ORIGINAL ARTICLE

Multiple Sclerosis: Change in Health-Related Quality of Life Over Two Years

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ABSTRACT: ***Background:*** Cross-sectional research has demonstrated poorer function and health-related quality of life (HRQOL) in those with multiple sclerosis (MS) but less is known about change over time. The goals of this study were to measure change in HRQOL and identify factors associated with change. ***Methods:*** HRQOL was assessed at baseline and annually over two subsequent years using the Multiple Sclerosis Quality of Life Inventory. Function was assessed using the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite. Annualized rate of change was calculated for all twenty outcomes. Mixed effects modeling (univariate followed by multivariate) was used to examine the associations among patient characteristics and the age- and sex-adjusted Physical Component Summary (PCS) and Mental Component Summary (MCS) at study initiation and over the two years of follow-up. ***Results:*** Of 300 participants, 288 (96%) provided at least one assessment and are included in this analysis. Although 14 of the 20 outcomes showed a mean decline, only two (SF-36 physical function, p=0.018 and the EDSS, p<0.001) were statistically significant. The SF-36 social function showed a significant improvement (p=0.031). Only two variables were significantly associated with a decreased rate of decline or improvement over two years, including being female (PCS, p=0.001) and use of visiting nurse services (MCS, p<0.001). ***Conclusions:*** HRQOL is relatively stable over two years of follow-up, particularly for mentally-oriented outcomes. Further research with a longer period of follow-up is needed to provide additional insight into factors associated with change in HRQOL in patients with MS.

RÉSUMÉ: Changement de la qualité de vie reliée à la santé au cours d'un intervalle de deux ans dans la sclérose en plaques. ***Contexte :*** Des enquêtes transversales ont démontré une diminution fonctionnelle et une diminution de la qualité de vie reliée à la santé (QVRS) chez les individus atteints de sclérose en plaques (SP). Cependant, le changement de la QVRS en fonction du temps est mal connu. Les buts de cette étude étaient de mesurer le changement de la QVRS et d'identifier les facteurs associés au changement. ***Méthodes :*** La QVRS a été évaluée au début de l'étude et annuellement au cours des deux années suivantes au moyen du Multiple Sclerosis Quality of Life Inventory (MSQLI). L'évaluation fonctionnelle a été effectuée au moyen de l'Expanded Disability Status Scale (EDSS) et du Multiple Sclerosis Functional Composite. Le taux de changement annualisé de chacune des vingt mesures de résultats a été calculé. Les associations entre les caractéristiques des patients et le Physical Component Summary (PCS) et le Mental Component Summary (MCS) ajustés pour l'âge et le sexe au début de l'étude et au cours des deux années du suivi ont été examinées par modélisation d'effets mixes (univariée puis multivariée). ***Résultats :*** Au moins une évaluation a été faite chez 288 (96%) des 300 participants et leurs données ont été incluses dans l'étude. Bien qu'une baisse de la moyenne ait été observée pour 14 des 20 mesures de résultats, seulement deux (le SF-36 physical function, p = 0,018 et l'EDSS, p < 0,001) étaient significatives au point de vue statistique. Une amélioration significative a été observée pour le SF-36 social function (p = 0,031). Seulement deux variables étaient significativement associées à un taux plus bas de déclin ou d'amélioration au cours de deux ans, dont le sexe féminin (PCS, p = 0,001) et l'utilisation des services d'infirmières visiteuses (MCS, p < 0,001). ***Conclusions :*** La QVRS est relativement stable au cours de deux ans de suivi, particulièrement en ce qui concerne les mesures de résultats concernant les aspects mentaux. Des études comportant une durée de suivi plus longue sont susceptibles d'offrir une meilleure compréhension des facteurs associés aux changements de la QVRS chez les patients atteints de SP.

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Assessment of health-related quality of life (HRQOL) in those with multiple sclerosis (MS) provides information about the individual's perception of function and health beyond that which can be obtained by physical assessment alone[1]. A number of cross-sectional studies have demonstrated poorer HRQOL in those with MS as compared to those without MS[1-5], particularly in the physically-oriented domains, although there is also evidence that the mentally-oriented domains remain comparable to the general population[6]. Higher levels of disability, depression and need for support services were associated with reduced HRQOL[1,3,6-8], while higher education and higher income were associated with better HRQOL[1].

However, considerably less is known regarding change in HRQOL over time, and the factors associated with this change. Three studies with mean follow-up times of four[9], five[10] and

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eight[11] years noted substantial declines in some of the physically oriented domains of HRQOL. However, two of these[9,10] found that mentally and socially oriented domains remained stable or improved, while the third[11] found declines in physical, psychosocial and total scores, possibly due to the longer study duration. They did note, however, that the decline in the psychosocial domain failed to attain statistical significance. An additional study which evaluated coping in a sample of 382 participants over a two-year period noted that global quality of life improved, particularly in the area of social and emotional support, and that women had higher levels of global quality of life and social/emotional support coping than men[12].

