Author(s): Rintala, Aki; Häkkinen, Arja; Paltamaa, Jaana

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Ten-year follow-up of health-related quality of life among ambulatory persons with multiple sclerosis at baseline

Aki Rintala[1], Arja Häkkinen[1,2], Jaana Paltamaa[3]

[1] Faculty of Sport and Health Science, University of Jyväskylä, P.O. Box 35, 40014 Jyväskylä, Finland

[2]Department of Physical Medicine and Rehabilitation, Central Finland Health Care District, Keskussairaalantie 19, 40620 Jyväskylä, Finland

[3] School of Health and Social Studies, JAMK University of Applied Sciences, P.O. Box 207, 40101 Jyväskylä, Finland

A. Rintala & A. Häkkinen

Faculty of Sport and Health Science, University of Jyväskylä, P.O Box 35, FI–40014 University of Jyväskylä, Finland

Corresponding author:

J. Paltamaa, School of Health and Social Studies, JAMK University of Applied Sciences, B.O. Box 207, FI–40101, Jyväskylä, Finland. e-mail: jaana.paltamaa@jamk.fi. Tel. +358 50 536 5459

ABSTRACT

Purpose: The aim of this 10-year follow-up study was to determine changes in health-related quality of life (HRQoL) over time among ambulatory persons with MS (PwMS) at the baseline using generic and disease-specific instruments.

Methods: Of 109 independently walking PwMS included in a population-based study in 2002, 77 (70.6%) were re-assessed in 2012. HRQoL was captured using the 36-Item Short Form Survey Instrument (RAND-36), 15D-instrument (15D) and the Multiple Sclerosis Quality of Life-54 (MSQOL-54). Repeated measures ANOVA and effect size (ES) calculations (Cohen's *d*) were used in the statistical analysis.

Results: The RAND-36 physical health composite score (PHC) (p=.003, ES=0.26) and 15D total score (p=.012, ES=0.25) declined from the baseline levels. In particular, lower scores were observed on the RAND-36 scales of physical functioning (p=.001, ES=0.27), pain (p=.020, ES=0.25), and general health perceptions (p=.002, ES=0.36), on the MSQOL-54 scales of physical functioning (p=.001, ES=0.27), pain (p=.040, ES=0.21), sexual functioning (p=.003, ES=0.43), and satisfaction with sexual functioning (p=.012, ES=0.38), and in the 15D dimensions of mobility (p=.004, ES=0.31) and sexual functioning (p=<.001, ES=0.59). Improvement was observed on the RAND-36 scale of social functioning (p=.049, ES=0.25). The other composite scores, scales, and dimensions remained unchanged.

Conclusions: The results of this study suggest that ambulatory PwMS at baseline reported reduced HRQoL in physical functioning after a 10-year follow-up period while emotional well-being was maintained and social functioning improved. The scores in the other HRQoL dimensions and scales remained unchanged. More long-term population-based studies are needed to precisely determine the development of HRQoL among PwMS.

Keywords Multiple sclerosis, Health-related quality of life, Patient-reported outcomes, Quality of life

Introduction

Multiple sclerosis (MS) is a progressive neurological chronic disease of the central nervous system [1]. Symptoms of MS are individual, with differences in the range of functional, psychological, and cognitive limitations. The most common symptoms are difficulty in walking [2, 3], depression [4, 5], and fatigue [6, 7]. Other frequent symptoms are bladder and bowel symptoms, cognition, cerebellar and sensory symptoms, motor weakness and spasticity, sexual dysfunction, and visual loss [8]. Various symptoms have different effects among persons with MS (PwMS) on their daily living activities, level of well-being and satisfaction in life, and overall quality of life [1]. Previous studies have indicated that MS symptoms affect quality of life [9, 10, 11]. Furthermore, depression [12, 13] as well as increased disability, anxiety symptoms, fatigue, and physical comorbidity have been noted to associate with decreased HRQoL in MS [9].

