Natural History of Multiple Sclerosis Symptoms

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The North American Research Committee on Multiple Sclerosis (NARCOMS) Registry is a database that contains information from over 35,000 patient volunteers on symptom severity in 11 domains commonly affected in multiple sclerosis (MS): mobility, hand function, vision, fatigue, cognition, bowel/bladder function, sensory, spasticity, pain, depression, and tremor/coordination. The Registry affords a unique opportunity to study the frequency and severity of domain-specific impairment in a contemporary, mostly treated MS cohort over the course of the disease. The objective of this work was to calculate symptom prevalence in each of the 11 domains for years 0 to 30 from symptom onset. The resulting "symptom prevalence tables" demonstrate that a majority of participants perceive at least some degree of impairment in most domains as early as the first year of disease. The severity of impairment increases with disease duration across all domains, but the patterns of disability accumulation differ. The symptom prevalence tables illustrate the magnitude of perceived impact of the disease and highlight the extent of unmet need in symptomatic management. The tables are easy to use and allow MS patients and their clinicians to compare an individual's own impairment in any of the 11 domains to that of NARCOMS participants with the same disease duration. **Int J MS Care. 2013;15:146–156.**

Multiple sclerosis (MS) is a notoriously polysymptomatic disease.[1] Point and lifetime prevalences of a variety of symptoms have been estimated[2-6]; however, with the exception of ambulatory function, little is known about how the frequency and severity of domain-specific impairment change over time in an MS cohort. The North American Research Committee on Multiple Sclerosis (NARCOMS) Registry is a database that collects information from patient volunteers on patient-perceived impairment in 11 domains commonly affected in MS.[7,8] Impairment in each domain is scored on a six- or seven-grade scale (Performance Scales; PS). The NARCOMS Registry thus affords a unique opportunity to study domain-specific impairment in MS. We used this dataset to compile "reference tables" of symptom prevalence and severity as a function of disease duration for each of the 11 domains assessed in the NARCOMS Registry. The resulting "symptom prevalence tables" provide a uniquely detailed, multidimensional view of MS impact over a 3-decade disease course. The tables allow MS patients to easily determine how their impairment in mobility, hand function, vision, fatigue, cognition, bowel/bladder function, sensory, spasticity, pain, depression, and tremor/coordination domains compares to that of NARCOMS participants with the same disease duration.

Methods

The NARCOMS Registry enrolled nearly 36,000 patients with a self-reported diagnosis of MS from 1996 to June 2011.[8] Participants complete the institutional review board–approved enrollment form, offered both online and on paper, which includes information on demographics, disease history, medication history, and

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DOI: 10.7224/1537-2073.2012-053

impairment in 11 domains as assessed with domain-specific PS. Ten of the domains—hand function, vision, fatigue, cognition, bowel/bladder function, sensory, spasticity, pain, depression, and tremor/coordination—are scored on six-grade scales; mobility function is scored on a seven-grade scale. The key elements of the Registry and some of the PS have been validated in a random sample of participants.[9-12]

Participants with a disease duration of 0 to 30 years at the time of PS completion were included in this study. Those with a disease duration of more than 30 years were excluded, as their number was too small for statistical analysis. Participants with unknown age or unknown disease duration at the time of PS assessment, or with a non-MS diagnosis, were also excluded. Each participant contributed only his or her initial PS scores to the algorithm.

For each of the 11 domains, we calculated the cumulative frequency distribution of PS grades in participants with the same disease duration. Cumulative frequency is equal to the percentage of participants within a given disease duration stratum with PS grades equal to or less than the reference PS grade divided by the total number of participants with the same disease duration. Cumulative frequencies represent probabilities that a NARCOMS registrant with a given disease duration will have a PS grade equal to or lower than a specified PS grade. An alternative and, perhaps, more intuitive interpretation of cumulative frequency is that it represents the prevalence (proportion) of participants whose impairment is equal to or less than a given PS grade relative to patients with the same disease duration. For each of the 11 domains, we compiled a "symptom prevalence table" that displays cumulative frequency distributions of PS grades for years 0 to 30 from symptom onset.

Results

There were 25,728 NARCOMS participants with a disease duration of 0 to 30 years who met the inclusion criteria; 6176 registrants were excluded because of missing age, missing age at symptom onset, or non-MS diagnosis, and 4026 registrants were excluded because of a disease duration of more than 30 years at the time of PS completion. Demographic and disease-related characteristics of the included patients are shown in Table 1.

Table 1. Demographic and disease-related characteristics of the NARCOMS cohort

Characteristic	Value
Number of participants	25,728
Female, %	74.5
Race, %	
White	89.3
African-American	4.6
Hispanic	2.4
Other	3.0
Age at symptom onset, mean (SD), y	31.4 (9.7)
Age at diagnosis, mean (SD), y	37.3 (9.7)
Age at enrollment, mean (SD), y	45.2 (10.0)
Unemployed, %	49.3
On immunomodulatory therapies,[a] %	51.9

Abbreviations: NARCOMS, North American Research Committee on Multiple Sclerosis; SD, standard deviation.

[a] Out of 10,658 respondents who answered the question.

Each symptom prevalence table consists of 31 multicolored stripes representing years of disease (Figures 1–11). The topmost stripe represents year 0 and the bottommost represents year 30 from symptom onset. The stripes are divided into six colored segments corresponding to the six PS grades, with the exception of the seven-grade mobility table, which is divided into seven colored segments (Figure 1). The color-coding scheme that matches grade with color is shown with each figure. The number of unique patient records used to construct a symptom prevalence table is given in parentheses in the respective legend. Minor variations in the number of responses for the mobility, hand function, fatigue, cognition, bowel/bladder function, sensory, and spasticity domain PS are due to the fact that some patients occasionally failed to complete all the forms. The PS for pain, depression, vision, and tremor/coordination began to be included as of 2002, and consequently have considerably fewer responses compared with the other domains.

Disease duration is shown on the vertical axis and prevalence (cumulative frequency) on the horizontal axis. The outer boundary of each grade-segment marks off the proportion (in percent) of NARCOMS registrants whose self-rated impairment is equal to or lower than the corresponding PS grade relative to the total number of registrants with the given disease duration, while the inner boundary represents the proportion of registrants with lower PS grades. Segment length is equal to the percentage of patients with the respective PS grade.

Examination of the symptom prevalence tables reveals that in nearly every domain, the majority of patients perceived some degree of impairment immediately after disease onset. Sensory symptoms and fatigue were especially ubiquitous: within the first year after onset, 85%

of patients reported some degree of sensory symptoms (Figure 7) and 81% some degree of unexplained fatigue (Figure 4). Minimal or mild cognitive impairment (PS = 1 or 2) was noted by half of the patients (50%) within the first year (Figure 5). Mobility, generally thought to be spared in the first decade of disease, has been "noticeably affected" (PS = 1 or 2) in 35% of patients in the first year, and an additional 15% had at least an occasional need for a mobility device (PS ≥3) (Figure 1).