One of the most commonly used measures of HRQOL is the Medical Outcomes Study Short-Form 36 (SF-36)[13,14]. It consists of 36 items encompassing eight HRQOL domains including physical function, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health. Domains are scored on standardized scales from 0-100, with higher values representing better HRQOL[13]. A Physical Component Summary (PCS) and a Mental Component Summary (MCS) can also be derived. These are standardized to a mean of 50, with a score above 50 representing better than average function and below 50 poorer than average function[14].

It has been recommended that the SF-36 be supplemented with a condition-specific measure of HRQOL to assess MS-specific symptoms such as fatigue, visual impairment and bowel and bladder function[3,15,16]. The MS Quality of Life Inventory (MSQLI)[15] short form contains 81 items, including the entire SF-36 and additional items for measuring fatigue, pain, sexual satisfaction, bladder control, bowel control, visual impairment, cognitive function (using the Perceived Deficits Questionnaire or PDQ[17]) and social support. An additional recommendation is that a functional assessment such as the Multiple Sclerosis Functional Composite (MSFC) be included as a clinical outcome in MS patients[16,17]. The MSFC consists of a timed 25-foot walk, 9-hole peg test and paced auditory serial addition test, and takes about 20 minutes to complete[18].

Functional status and well-being often form the conceptual basis of HRQOL, including the dimensions of physical, social, mental health and general health. The Wilson and Cleary model links such variables, along with biological and physiological variables, into a model where all variables are linearly associated with each other and also affect overall quality of life[19]. Aspects of the environment and characteristics of the individual are also considered. This conceptual model was used as the framework for the study.

This study builds on a recently published cross-sectional study of HRQOL in a sample of 300 persons with MS[1]. The sample was followed over two years, providing the opportunity to assess change as well as to identify factors associated with change.

Methods

A detailed description of the methodology is available elsewhere[1,20], but in brief, all individuals with an appointment at the MS Clinic of Kingston General Hospital in Kingston, Ontario, Canada, between September 2000 and August 2001 were invited to participate in the baseline component of this longitudinal study of HRQOL. At baseline, participation involved a clinical assessment, a patient questionnaire for information such as education, marital status and use of support services, a detailed chart review to obtain clinical characteristics, and the administration of the MSQLI and the MSFC. Over the next two years, those who consented received the MSQLI either via mail prior to a scheduled visit close to 12 months since their baseline assessment, or at the clinic for those who came for an unscheduled visit close to the time for the 12-month assessment. The MSFC was also administered during this visit, and the clinic neurologist assessed change in Expanded Disability Status Scale (EDSS). Chart review was utilized to obtain updated clinical characteristics such as use of aids, medications and number of relapses since the last visit. Ethics approval for the study was obtained from the Queen's University and Affiliated Teaching Hospital Research Ethics Board.

Data were managed and scored using SPSS (Version 12.0 for Windows, Chicago, IL, 2004) and imported into SAS (Version 9.1 for Windows SAS Inc, Cary, NC, 2003) for statistical analysis. Medical Outcomes Study 36-item health survey short form data were scored to create the eight domain scores and two orthogonal component summaries (MCS and PCS) as per the published scoring algorithm[14]. Following descriptive analyses, the unadjusted annualized change was calculated for each of the 20 outcomes (eight SF-36 domain and two summary scores, EDSS, MSFC, and the additional eight subscales from the MSQLI). Subsequent analyses focused on the PCS and the MCS, as they represent a summary of the SF-36 and are correlated with a number of the other outcomes[1] and are therefore likely to be reasonably representative of HRQOL in MS.

The PCS and MCS scores were first age- and sex-adjusted such that the adjusted scores represent the difference between the patients' observed scores and the Canadian normative data[21]. A negative score indicates the patient is below the norm for their age and sex. Baseline and follow-up scores were plotted for each of the two summary components using plotting characters to distinguish patients with progressive and relapsing remitting disease. The MCS and PCS were then modeled separately using a mixed effects model with random patient slopes and intercepts. The mixed effects model includes all patients with at least one assessment and efficiently combines information from patients with varying assessment timing. With this model, the intercepts and slopes estimate the baseline (first assessment) and annual change scores respectively. Interaction terms were then added to the models to estimate the effect of the baseline patient characteristics on these intercepts and slopes. Since this is not an inception cohort, time since diagnosis was included as a predictor variable. This allowed us to assess if the time since diagnosis modified the baseline HRQOL (intercept), its annual rate of change (slope), or the association between these and other baseline patient characteristics (interactions). For each summary component, we first examined each characteristic in isolation and then developed a multivariate model including all baseline patient characteristics retained by a backward selection procedure with $p>0.1$ as criterion for removal.

Close to 60 variables were collected at baseline and these have been previously described[1]. There were too many for valid modeling of longitudinal outcomes, so prior to analysis the list was refined using a combination of *a priori* evidence[1,3-6,19] and content considerations based on discussion with clinical staff at

the MS Clinic. In addition, low-frequency items were either eliminated from the analysis (n<5%) or collapsed (e.g. primary progressive, secondary progressive and progressive relapsing). The combination of individual characteristics, physiological characteristics and interventions such as medications and support services selected is appropriate within the framework of the Wilson and Cleary model[19].