Health-related quality of life (HRQoL) comprises both clinical and psychosocial aspects that are assessed with a multidimensional variety of physical, mental, social, and economic scales [14, 15]. Over the last decade, most MS-related HRQoL studies have used rather short follow-ups [14, 16-22]. Only one epidemiological study with a follow-up period of more than ten years has been published [23]. Most studies have used instruments that are either generic, such as the Short Form (36) Health Survey (SF-36) [17-18, 20-21], or diagnosis-specific, such as the Multiple Sclerosis Quality of Life-54 (MSQOL-54) [14, 19, 21-23]. Moreover, little is known about the possible factors contributing to changes in HRQoL among PwMS [22]. Deterioration has been observed on the physically-oriented scales of the SF-36 (i.e., physical functioning, role-physical), and MSQOL-54 (i.e., physical functioning, role-physical, and sexual functioning) questionnaires [17-19, 21]. Some studies, however, have also reported improved scores on HRQoL scales oriented to mental functioning over time among PwMS [14, 21, 23]. To our knowledge, no previous studies have used both generic and diagnosis-specific HRQoL instruments in the same population-based and long-term follow-up study among PwMS. Additionally, population-based samples are rare in long-term follow-ups.

The aim of this 10-year follow-up study was to determine changes in HRQoL over time among ambulatory PwMS at baseline using generic (i.e., overall) and disease-specific HRQoL instruments.

Methods

Participants

This 10-year follow-up study was part of a larger study [24]. The participants were recruited using a population-based database in the Central Finland Health Care District containing 277 patients with a definite diagnosis of MS in 2000 [25]. Subjects who met the eligibility criteria were ambulatory with no major additional diseases. Of the 120 ambulatory PwMS who volunteered to participate in the physical functioning measures in 2000, 109 attended the follow-up measures in 2002 [26] and 77 completed the follow-up study in 2012. The study design was approved by the Ethics Committee of the Central Finland Health Care District. The participants provided written informed consent prior to enrolment.

Data sources

Participants filled out self-report questionnaires twice, at baseline in 2002 and at follow-up in 2012. Three HRQoL instruments were used: the 36-Item Short Form Survey Instrument (RAND-36) and the 15D-instrument (15D) (i.e., generic HRQOL scales), and the Multiple Sclerosis Quality of Life-54 (MSQOL-54) scale (i.e., disease-specific scale).

The RAND-36 comprises 36 items that are transformed into a score between 0 and 100, where a higher value indicates a higher quality of life. Items are distributed into eight scales using a weighted calculation formula: physical functioning, role limitations caused by physical health problems, role limitations caused by emotional health problems, social functioning, emotional well-being, energy/fatigue, pain, and general health perceptions. From these scales two composite scores are formulated: the physical health composite score (PHC) and the mental health composite score (MHC) [27, 28].

The MSQOL-54 includes all items from the RAND-36 along with 18 additional disease-specific items that are distributed among 12 multi-item scales and two single items: physical health, role limitations caused by physical health problems, role limitations caused by emotional health problems, pain, social functioning, energy, emotional well-being, health perceptions, cognitive functioning, health distress, sexual functioning, overall quality of life, change in health, and satisfaction with sexual functioning. Two composite scores are calculated from the 12 scale scores.

The scoring criteria require answers to at least 50% of the items. The score for each item is transformed into a score between 0 and 100, where a higher value indicates a higher quality of life. Items are then calculated into scales by a weighted calculation formula [29].

The 15D comprises 15 dimensions: mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality, and sexual activity. For each dimension, the level checked by the respondent is coded from 1 to 5 (1=the highest/best level, 5=the lowest/worst level). The 15D questionnaire has one summary score calculated from the 15 dimensions. The 15D total score is on a scale from 0 to 1, where a higher value indicates a greater quality of life. To derive the 15D total score, a response must be given to each dimension [30].

In addition, the following sociodemographic characteristics were collected with a questionnaire: age, gender, employment status, co-habiting status, use of walking aids outside, relapses during the previous year, and disease-modifying treatments. Clinical characteristics, including disease duration since diagnosis, clinical course of MS, and the Expanded Disability Status Scale (EDSS) were collected from medical records. The EDSS was used to determine the progression of the disease and the degree of neurological impairment in MS. It contains eight functional groups (pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral or mental, and other or miscellaneous). Neurological impairment is evaluated for each group and summed within the eight groups. The total scale is scored from 0 (normal neurological condition) to 10 (death due to MS) in half-point increments [31]. A neurologist assessed the participants' EDSS at baseline and the Subjective Expanded Disability Status Scale (SDSS) was used at the 10-year follow-up. Previous studies have indicated consistency between the EDSS and SDSS [32-33].