"Left-shifting" of segment boundaries from top to bottom reflects a continuous decrease of the proportion of participants in the milder grades along with increase of the proportion in the more severe grades. Worsening impairment was evident throughout the first decade for all 11 domains. In some domains, such as mobility, hand function, bowel/bladder function, and spasticity (Figures 1, 2, 6, and 8), increase in the proportion of participants in moderate-to-severe grades continued throughout the 3 decades of observation, while in other domains, such as vision, cognition, sensory, pain, and depression (Figures 3, 5, 7, 9, and 10), there was little change in the cumulative frequency distribution of PS grades during the third decade of disease.

Discussion

The symptom prevalence tables presented here allow patients and their clinicians to determine how domain-specific impairment in an individual with MS compares to that of NARCOMS registrants with the same disease duration. For example, a patient who has had the disease for 15 years and rates his or her fatigue level as "severe" (PS grade 4: "Every day, fatigue forces me to modify my daily activities; I am always tired") will find that among registrants with a 15-year disease duration, 65% recorded a lesser degree of fatigue, 6% recorded a higher degree, and the remaining 29% also rated their fatigue as "severe" (Figure 4). The symptom prevalence tables can improve patients' and clinicians' understanding of how the disease affects various neurologic functions throughout the disease course and help validate patient self-reports, especially in difficult-to-quantify areas such as fatigue, mood, sensory, and pain. The tables offer a measure of reassurance to those with an overly pessimistic view of their prognosis. For example, as the mobility prevalence table (Figure 1) demonstrates, wheelchair use is not an inevitable outcome in MS; after 30 years of disease, only about one in five NARCOMS participants reported the need for wheelchair use or worse, and about the same proportion recorded no or minimal mobility problems. At the same time, the tables illustrate the high burden of morbidity of the disease and the very considerable extent of unmet need in symptomatic management of MS.

Examination of the symptom prevalence tables revealed interesting differences in patterns of disability accumulation. In the mobility, hand function, bowel/bladder function, and spasticity domains (the "spinal factor"[13]), worsening impairment in the NARCOMS cohort—visually apparent in the "left-shifting" of segment boundaries from top to bottom in Figures 1, 2, 6, and 8—was observed over the 3 decades of disease. In some of the other domains such as vision, cognition, sensory, pain, and depression (Figures 3, 5, 7, 9, and 10), there was little change in distribution of PS grades after 15 years of disease. We suggest that the interdomain differences in disability accumulation could be interpreted in the context of a two-phase model of MS.[14,15] The pervasive, though usually nondebilitating, worsening across all domains in the early phase—including cognitive and psychiatric areas—may result from widespread inflammatory activity throughout the central nervous system. During the later, treatment-recalcitrant phase,[16] inflammation is not as prominent, relapses are less consequential,[17] and there are fewer new lesions formed.[18] Accumulation of disability is thought to be due mostly to "virtual hypoxia" and energy failure,[19] which would be expected to preferentially cause axonal degeneration of the high-energy-demanding neural network underlying "spinal" functions.

Alternatively, the observed differential effect of the disease on different domains could be due to patients' being less aware of change in some domains than in others, or lesser responsiveness of some of the PS at the higher end of impairment. This latter hypothesis may explain why the vision and cognition PS had relatively little correlation with "objective measures" of disability—low-contrast acuity and Paced Auditory Serial Addition Test (PASAT)—in a validation study, while the mobility PS had excellent correlation with the Timed Walk test and Expanded Disability Status Scale (EDSS).[9] A "ceiling effect" may also be at play, especially in those domains in which a significant proportion of patients reported moderate-to-severe impairment early on in the disease course (eg, fatigue). Further study is warranted to ascertain whether the divergence in trajectories of disability accumulation in different domains is inherent to the nature of the disease or the result of measurement artifact.

A potential limitation of our study is the use of a volunteer registry, which may not be representative of the MS population at large. It is therefore important to compare demographic and disease-related characteristics of the NARCOMS cohort with published series. Age at symptom onset, age at disease diagnosis, gender ratio, and employment rate in NARCOMS (Table 1) are similar to recently published clinic population data, such as those of the New York State Multiple Sclerosis Consortium.[20] With regard to mobility, the proportion of NARCOMS registrants who reported a need for a cane or a worse degree of disability after 30 years of disease was 50% (Figure 1), which is the mean time-to-cane recorded in two recent Canadian natural history studies but is considerably longer than that reported in some of the older studies (reviewed in Tremlett et al.[21]). The proportion of NARCOMS participants with no or minimal gait dysfunction after 30 years of disease

Figures 1–11. Symptom prevalence tables

In the key, the color code shows the correspondence of various colors with grades on the Performance Scale (PS) for that domain.

A symptom prevalence table is used as follows: Consider a hypothetical patient who has had the disease for 15 years and rates his or her fatigue level as "severe" (PS grade 4: "Every day, fatigue forces me to modify my daily activities; I am always tired"). To understand how this patient's fatigue compares to that of NARCOMS registrants with the same disease duration, we examine the boundaries of the light-blue segment that corresponds to PS = 4 on the stripe representing 15 years on Figure 4. The inner boundary of 65% means that a lesser degree of fatigue (PS ≤3) was reported by 65% of the NARCOMS registrants after 15 years of disease; the outer boundary of 94% signifies that 6% reported worse fatigue. The length of the segment is 29%, which equals the percentage of participants with a 15-year disease duration who recorded their PS score as 4.