Results

Of the 300 participants, 288 (96%) provided at least one PCS and MCS assessment and are included in this analysis. Second and third assessments were available in 264 (88%) and 193 (64%) participants respectively. The median time between the first (baseline) and second assessment was 1.1 years (range 0.7 to 1.6), and between the first and third was 2.1 years (range 1.6 to 3.1). The median time from diagnosis to our baseline assessment was 12 years and ranged from 9 months to 41 years. Baseline patient characteristics are described in Table 1.

Figure 1 (PCS) and Figure 2 (MCS) describe the age- and sex-adjusted scores at baseline and the last available follow-up. The two points corresponding to the same patient were connected, showing the change of that patient's score. Patients with progressive and with relapsing remitting disease are distinguished by color and point character. Scores below zero indicate that the participant scored below the norm for his or her age and sex. Almost all fell below the norm for the PCS, although this was less pronounced for the MCS. The pattern of change shows wide variability, with some showing little change while others had large declines or increases in scores.

Previously published work with the baseline data has already demonstrated that the group, as a whole, fell well below the age- and sex-adjusted normative data for the SF-36 (normative data are not available for the remaining outcomes), with statistically

Table 1: Baseline patient characteristics for variables used in mixed modeling, for subset of patients with PCS and MCS outcomes data for at least one time point

Patient characteristic	n/N	Percent	Mean ± Std
Age at first assessment (years)	288		47.0 ± 10.5
Age at onset (years)*	255		32.4 ± 9.6
Duration of MS (years)	255		14.0 ± 9.5
Female	213 / 288	74.0	
Live alone, no caregiver	31 / 288	10.8	
Positive family history	77 / 288	26.7	
Education level > high school	183 / 287	63.8	
Working (full or part time)	90 / 280	32.1	
Retired	22 / 280	7.9	
On disability	136 / 280	48.6	
EDSS Moderate	130 / 287	45.3	
EDSS Severe	22 / 287	7.7	
Clinical course relapsing/remitting	167 / 288	58.0	
Relapse in past year	46 / 257	17.9	
Taking interferon (any kind)	76 / 288	26.4	
Taking Copaxone®	40 / 288	13.9	
Medication for fatigue	22 / 288	7.6	
Medication for pain	50 / 288	17.4	
Depression	54 / 276	19.6	
High blood pressure	43 / 279	15.4	
Sleep disorders	24 / 282	8.5	
Thyroid disorder	22 / 281	7.8	
Allied health services	145 / 288	50.3	
Counseling	48 / 280	17.1	
Homemaker services	72 / 281	25.6	
Complementary health services	45 / 280	16.1	
Support group	62 / 278	22.3	
Visiting nurse services	73 / 280	26.1	
Use of Urology services or catheter	61 / 278	21.9	

* Precise date of onset was unavailable for 30, therefore age at onset could not be calculated. Other denominators may be less than 288 due to sporadic missing data.

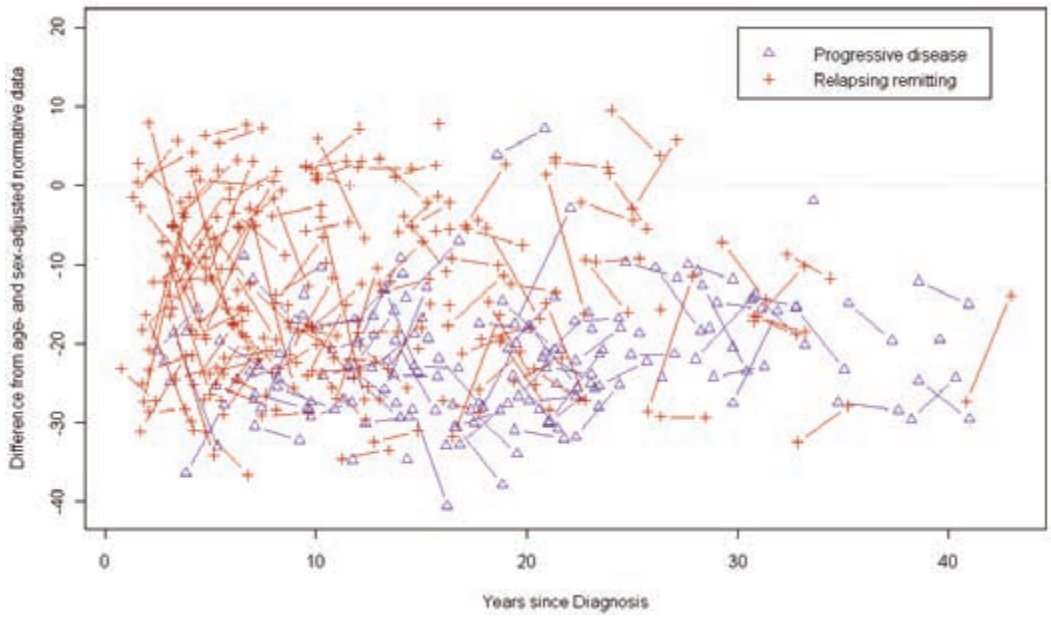

Figure 1: *Change over two years for the Physical Component Summary. Baseline scores are not the raw scores, but rather the difference between the age-and sex-adjusted normative data and the score of each participant.*

