysfunction (Wang et al., 2018), bowel problems (Dibley et al., 2017), spasticity (Svensson et al., 2014), tremor (Berk et al., 2002), and dizziness (Marrie et al., 2013). Despite their infrequent reporting by other studies, we found that these symptoms can have a substantial effect on HRQoL. Among the understudied symptoms, paralysis stood out as a determinant in reducing both self-perceived health status and HRQoL for participants with PMS. Future studies could therefore consider including paralysis in their assessments.

Most studies on MS and HRQoL have made use of the generic SF-36 and the disease-specific MSQOL-54 measures. With such instruments as outcomes, probably symptoms like fatigue and depression would have gained importance, while bladder and bowel problems might have been overshadowed. Additionally, with MSQOL-54 sexual dysfunction and memory problems would have also become more relevant, as it is explicitly enquired about them in several questions.

Our work adds to the literature by introducing a framework for judging the relevance of symptoms from different perspectives. It might also encourage physicians to make active use of pharmacological and non-pharmacological treatment attempts to try to tackle significant symptoms, such as depression, walking

difficulties, spasticity or fatigue. At the individual level, such knowledge could be used to design specific rehabilitation or symptomatic treatment strategies to improve symptoms and therefore HRQoL. At the population level, it might help to assess the adequacy of health resources by providing indications on access barriers for treatment of specific symptoms (e.g. due to inadequate provider supply). Moreover, this is, to our knowledge, the first analysis to stratify by MS disease course (RRMS and PMS). As our results reveal, the impact of certain symptoms on HRQoL can differ dramatically by MS disease course, and failure to take such differences into account may lead to biased results.

4.1 Study limitations and strengths

Some limitations about our study should be noted. This analysis is based on observational, patient-reported data, and residual confounding cannot be completely excluded. Moreover, although some frequently reported symptoms were excluded from our models, likely due to sample size limitation, they could nevertheless exert some relevant effects on HRQoL. In addition, certain symptoms known to be negatively associated with HRQoL, such as sleep quality (Lobentanz et al., 2004) and cognitive impairment (Fernández et al., 2011), were not included as part of the registry surveys. Finally, the data collection by means of self-report can be prone to biases (e.g. recall bias) and underreporting (e.g. due to a possible social stigma). Nevertheless, other studies have demonstrated the reliability of patient-reporting (Hosseini et al., 2018; Musch et al., 2018).

This study also has notable strengths. First, the analysis was based on a large sample of the Swiss population of PwMS. Moreover, the available information covered in our study, such as social status, education, smoking, and alcohol consumption, is comprehensive, thus covering many aspects rarely addressed in other studies.

Additionally, the stratification according to disease course has enabled the different symptoms between RRMS and PMS to emerge (Beiske et al., 2007; Miller et al., 2003). Not least, the population view

combining the frequency of symptoms and reduction of the individual burden might lead to a more efficient symptom management.

4.2 Prospect for future research

Future research could assess the symptoms collected in this study as well as sleep problems and cognitive impairment, in order to externally validate our models. Based on our findings, we advocate the use of median regression models and also to fit separate models for persons with RRMS and PMS in order to obtain less biased results.

4.3 Conclusion

Our findings demonstrate that the symptoms which are prone to compromise HRQoL in PwMS may vary substantially, depending on the underlying disease course. Specifically, while HRQoL of individuals with a RRMS course is most affected by balance problems, spasticity, and depression, the biggest HRQoL losses in persons with a PMS are caused by spasticity, paralysis, weakness, and pain. Many symptoms with the largest effects in individuals also substantially contribute to the population disease burden.

Conflict of Interest

AC has received compensation for activities with Actelion, Allmirall, Bayer, Biogen, Celgene, Genzyme, Merck, Novartis, Roche and Teva. He receives research support from Genzyme and UCB.

AS has received speaker honoraria and/or travel compensation for activities with Almirall Hermal GmbH, Biogen, Merck, Novartis, Roche and Sanofi Genzyme, none related to this work.

CPK has received honoraria for lectures as well as research support from Biogen, Novartis, Almirall, Bayer Schweiz AG, Teva, Merck, Sanofi Genzyme, Roche, Celgene and the Swiss MS Society (SMSG).

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PC has received honoraria for speaking at scientific meetings, serving at scientific advisory boards and consulting activities from: Abbvie, Actelion, Almirall, Bayer-Schering, Biogen Idec, EISAI, Genzyme, Lundbeck, Merck Serono, Novartis, Pfizer, Teva, and Sanofi-Aventis. His research is also supported by the Swiss Multiple Sclerosis Society, the Swiss National Research Foundation and the SOFIA Foundation.

LB, HB, GD, CG, JKe, CP, MAP, VvW have nothing to disclose.

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