***Figure 1.* Mobility (N = 23,860)**

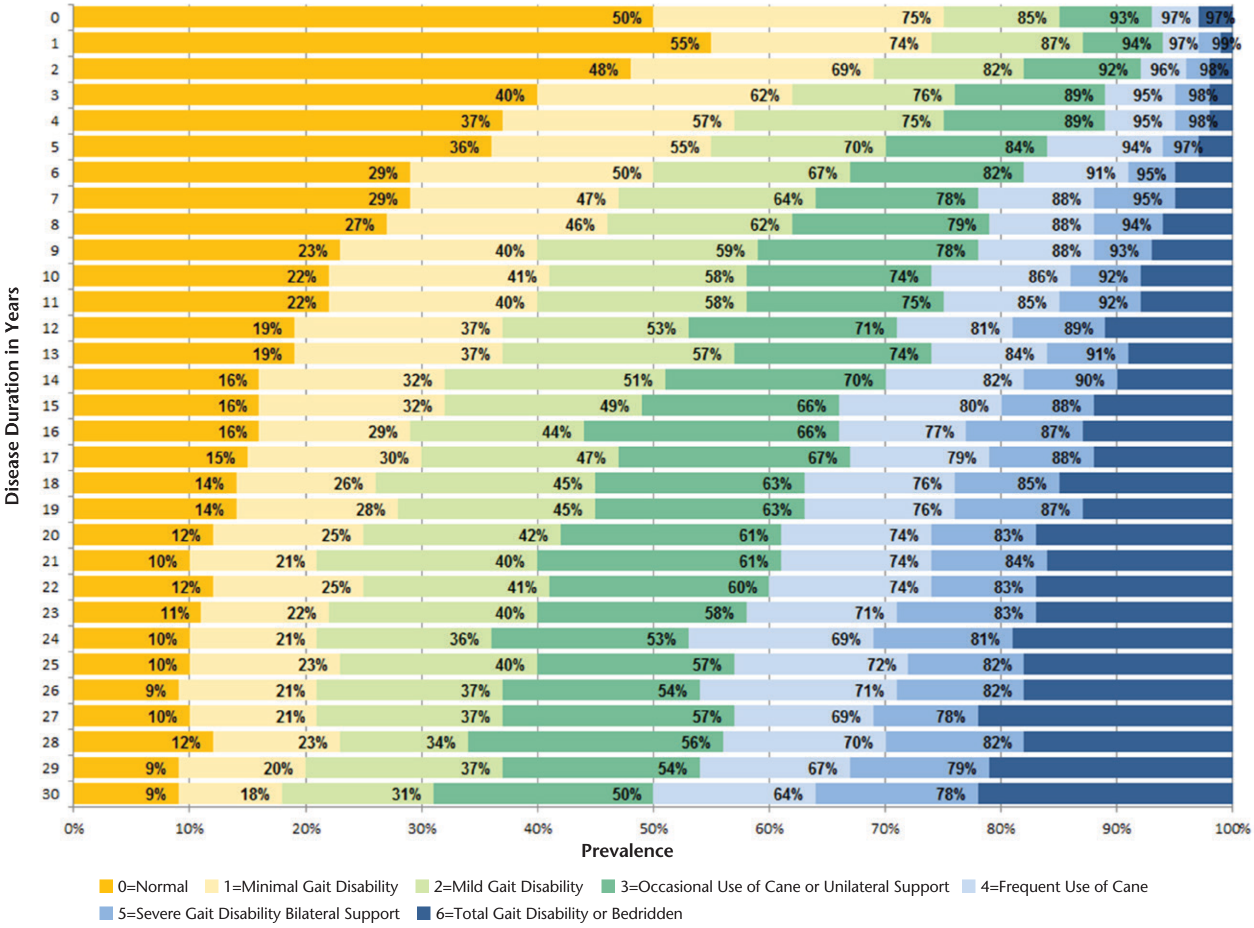


Figure 2. Hand function (N = 23,931)

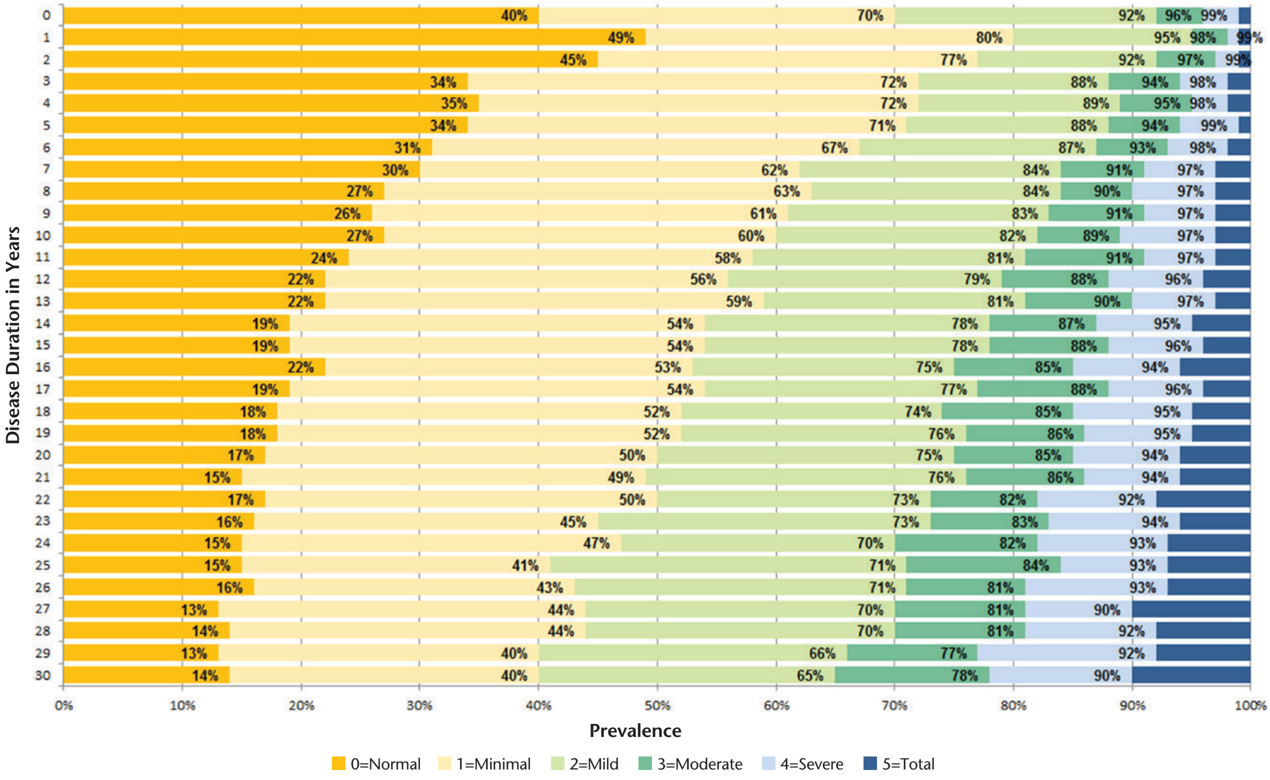


Figure 3. Vision (N = 23,880)