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Table 2: Unadjusted annual change for MSQLI and MSFC outcomes, and percent which declined, saw no change or improved over two years

Domain and Possible Range of Scores	Intercept	Parameter Estimate for Annual Change	p-value	Percent Declined/ No change/ Improved
Physical Function (0-100)	40.6	-1.38	0.018	48 / 16 / 30
Role Physical (0-100)	24.6	1.79	0.081	18 / 51 / 21
Bodily Pain (0-100)	59.2	-0.38	0.530	38 / 25 / 34
General Health (0-100)	51.3	-0.65	0.221	44 / 9 / 43
Vitality (0-100)	34.9	0.95	0.074	38 / 14 / 44
Social Function (0-100)	57.5	1.51	0.031	30 / 28 / 40
Role Emotional (0-100)	55.7	-1.52	0.262	24 / 49 / 17
Mental Health (0-100)	67.1	-0.02	0.959	44 / 13 / 38
Physical Component Summary (8-73)	33.5	-0.10	0.661	42 / 0 / 43
Mental Component Summary (10-74)	45.9	0.06	0.843	44 / 0 / 41
Expanded Disability Status (0-10) **	3.8	0.13	<0.001	30 / 54 / 8
Modified Fatigue Impact (0-20) **	12.2	-0.16	0.124	34 / 16 / 42
Pain Effects (6-30) **	14.9	0.16	0.332	40 / 13 / 36
Sexual Satisfaction (4-24) **	11.5	0.08	0.680	28 / 11 / 22
Bladder Control (0-22) **	5.4	0.21	0.127	34 / 27 / 28
Bowel Control (0-26) **	4.0	0.04	0.763	34 / 25 / 31
Impact of Visual Impairment (0-15) **	2.0	0.06	0.373	31 / 42 / 24
Perceived Deficits (0-20) **	7.4	0.18	0.099	44 / 14 / 38
Social Support Survey (0-100)	75.7	0.45	0.426	36 / 22 / 39
MS Functional Composite (z-score)	0.04	-0.02	0.259	27 / 0 / 29

** Higher scores represent poorer function.

Intercept and parameter estimates are based on the mixed effects model with random intercepts and slopes.

significant differences for all eight domains and both summary components of the SF-36 ($p<0.001$ for all, one-sample t-test)[1]. Table 2 contains the unadjusted annualized change for all outcomes, as well as the percent that declined, saw no change, or improved. The possible ranges for the scores are also provided. A response to the Sexual Satisfaction scale was provided by 152 (59.6%), as this scale is only appropriate for those in a relationship with one primary partner. The MSFC was completed by only 55.8% by year two (as compared to 81.7% at the time of the initial assessment), with many citing fatigue or simply refusing to complete the MSFC and in particular, the PASAT portion thereof.

Although 14 of the 20 outcomes showed a mean decline, most of the changes were small and only two (SF-36 physical function, $p=0.018$ and the EDSS, $p<0.001$) were statistically significant, while a third, perceived deficits, showed a trend towards significance ($p=0.099$). Given that a five-point change is considered clinically relevant for the SF-36[13], the magnitude of the change was small even when the results were statistically significant. For example, the change for the physical function domain was -1.38 points, suggesting that if the change is linear over time, it would take four years before the change became clinically relevant. Six of the outcomes showed small improvements, with the SF-36 social function attaining statistical significance (1.51, $p=0.031$). Vitality and role physical approached significance, at $p=0.074$ and $p=0.081$ respectively, but again, the magnitude of the change was small.

Table 2 also contains the percentage of participants who worsened, stayed the same or improved over the two years. For 10 of the outcomes, the largest percentage was in the "declined" category (e.g. for physical function, 48% worsened as compared