Statistical methods

Comparison between baseline and follow-up values in sociodemographic and clinical characteristics were performed with Pearson's chi-square or Fisher's exact test (p -value). A repeated measures ANOVA was used to estimate changes in HRQoL. The effect sizes with confidence interval (95% CI) were calculated with Cohen's d using a formula for dependent samples with the mean difference between pre-post scores divided by the baseline and follow-up standard deviations, taking into account the correlation between pre-post scores [34]. An effect size of ≥ 0.20 was considered small, ≥ 0.50 medium, and ≥ 0.80 large [35].

Due to missing data because of nonresponses, the sample size varies somewhat across the HRQoL instruments. In the MSQOL-54, missing data were found in sexual functioning (22%, *n*=17) and satisfaction with sexual functioning (1%, *n*=1). PHC was calculated from the scales by excluding missing data from the sexual functioning scale if the participants had answered fewer than 50% of the questions in the scale. In the 15D, two participants were excluded from the analysis due to at least four missing answers in the 15D dimensions.

Results

Participants

At follow-up, the participants comprised 61 (79%) females and 16 (21%) males with a mean (SD, range) age of 57 (10.8, 31–83) years. Ninety percent of the participants had primary remitting MS, including both relapsing-remitting and secondary-progressive MS, and 8% had primary progressive MS. For one subject, the clinical course of MS was unknown. The mean (SD) disease duration since diagnosis was 20 (6.6) years, with a range of 12–38 years. Sociodemographic and clinical characteristics are presented in Table 1. No statistically significant difference was observed between drop-outs (*n*=32) and participants (*n*=77) with respect to age (p = .655), gender (p = .124), clinical course of MS (p = .531), or disease duration since diagnosis (p = .112). A statistically significant difference was found between participants and drop-outs in the EDSS (p = .027) as well as in the use of walking aids outside (p = .030), where severe disability and the use of the walking aids were more visible among drop-outs than among participants.

Table 1 Sociodemographic and clinical characteristics of the participants (*n*=77)

Outcome data

Changes in HRQoL composite and total scores among PwMS are presented in Table 2. Statistically significance deterioration was found in the RAND-36 PHC (p = .003, ES = 0.26) and 15D total score (p = .012, ES = 0.25). The other composite scores remained unchanged.

Changes in specific HRQoL scales and dimensions are presented in Table 3 and in Figure 1. Statistically significant deterioration was observed on the RAND-36 scales of physical functioning (p = .001), pain (p = .020), and general health perceptions (p = .002). Improvement was indicated on the RAND-36 scale of social functioning (p = .049). In both deterioration and improvement, the effect sizes were small, ranging from 0.25 to 0.36. In the RAND-36 follow-up, 33% of the respondents reported no limitations on the role-physical scale and 57% on the emotional well-being scale; in other words, these respondents scored the maximum number of points (100/100).

On the MSQOL-54 scales**,** statistically significant deterioration occurred in scores for physical functioning (p = <.001), pain (p = .040), sexual functioning (p = .003), and satisfaction with sexual functioning (p = .012). The effect sizes varied from 0.21 for pain to 0.43 for sexual functioning. Overall, no limitations were reported in the follow-up by 33% of respondents on the role-physical scale, 58% on the role-emotional scale, 30% on the social functioning scale, 29% on the sexual functioning scale, and 23% on the satisfaction with sexual functioning scale.

In the 15D dimensions, deterioration was observed in mobility (p = .004) and sexual activity (p = <.001). The effect sizes for mobility (ES = 0.31) was small, and for sexual activity it was medium (ES = 0.59). In the follow-up on the 15D dimensions, maximum scores were recorded for 95% of the respondents in eating, 78% in hearing, and 26% in discomfort.

Table 2 Changes in RAND-36 and MSQOL-54 composite scores and 15D total score among PwMS at the 10-year follow-up

Table 3 Changes in RAND-36 and MSQOL-54 scales and 15D dimensions among PwMS at the 10-year follow-up

Fig. 1 Changes in health-related quality of life among PwMS at the 10-year follow-up (*p -value * < 0.05, ** < 0.01, *** < 0.001)

Discussion

The aim of this 10-year follow-up study was to determine changes in HRQoL among ambulatory PwMS at baseline in a population-based cohort study. The results indicated that the deterioration in

perceived HRQoL during the 10-year follow-up period pertained to physical functioning irrespective of the outcome instrument. Mental functioning remained unchanged, and one social functioning scale improved.