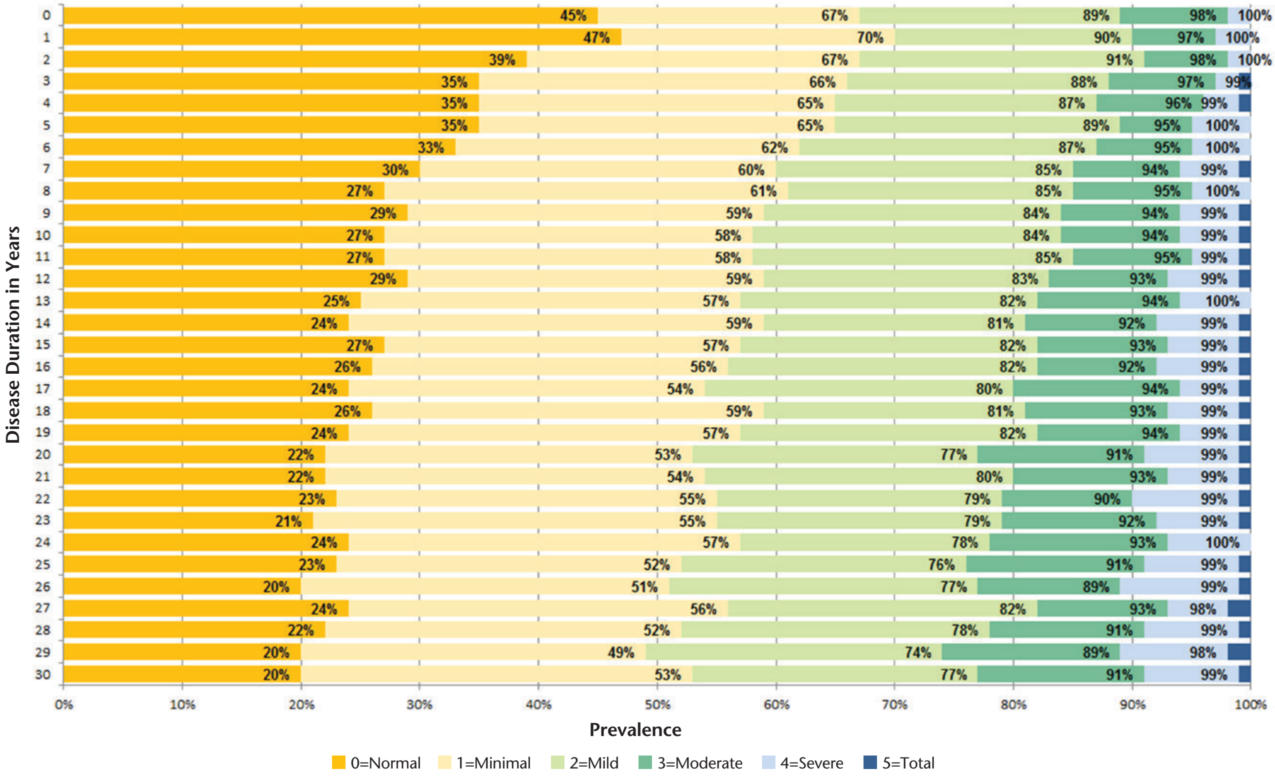


Figure 4. **Fatigue (N = 23,918)**

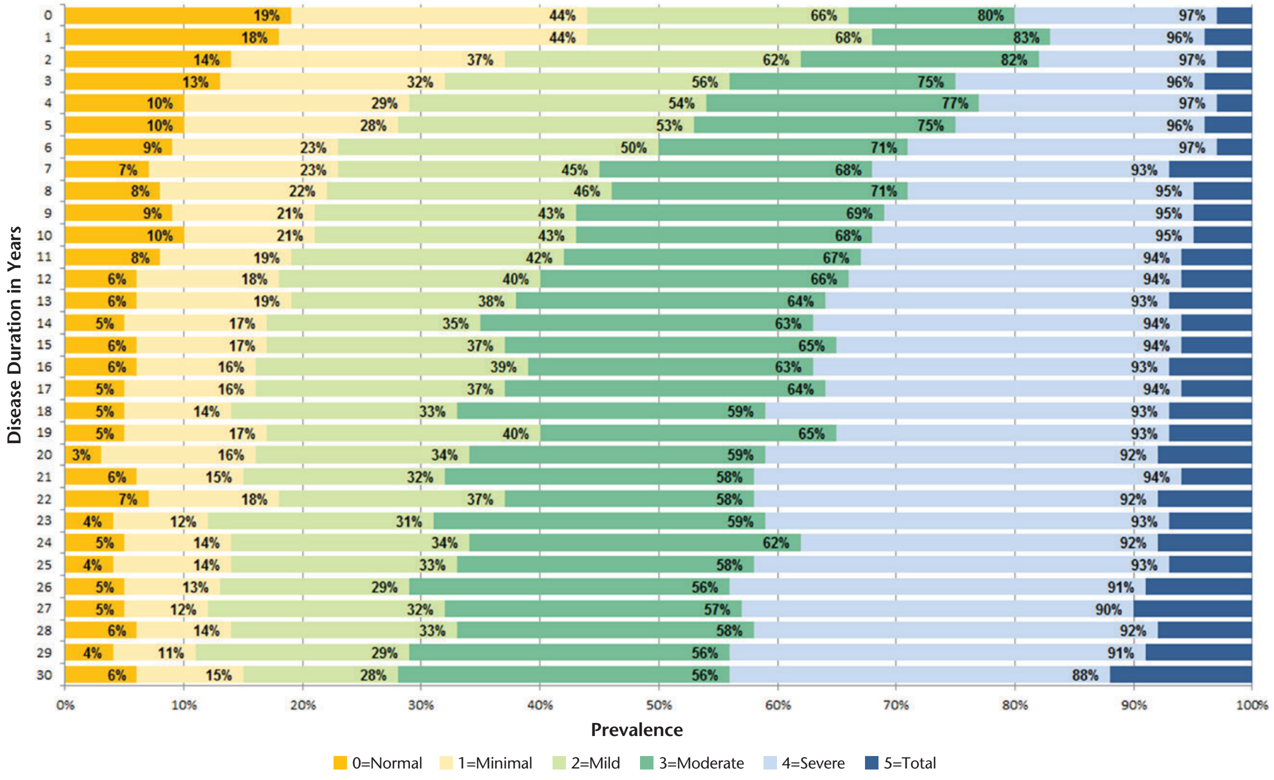


Figure 5. **Cognition (N = 23,961)**