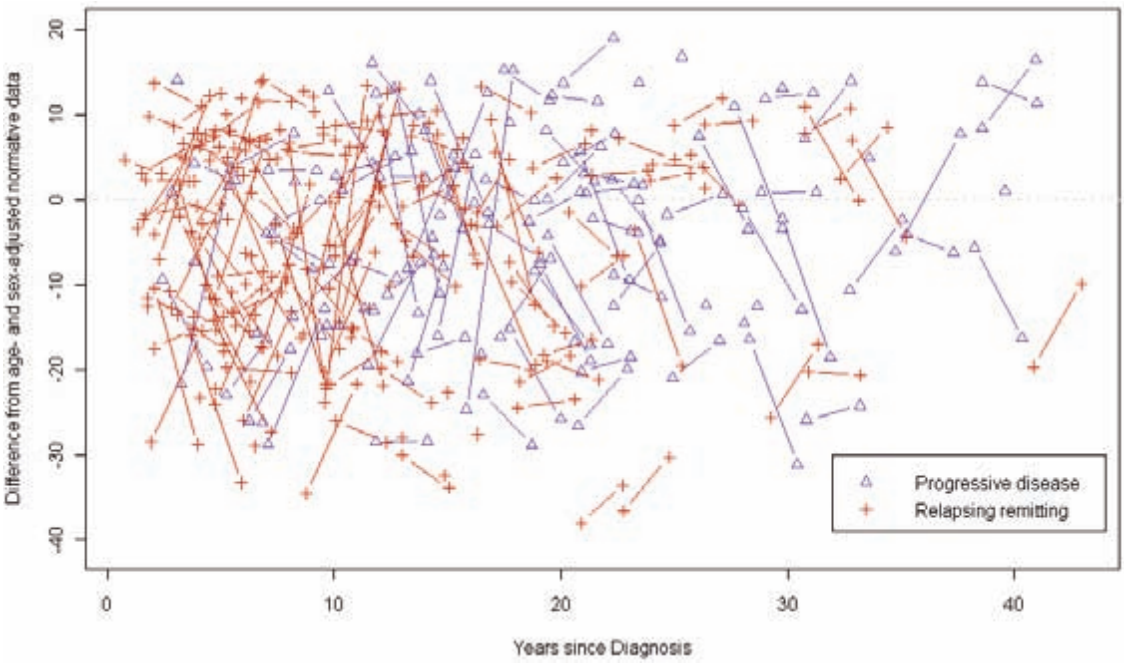

Figure 2: *Change over two years for the Mental Component Summary. Baseline scores are not the raw scores, but rather the difference between the age-and sex-adjusted normative data and the score of each participant.*

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to 16% who stayed the same and 30% who improved). For four outcomes (role physical, role emotional, EDSS and visual impairment), the largest percentage was in the "no change" group. For six outcomes, the largest percentage was in the "improved" category.

Table 3 (PCS) and Table 4 (MCS) contain the results of the mixed effects modeling. The univariate results are presented on the left side of the two tables, with the multivariate results presented to the right. The intercept and slope (β_0 and β_1) estimate the effect of the patient characteristics on the PCS and MCS at the first study visit (baseline), and on the annual rate of change from the first visit respectively. Negative β_0 estimates indicate that the particular characteristic is associated with a lower PCS or MCS at the baseline assessment, while a negative β_1 indicates that the characteristic is associated with a reduced rate of improvement or an accelerated rate of deterioration from baseline. When the estimates are positive, they suggest that the characteristic is associated with a reduced rate of deterioration or an increased rate of improvement.

In the univariate model of the PCS, some of the strongest negative associations with the baseline scores were for an employment status other than working (disability, retired or other, p<0.001), and for an EDSS of moderate or severe as compared to mild (p<0.001). Use of a variety of services and medications including interferon also had negative associations with the baseline scores, suggesting that those who were using these services or drugs were actually those with poorer function and lower HRQOL. Positive associations were noted for use of Copaxone® (p=0.007), higher education level (p<0.001) and a clinical course of relapsing remitting as compared to any form of progressive (p<0.001).

The effects of the baseline characteristics on change from baseline (β_1) were very small, suggesting that none of these characteristics substantially modified change in HRQOL over the two year follow-up from baseline. Being female and living with another person (or having a caregiver) were associated with a slower rate of decline or improvement in HRQOL (p=0.005 and p=0.066 respectively) as compared to males and those who lived alone. For the multivariate model, all retained variables with the exception of higher education level and a relapsing remitting clinical course were associated with poorer baseline