The scores on the two generic instruments, the RAND-36 physical health composite and the 15D total score, indicated deterioration, but the mental health composite scores remained unchanged. The physical and mental composite scores of the disease-specific MSQOL-54 also remained unchanged. The unchanging composite scores on the MSQOL-54 support a finding from a previous epidemiological study [23] with a similar follow-up period (11 years), participant age (mean age of 48 years), EDSS (0.0 to 6.5), and disease duration (average of 19 years). However, deterioration in the MSQOL-54 physical and mental health composite scores has been reported in a previous clinic-based study [22] with a six-year follow-up period and a disease duration of nine years. The inclusion of non-ambulatory participants by Tepavcevic et al. [22] may partly explain the different results.

A more detailed analysis revealed deterioration on the RAND-36 and MSQOL-54 physical functioning scales as well as in the 15D mobility dimension. These results conflict with a previous epidemiological study, with an 11-year follow-up and a disease duration of 19 years, where no deterioration was found in disease-specific physical functioning [23]. This discrepancy between our results and those reported by Giordano et al. [23] may be partly explained by the fact that in the Giordano et al. [23] study 19% of the participants were non-ambulatory at baseline. In addition, another epidemiological study (N=205), with 83% of the ambulatory participants at the baseline and a disease duration of 17 years, found a deterioration on the MSQOL-54 physical functioning scale at the five-year follow-up [21]. Clinic-based studies with follow-ups of less than six years also reported deterioration on the MSQOL-54 and SF-36 physical functioning scales [20, 22]. In our study, deterioration in the 15D mobility dimension indicated consistency with MSQOL-54 and RAND-36 physical functioning. From a clinical perspective, this finding might be interesting, because only one item from the 15D represents mobility whereas ten items from the RAND-36 and MSQOL-54 are distributed along a physical functioning scale. However, no previous data exist on the use of the 15D mobility dimension among PwMS.

Furthermore, in our study, the MSQOL-54 pain scale and the 15D pain dimension indicated deterioration. To our knowledge, deterioration on the pain scale has not been reported in previous epidemiological or clinical studies using the RAND-36 or MSQOL-54 instruments [20-23] although the presence of chronic pain among PwMS has been noted [36-37]. Our study indicated deterioration in sexual activity on the 15D and the MSQOL-54 as well as in satisfaction with

sexual functioning on the MSQOL-54. Only one six-year, clinic-based follow-up study has reported deterioration in sexual functioning and in satisfaction with sexual functioning on the MSQOL-54 [22] among participants with a similar EDSS level and disease duration.

In our study, HRQoL in mental functioning remained stable, and it improved in social functioning. When the progressivity of MS is taken into account, these findings can be considered to be a positive aspect in the change of HRQoL over time. Giordano et al. [23] found improvement in emotional well-being, but in our findings it remained unchanged. Improvement in social functioning on the RAND-36 scale was in line with previous long-term community-based studies using the MSQOL-54 [21, 23]. However, improvement on only a single scale could be partly explained by response shift, especially in follow-up studies [23, 38]. Due to changes in their disease or symptoms, respondents may have changed their values and the quality of life they require [39-40]. In clinical practice, the response shift phenomenon should be taken into account in the interpretation of HRQoL results.

In sum, the scores on most of the HRQoL scales and dimensions in our 10-year follow-up study indicated unchanged scores despite how the variables used to describe physical functioning, such as indicated by the EDSS, worsened and the use of walking aids outside increased over time. At follow-up, 88% of the participants remained ambulatory (EDSS < 6.5) even though mean disease duration was 20 years (SD 6.6). Similar findings were reported in the study by Pittock et al. [41], where 87% of the participants scored lower than 4.0 on the EDSS at the 20th year of disease duration. It has also been reported that an EDSS rating of two or lower for more than 10 years indicates a more than 90% chance of MS remaining stable [41]. In contrast, a more severe degree on the EDSS has been reported to associate with deterioration in HRQoL physical functioning [42, 43], and walking impairment has indicated lower HRQoL [44]. In our study, persons with a higher EDSS rating and users with walking aids outside were among the drop-outs. When the results for drop-outs and the results of those who indicated no change in HRQoL are taken into account, our findings possibly suggest that sustained ambulatory behavior over time could be a positive predictor of HRQoL. However, more studies should be conducted to determine if this finding is accurate among PwMS in a population-based sample.