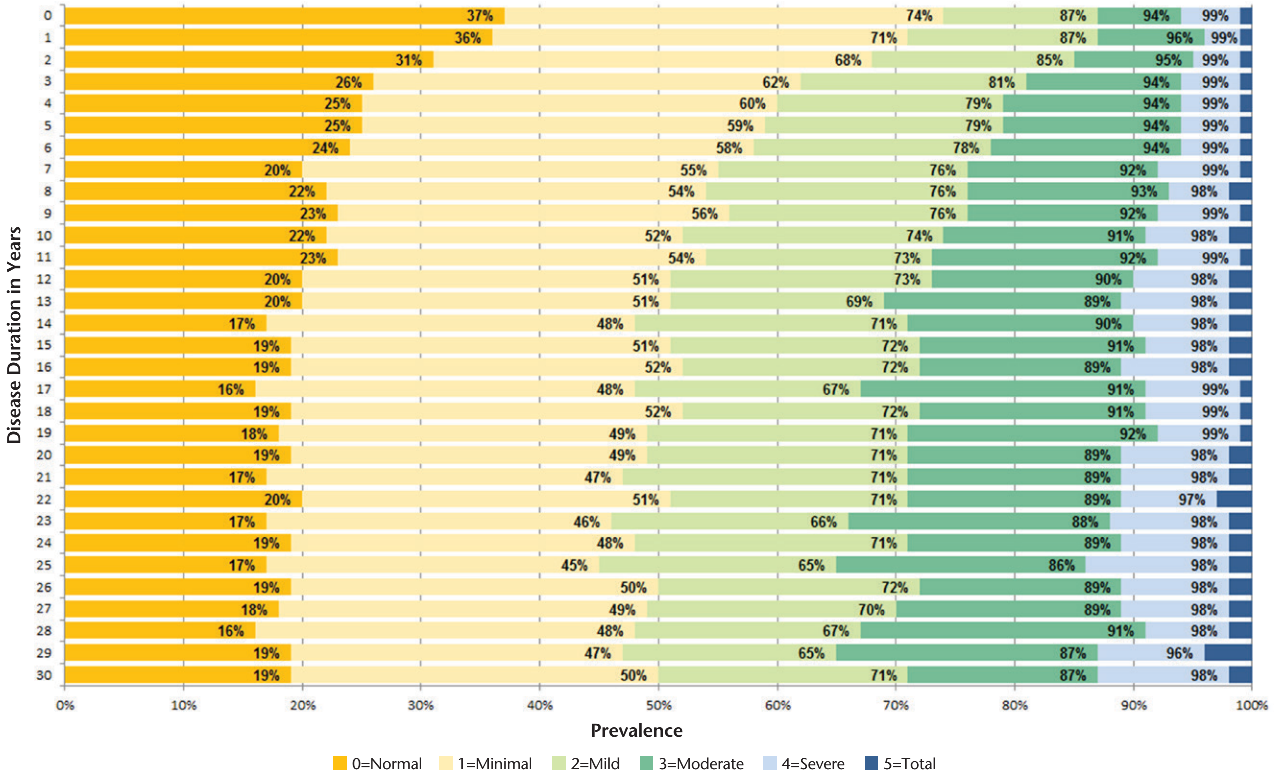


Figure 6. Bladder/bowel function (N = 23,816)

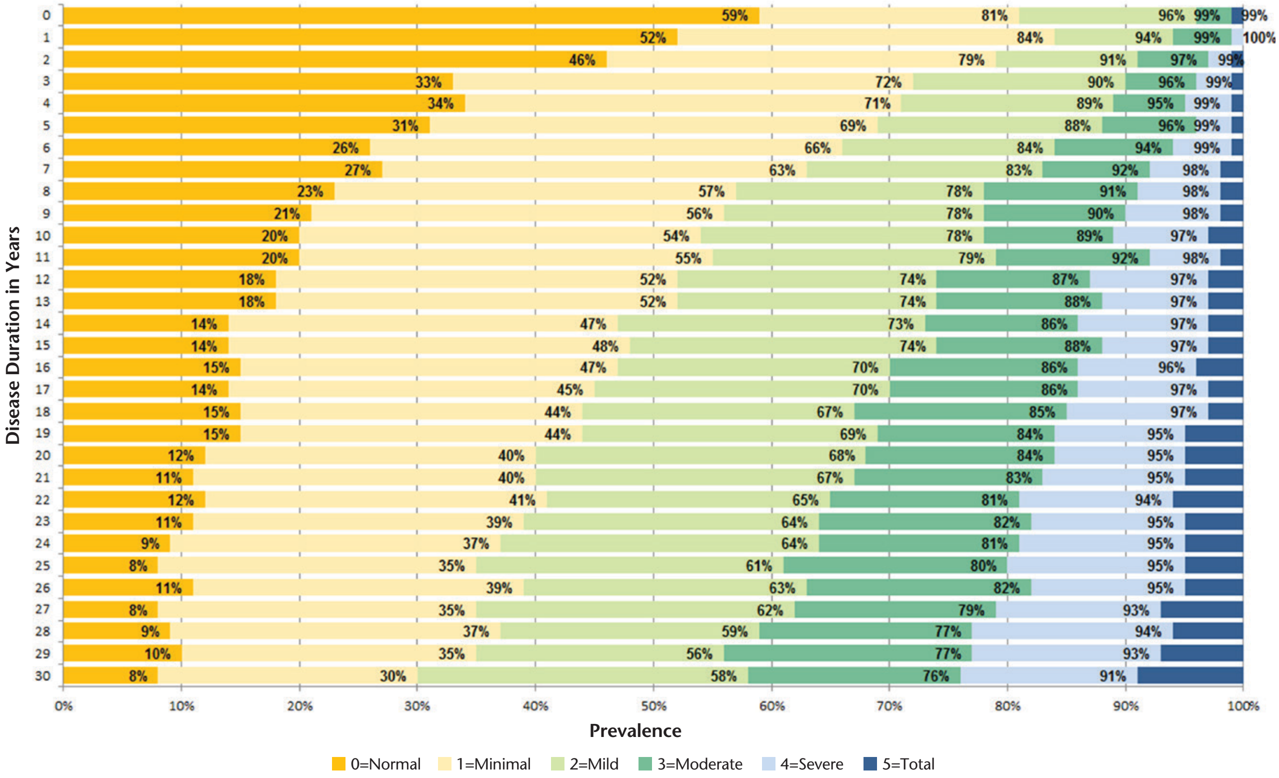


Figure 7. Sensory (N = 23,830)