Table 3: Adjusted* association between patient characteristics and PCS trends

	Univariate model				Multivariate model **			
	Difference at Baseline†		Difference in Annual Rate of Change‡		Difference at Baseline†		Difference in Annual Rate of Change‡	
Patient characteristic	β_0±SE	p-value	β_1±SE	p-value	β_0±SE	p-value	β_1±SE	p-value
Age at diagnosis (per decade)	-1.30 ± 0.67	0.053	-0.00 ± 0.02	0.972				
Years since diagnosis (per decade)	-1.41 ± 0.67	0.037	0.00 ± 0.02	0.925				
Female	1.95 ± 1.35	0.151	0.12 ± 0.04	0.005			0.14 ± 0.04	0.001
Live with someone or have a caregiver	0.38 ± 1.92	0.843	0.12 ± 0.06	0.066			0.11 ± 0.06	0.077
Family history	1.82 ± 1.34	0.175	-0.01 ± 0.04	0.888				
Formal education beyond high school	4.77 ± 1.21	<0.001	-0.05 ± 0.04	0.249	2.04 ± 1.00	0.042		
Employment status: Other (Reference=Work)	-6.67 ± 1.71		0.01 ± 0.06		-4.79 ± 1.61			
Employment status: Retired	-6.30 ± 2.12	<0.001	-0.04 ± 0.07	0.335	-0.90 ± 1.97	<0.001		
Employment status: On disability	-10.95 ± 1.22		0.06 ± 0.04		-5.24 ± 1.18			
EDSS Moderate (Reference=Mild)	-8.01 ± 1.13	<0.001	0.02 ± 0.04	0.889	-2.78 ± 1.25	0.086		
EDSS Severe	-10.76 ± 2.13		0.01 ± 0.08		-1.84 ± 2.22			
Relapse/Remitting (versus Progressive)	8.56 ± 1.10	<0.001	-0.02 ± 0.04	0.641	4.84 ± 1.31	<0.001		
Relapse in past year	0.30 ± 1.63	0.854	0.03 ± 0.05	0.625	-2.91 ± 1.24	0.020		
Taking interferon	-2.03 ± 1.35	0.133	0.00 ± 0.04	0.952	-2.07± 1.13	0.068		
Taking Copaxone®	4.60 ± 1.70	0.007	-0.06 ± 0.05	0.302				
Medication for fatigue	-2.70 ± 2.23	0.227	0.00 ± 0.07	0.966				
Medication for pain	-6.77 ± 1.52	<0.001	-0.00 ± 0.05	0.976	-6.20 ± 1.22	<0.001		
Depression	-2.09 ± 1.53	0.175	-0.06 ± 0.05	0.251				
High blood pressure	-4.83 ± 1.67	0.004	0.09 ± 0.05	0.099	-2.88 ± 1.31	0.029		
Sleep disorders	-4.18 ± 2.17	0.055	0.02 ± 0.07	0.747				
Thyroid disorder	-1.71 ± 2.24	0.446	-0.09 ± 0.07	0.192				
Allied health services	-6.43 ± 1.13	<0.001	0.02 ± 0.04	0.558	-2.24 ± 1.03	0.031		
Counseling	-2.96 ± 1.59	0.064	0.04 ± 0.05	0.398				
Homemaker services	-5.72 ± 1.33	<0.001	0.01 ± 0.04	0.796				
Complementary health services	-2.29 ± 1.64	0.165	-0.06 ± 0.05	0.239	-4.14 ± 1.37	0.003		
Support group	-3.83 ± 1.44	0.009	0.08 ± 0.05	0.085				
Visiting nurse services	-6.02 ± 1.34	<0.001	0.01 ± 0.04	0.895				
Use of Urology services or catheter	-7.42 ± 1.41	<0.001	-0.01 ± 0.05	0.797	-2.29 ± 1.23	0.063		

* Predictors were modeled separately by a mixed model with random patient slopes and intercepts but fixed patient characteristics. † β_0 estimates the association between the patient characteristic and the PCS at the first study visit. Significant negative estimates imply that the given characteristic is associated with a lower PCS at the first study observation. ‡ β_1 estimates the expected increase in the annual rate of change in PCS. Significant positive estimates imply that the given characteristic is associated with a decreased rate of deterioration or an increased rate of improvement during the study period. ** Multivariate mixed model was obtained by backward selection procedure using p>0.1 criterion for removal.

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Table 4: Adjusted* association between patient characteristics and MCS trends

	Univariate model				Multivariate model **			
	Difference at Baseline†		Difference in Annual Rate of Change‡		Difference at Baseline†		Difference in Annual Rate of Change‡	
Patient characteristic	β_0±SE	p-value	β_1±SE	p-value	β_0±SE	p-value	β_1±SE	p-value
Age at diagnosis (per decade)	0.61 ± 0.78	0.437	-0.01 ± 0.03	0.844				
Years since diagnosis (per decade)	0.69 ± 0.79	0.384	-0.02 ± 0.03	0.434				
Female	1.30 ± 1.60	0.418	-0.01 ± 0.06	0.866				
Live with someone or have a caregiver	1.68 ± 2.26	0.457	-0.11 ± 0.08	0.186				
Family history	1.75 ± 1.58	0.268	-0.05 ± 0.06	0.365				
Formal education beyond high school	2.90 ± 1.46	0.048	0.02 ± 0.05	0.766	3.90 ± 1.22	0.002		
Employment status: Other (Reference=Work)	-5.63 ± 2.18		-0.11 ± 0.08		-5.94 ± 1.89			
Employment status: Retired	0.19 ± 2.70	<0.001	0.01 ± 0.10	0.154	0.46 ± 2.45	0.001		
Employment status: On disability	-7.53 ± 1.55		0.07 ± 0.06		-4.38 ± 1.48			
EDSS Moderate (Reference=Mild)	-1.20 ± 1.46	0.265	-0.04 ± 0.05	0.735	-1.75 ± 1.62	0.008		
EDSS Severe	3.16 ± 2.74		-0.03 ± 0.10		5.92 ± 2.92			
Relapse/Remitting (versus Progressive)	-0.15 ± 1.42	0.919	-0.02 ± 0.05	0.740	-3.07 ± 1.64	0.063		
Relapse in past year	0.77 ± 1.91	0.689	0.03 ± 0.07	0.688				
Taking interferon	-0.83 ± 1.59	0.603	0.00 ± 0.06	0.932	2.88 ± 1.41	0.042		
Taking Copaxone®	0.00 ± 2.02	0.999	0.09 ± 0.07	0.204				
Medication for fatigue	1.51 ± 2.63	0.565	-0.11 ± 0.09	0.222				
Medication for pain	-1.41 ± 1.85	0.446	0.12 ± 0.06	0.062				
Depression	-12.60 ± 1.65	<0.001	0.11 ± 0.07	0.106	-9.67 ± 1.61	<0.001		
High blood pressure	-3.89 ± 1.99	0.052	0.01 ± 0.07	0.843	-4.61 ± 1.65	0.006		
Sleep disorders	-6.62 ± 2.53	0.010	0.06 ± 0.09	0.517				
Thyroid disorder	-2.33 ± 2.65	0.380	0.06 ± 0.09	0.491				
Allied health services	-4.03 ± 1.38	0.004	0.08 ± 0.05	0.115				
Counseling	-8.25 ± 1.82	<0.001	0.07 ± 0.07	0.296	-3.99 ± 1.66	0.018		
Homemaker services	-3.74 ± 1.61	0.022	0.05 ± 0.06	0.375				
Complementary health services	-3.99 ± 1.94	0.041	0.06 ± 0.07	0.412	-3.62 ± 1.66	0.030		
Support group	-3.81 ± 1.71	0.027	-0.00 ± 0.06	0.965				
Visiting nurse services	-4.56 ± 1.61	0.005	0.19 ± 0.06	0.001	-4.15 ± 1.54	0.008	0.21 ± 0.06	<0.001
Use of Urology services or catheter	-2.93 ± 1.72	0.090	0.03 ± 0.06	0.671				