Assessing whether the HRQoL of PwMS has changed over time is important in clinical practice and research. Therefore, the instruments used should be responsive to this possibility [45]. At the 10-year follow-up, our study found deterioration of 3 to 13 units from the baseline values, which ranged from 42 to 74 for the RAND-36 instrument. According to previous studies using the SF-36 instrument, which is similar to the RAND-36, from 3 to 5 units [46] and from 2 to 8 units

[47] have been established as the definition of a minimal clinically important difference (MCID). When we compare these values to our results, our study findings for the RAND-36 can be considered clinically responsive. In addition, for the SF-36 scales, a negligible to small change in effect size (0.01 to 0.30) has been proposed as a definition of a minimal detectable change (MDC) [48], which also supports our findings. To our knowledge, neither an MDC nor MCID has been established for MSQOL-54 [49], but in previous studies the deterioration in HRQoL has varied from 1.3 to 11.3 units, which is consistent with our findings [20-23]. For the 15D, deterioration of 0.02 to 0.14 units was found in baseline values ranging from 0.79 to 0.85. One previous study has established 0.02 units as the minimum important change (MIC) for the 15D [50]. In sum, more studies to investigate either the MDC or MCID for HRQoL among PwMS are needed.

PwMS at the 10-year follow-up reported a lower quality of life than the Finnish general population in all of the RAND-36 domains and 15D dimensions, the exception being the RAND-36 scale for emotional well-being. The main differences were found in the RAND-36 scales for physical functioning (57.5 vs. 84.9) and role limitations due to physical health problems (52.6 vs. 74.8) [51]. In the 15D, similar differences were also found in mobility (0.71 vs. 0.94), excretion (0.74 vs. 0.90), usual activities (0.78 vs. 0.93), and sexual activity (0.71 vs. 0.91) [52]. In addition, in the RAND-36 we found a level of emotional well-being (74.1) similar to that in the Finnish general population (73.7) [51], along with improved social functioning. These results indicate positive HRQoL in PwMS with an average disease duration of 20 years.

The major strength of our study is the 10-year population-based cohort that provides information on the changes in HRQoL among ambulatory PwMS at baseline outside the clinical-based setting. To our knowledge, no previous long-term community cohort studies have reported data obtained from both generic and disease-specific instruments in the same population-based study. Our results suggest that the instruments were parallel to each other for capturing the changes in HRQoL among PwMS. For clinical use these findings may be interesting, because the HRQoL instruments vary in the amount of items for participants to answer. However, the changes were seen as small according to the effect sizes. More research is required to determine the validity of this finding.

This study has its limitations. The study sample (N=77) can be considered too small to fully reflect HRQoL across the full spectrum of PwMS. In addition, drop-outs had more severe disabilities than those who participated throughout the study, and therefore our results can be generalized only to ambulatory PwMS. At study outset, the clinical course of MS was defined as either primary-remitting (i.e., relapsing-remitting or secondary-progressive) or primary

progressive. However, the categories of relapsing-remitting and secondary remitting could not be distinguished from each other in the study sample. Missing values, especially on the MSQOL-54 sexual functioning scale (22%), may have had an effect on the physical health composite outcome. In previous studies, the proportion of missing values on the sexual scale has been 5–10% [21, 23, 52], the underlying reasons being highly personal or cultural issues. In our study, 85% of the non-respondents were living without a partner, which may be one reason for the missing data.

Conclusion

The results of this study suggest that ambulatory PwMS at baseline reported reduced HRQoL in physical functioning after a 10-year follow-up period while emotional well-being was maintained and social functioning improved. The scores in the other HRQoL dimensions and scales remained unchanged. More long-term population-based studies are needed to precisely determine the development of HRQoL among PwMS.

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Conflict of interest

The authors declare that they have no conflict of interest.

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