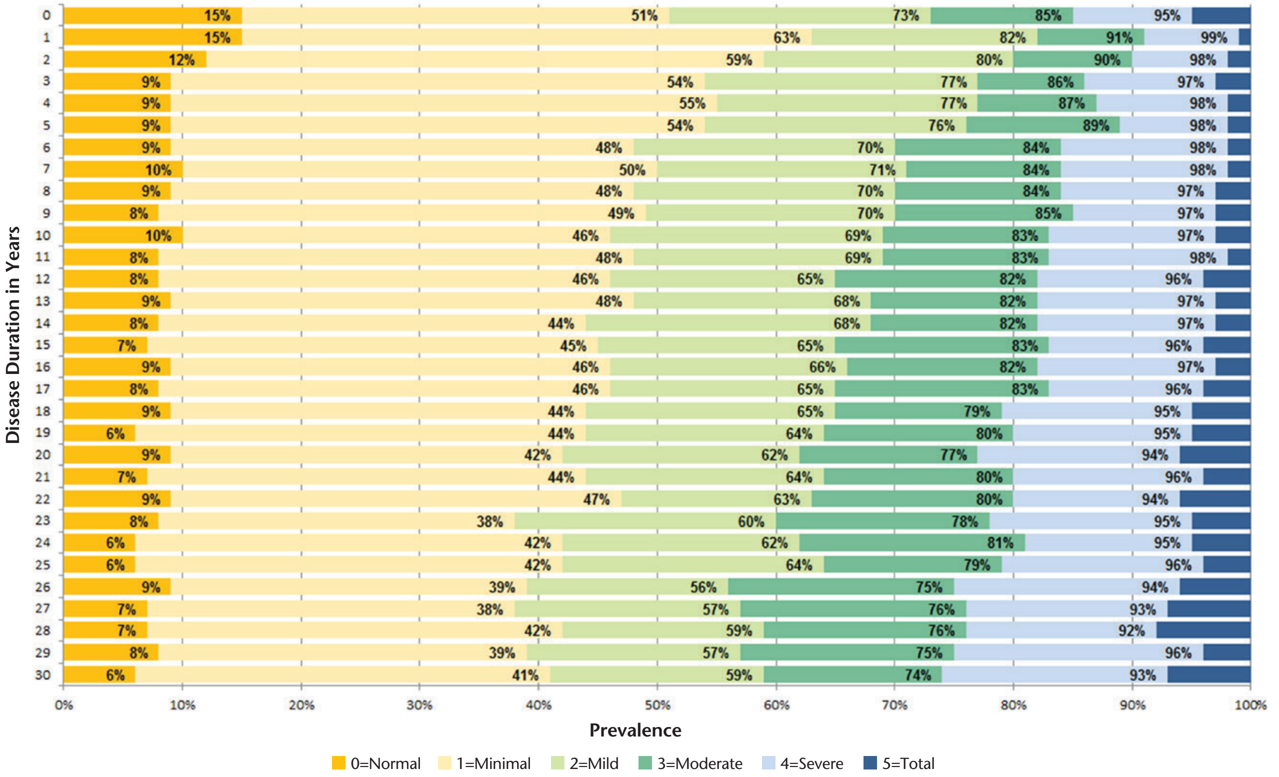


***Figure 8.* Spasticity (N = 23,842)**

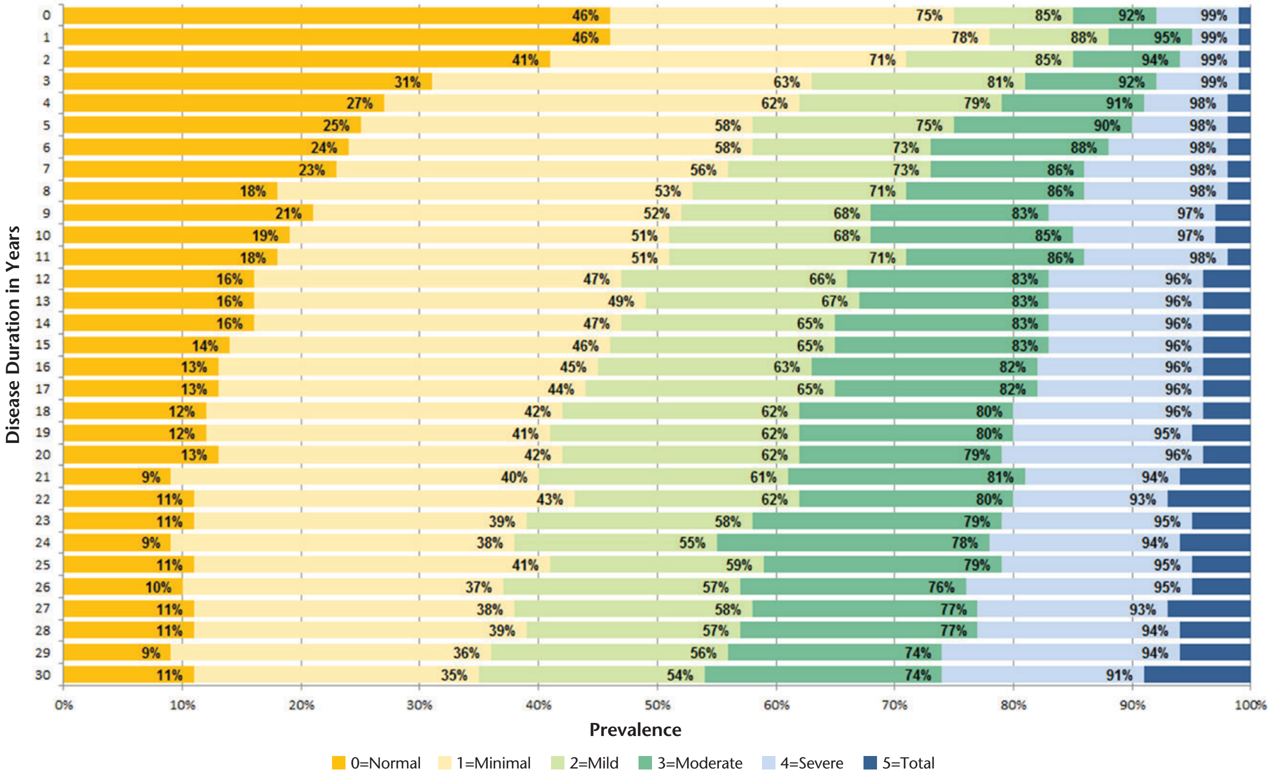


***Figure 9.