* Predictors were modeled separately by a mixed model with random patient slopes and intercepts but fixed patient characteristics. † β_0 estimates the association between the patient characteristic and the MCS at the first study visit. Significant negative estimates imply that the given characteristic is associated with a lower MCS at the first study observation. ‡ β_1 estimates the expected increase in the annual rate of change in MCS. Significant positive estimates imply that the given characteristic is associated with a decreased rate of deterioration or an increased rate of improvement during the study period. ** Multivariate mixed model was obtained by backward selection procedure using p>0.1 criterion for removal.

HRQOL as compared to where they should be for their age and sex. The same two variables that were associated with slower decline in the univariate models remained significant or close to significant in the multivariate estimates of change, including being female (p=0.001) and those who lived with someone or had a caregiver (p=0.077).

For the MCS, participants with a history of depression scored 12.6 points lower, on average, at baseline than those without depression (p<0.001). Overall, employment status other than working or retired was associated with poorer mental health (p<0.001). Similar to the findings for the PCS above, use of a variety of services and medications were negatively associated with MCS at the time of the first visit, again suggesting that those using these services had poorer HRQOL at baseline. Almost nothing was associated with change in mental health over the two years. Only the use of visiting nurse services was associated with a reduced rate of decline or improvement for both the univariate and the bivariate model (p=0.001 and p<0.001 respectively), but the estimates also indicate that this group was functioning at a significantly lower level (approximately four points) at baseline, suggesting that participants using visiting nurse services actually had poorer function and lower HRQOL throughout the study period.

It should be noted that certain characteristics are significant univariate predictors for PCS or MCS but are not represented in the corresponding multivariate model. This occurs when there is a fair amount of correlation between the characteristics. Thus, after adjusting for one characteristic, another may no longer significantly contribute to the multivariate model. The multivariate analysis therefore does not necessarily imply that the eliminated characteristics are not associated with PCS or MCS, but rather that they are not associated with the outcomes independently of other predictor variables retained by the model. Quadratic terms of all continuous predictors were tested to assess for non-linear associations, but none were significant. Finally, interactions terms between all predictor variables and: age at diagnosis, time since diagnosis, sex, and clinical course were tested, but none were identified as statistically significant after

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adjusting for the large number of tests. In particular, there was no suggestion that the time from diagnosis of MS modified any of the associations between the patient characteristics and the baseline scores or the rates of change from baseline.

Discussion

The goal of the longitudinal component of the study was to identify factors associated with change in HRQOL and functional outcome. The intent was to identify the characteristics of those at risk for a deteriorating HRQOL outcome in the subsequent few years, so that interventions could be planned. This was particularly relevant since the baseline data had already demonstrated that there was a substantial burden of illness associated with MS, with all differences between the study population SF-36 scores and the age- and sex-adjusted normative data attaining statistical significance[1]. These findings are supported by additional Canadian research using the Health Utilities Index to compare respondents with and without MS, which noted that the magnitude of disease burden is severe relative to the general population[22].

The results do support previous findings in that while the physically oriented domains and functional ability tended to decline, social function and other mentally-oriented domains remained stable and even improved[9-11]. The stability of mental health despite significant disability has been noted previously and may reflect patient adaptation to the disease and effective supportive care[23,24]. The current study is of shorter duration than the other three longitudinal ones, but if the results of our study are extrapolated over a longer period of follow-up the results are in fact quite similar.