* Pain (N = 7494)**

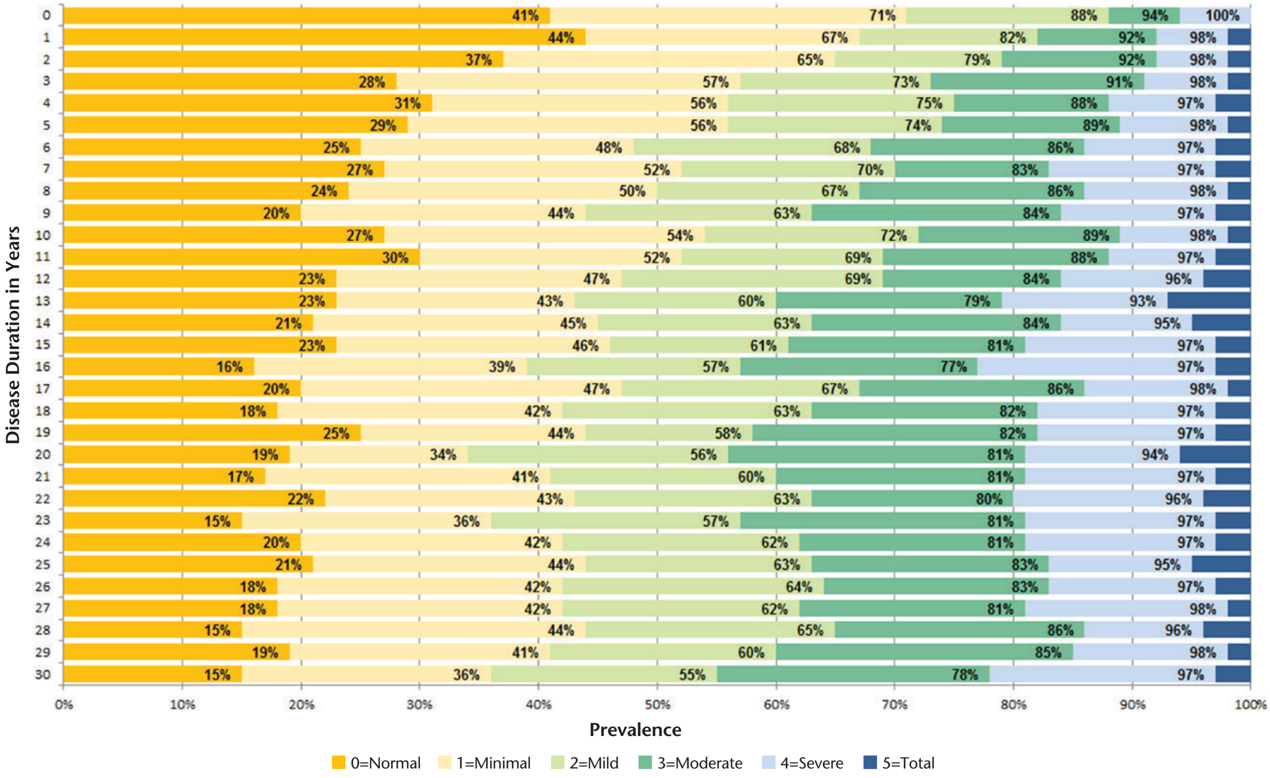


Figure 10. Depression (N = 9607)

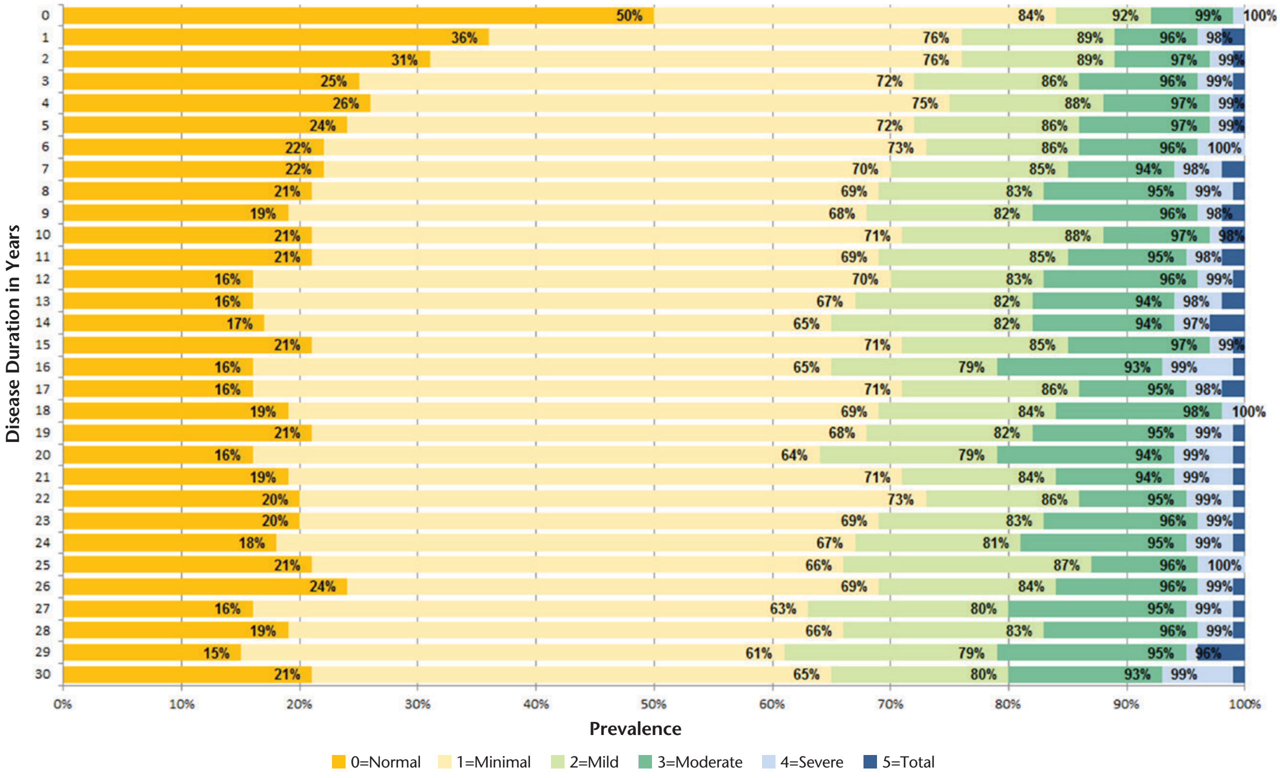
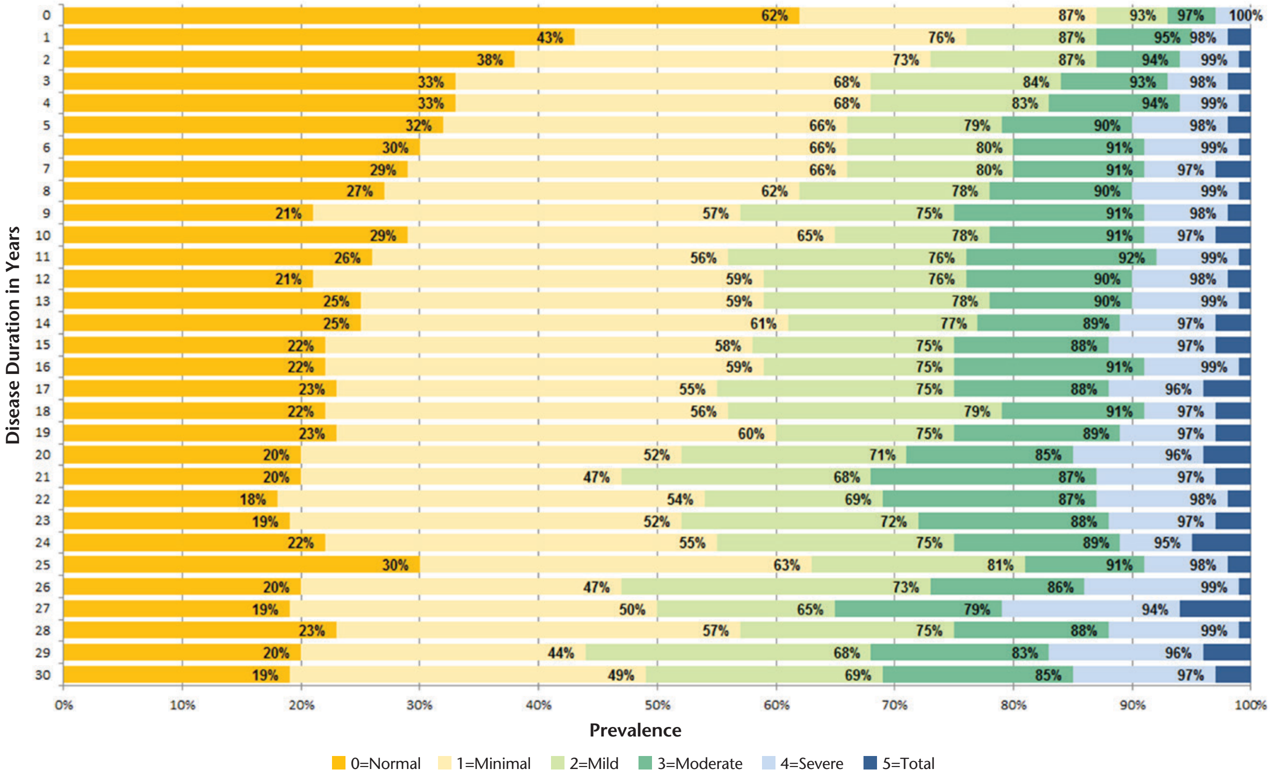


Figure 11. Tremor/coordination (N = 7499)



was 18%, which is comparable to rates of "benign" or "nonprogressive MS" recorded around the world.[22-25] The apparent slowing of the disease course has been discussed extensively in our two recent publications.[26,27] It is plausible that changes in rate of disease accumulation are due, at least in part, to improvements in prophylactic and symptomatic management of MS, including, importantly, greater emphasis on physical therapy and exercise to maintain ambulatory function.

Despite the reassuring similarities in demographic and ambulatory characteristics between NARCOMS and clinic- and population-based cohorts, it is highly probable that the most severely affected patients are underrepresented in a volunteer registry. Thus, the symptom prevalence tables likely provide "lower bound" estimates of prevalence for the "extreme disability" grades. It should also be borne in mind that the symptom prevalence tables do not always capture the dynamic nature and complexity of the disease. A patient can have a marked increase in symptoms in various domains at the time of relapse, but this would not be reflected on the survey response a few months later. Or, a patient may get used to or learn to adapt to limitations using various accommodations and assistive devices, in which case an apparent decrease in disease impact on quality of life would not be accompanied by a decrease in disability.

The symptom prevalence tables contain a wealth of information on prevalence and severity of patient-perceived impairment in MS and afford unique insight into how MS patients perceive their disability in the domains of cognition, depression, pain, fatigue, vision, hand function, mobility, spasticity, bowel/bladder function, sensory, and tremor/coordination throughout a 30-year disease course. In contrast to the Disability Expectancy Table, which represents "overall disability" outcomes in a NARCOMS cohort,[28] the symptom prevalence tables allow patients and their clinicians to compare an individual patient's impairment to that of NARCOMS registrants on a domain-by-domain basis. The tables demonstrate that disease impact transcends ambulatory and motor functions, which are the focus of traditional disability assessment scales in MS (such as the EDSS), and extends to nearly every neurologic domain. Proper evaluation of MS patients in clinical practice as well as in clinical trials should seek to assess the extent of impairment across multiple domains—psychological, cognitive, visual, sensory, autonomic, and fatigue, as well as motor. The symptom prevalence tables can improve understanding of this frequently mystifying neurologic disorder among MS sufferers as well as clinicians who take care of them, specialists (neurologists, urologists, ophthalmologists, physiatrists) and primary-care providers alike. We believe that the tables will provide optimal benefit if they are used in the context of clinician-patient discussion of an individual's symptoms and their management. ☐

PracticePoints

- The North American Research Committee on Multiple Sclerosis (NARCOMS) Registry affords a unique opportunity to study the frequency and severity of domain-specific impairment in a contemporary, mostly treated MS cohort over the course of the disease.
- The symptom prevalence tables presented here chart the frequency and severity of impairment over time in 11 neurologic domains among more than 25,000 NARCOMS participants.
- The symptom prevalence tables are easy to use and allow patients to determine how their impairment in the various domains compares to that of NARCOMS participants with the same disease duration.

Financial Disclosures: Dr. Kister has received research support from the National Multiple Sclerosis Society (NMSS). Dr. Chamot has received research support from the National Institutes of Health (NIH) and NMSS. Dr. Cutter has received honoraria from GlaxoSmithKline, Biogen Idec, EMD Serono Inc, the National Institute of Neurological Diseases and Stroke (NINDS), Consortium of Multiple Sclerosis Centers (CMSC), Novartis, Bayer Pharmaceuticals, and Teva Pharmaceuticals Industries Ltd; has served on independent data and safety monitoring committees for Sanofi-Aventis, BioMS Medical Corp, GlaxoSmithKline, and Teva Pharmaceutical Industries Ltd; has received research support from the CMSC (Director, NARCOMS Data Center) and NMSS; and serves as President of Pythagoras, Inc. Dr. Herbert has received personal compensation for activities with Biogen Idec, EMD Serono, Teva Neuroscience, and Bayer as a consultant and has received research support from Teva Neuroscience, Novartis, Biogen Idec, Bayer, EMD-Serono/Pfizer, BioMS, and INC Research. Ms. Bacon, Ms. Salter, and Ms. Kalina have nothing to disclose.

Funding/Support: This work was supported by a grant from the National Multiple Sclerosis Society (RG 4542-A-2) and by an unrestricted, Investigator-initiated research grant from Biogen Idec. The NARCOMS Registry is supported in part by the Consortium of Multiple Sclerosis Centers and its Foundation.

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CORRECTION

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