It is of particular interest that for many of the outcomes, there were similar numbers of participants who worsened, stayed the same and improved. This suggests that some participants saw substantial declines while others saw substantial improvements, effectively canceling each other out, and as a result the mean changes tended to be small. Of the eight SF-36 domains, only the physical and the social function domains had statistically significant changes, with the former showing decline and the latter improvement. In both cases, the mean change was well below the five points considered by the developers to be clinically and socially relevant[13].

The symptom status and functional status components of the Wilson and Cleary model[19] were well represented in the findings at the first study visit for both the PCS and the MCS, along with additional patient characteristics such as employment status and education. The positive effect of higher education levels and the importance of sustaining employment after a diagnosis of MS have been noted in other research[25]. However, very few of the symptoms and functional components were associated with change from baseline. The two figures clearly show a diverse pattern of change, with almost equal numbers of patients seeing an increase or a decrease in their HRQOL over the two years of the study, both for the relapsing remitting and progressive patients. The inability to develop good models of change suggests two things. First, it is likely that a two-year follow-up is not a sufficient length of time to demonstrate change. Second, it is possible that many of the factors associated with changes in HRQOL may be beyond the scope of the typical assessment of MS patients, even when augmented by additional socio-demographic and clinical information[23].

The use of a number of services such as homemaker services, visiting nurse, allied health, urology, counseling and support groups, and the use of medication for fatigue and pain, were consistently associated with poorer HRQOL at baseline, likely because those with poorer function and HRQOL were more likely to use these services and medications. However, most of these predictors appear to have little effect on change from baseline. This may in part be explained by the possibility that they are already scoring so poorly that they were unable to score much lower (e.g. floor effect). The use of visiting nurse services was the sole significant predictor of a reduced rate of decline or an improvement for the MCS. Nurses can take on a variety of roles, including advocacy, coordination of allied health care services, interpretation of the health care system, teaching, education, support and encouragement, active listening, initiation of treatments, suggestions for symptom management, and support and contact with other family members, to name a few. The specific role of the visiting nurse was not documented within the study, but would be of interest for future research.

The association of disease-modifying drugs was also interesting. For the PCS, those taking interferon tended to have a poorer score at the initial visit, while those taking Copaxone® tended to have a higher score, but the impact of these two drugs on change over time was negligible. Neither interferon nor Copaxone® were strongly associated with the MCS in the univariate analysis. However, interferon was weakly but significantly associated with a higher MCS at the initial visit in the multivariate model, when other factors such as employment status, EDSS and clinical course were controlled.

There was little association between gender and the MCS. However, for the PCS, females tended to score somewhat higher than males both at the initial visit and showed less decline over time. The difference fell short of statistical significance at the initial visit but did attain significance for the change, and is consistent with previous research[9,12]. Age at onset and duration of MS were weakly associated with poorer PCS scores at the time of the initial visit, but had little effect on change over the two years. Conversely, although not significant, both age and duration were weakly but positively associated with the MCS, which is consistent with other research that has noted that as age increases or disease progresses, physical aspects of HRQOL decline while the mental aspects tend to improve[23,24,26].

There are several limitations to this study. First, there was some loss to follow-up, although the use of a mixed modeling approach did permit the maximum use of available data at all three points in time, allowing us to retain the data for 96% of the original participants and precluding the need for multiple imputation. It should also be noted that the linearity assumed by the model may not extrapolate to longer follow-up periods. Finally, only two of the 20 outcomes were modeled in detail, while the remaining 18 are only described in a simple, unadjusted form. The current guidelines continue to suggest that a combination of generic, condition-specific and functional measures may provide the best information with regard to understanding HRQOL within the context of MS[3,15-17], but analytically this volume of outcomes represents a substantial challenge and we chose to model the two outcomes that were the most representative of the 20 that were available.

Despite these limitations, this study provides valuable insight into the changes in HRQOL of those with MS. In particular, the

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finding that HRQOL is relatively stable over two years of follow-up is good news. Only two of the 20 outcomes saw statistically significant mean declines over two years, while one outcome saw a statistically significant improvement. In fact, a substantial number of participants saw no change and even improvement in outcomes. The sample size was larger than most studies of HRQOL in this population, and this study is one of the few to follow those with MS over time, while assessing both generic and condition-specific measures of HRQOL.

It is clear from previous work that there is a substantial burden of illness associated with MS when compared to the general population[1-6]. However, one of the main findings of this study is that while the HRQOL of this population is lower than the general population, it remains quite stable over a two-year time frame in patients who have been diagnosed for some time, particularly for the mentally-oriented domains. This suggests that much of the deterioration of quality of life may occur relatively early in the clinical course. The positive effect of visiting nurse services on mental aspects of HRQOL is of interest, and future research into which nursing services influence HRQOL may be warranted. In addition, a longer period of follow-up will provide valuable insight into the factors associated with long term change in HRQOL in those with MS.

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