Health-related quality of life in partners of persons with MS: a longitudinal 10-year perspective

Kristina Gottberg,1,2 C Chruzander,2,3 U Einarsson,4 S Fredrikson,2 S Johansson,3,4 L Widén Holmqvist2,3

ABSTRACT

Objectives: Multiple sclerosis (MS) impacts the health-related quality of life (HRQL) in partners, but knowledge on the longitudinal perspective is needed. The aim was to analyse HRQL in partners of persons with MS living in Sweden a decade ago and after 10 years.

Materials and methods: Partners were identified through a population-based study of persons with MS in Stockholm. Information on HRQL (the Sickness Impact profile), personal factors and disease-specific factors, and measures of functioning of persons with MS was collected at both time points mainly by home visits.

Results: Some 64 of 102 identified partners (63%) agreed to participate at baseline, and at 10 years 40 of 54 eligible partners were included (74%). HRQL in partners was worse than in a Swedish, aged-grouped reference population at both baseline and follow-up. Depressive symptoms in persons with MS were independently associated with worse HRQL in partners.

Conclusions: Depressive symptoms in persons with MS were associated with worse HRQL in their partners, and HRQL of partners was continuously impacted in the longitudinal perspective. This knowledge needs to be accounted for in the planning of MS care, together with the development of evidence-based support for depressive symptoms, and engagement in recreational life in both partners and persons with MS.

INTRODUCTION

Being in a relationship with and/or being a caregiver to a person with a chronic neurological condition has a substantial impact on health-related quality of life (HRQL). During the last two decades, there has been an increase in the number of studies that have focused on the situation of partners and caregivers of people with multiple sclerosis (MS), emphasising that MS not only affects the person with the diagnosis, but also their partner and family in different ways. Caregivers’ HRQL is affected more compared with the general population. Factors negatively influencing HRQL in partners and/or caregivers are neuropsychiatric symptoms, depression in persons with MS (PwMS), and a lack of social support. The focus in these studies has been on caregivers, significant others, and next of kin. The most common definition of the group investigated in MS caregiver studies is the adult person who is living together in a relationship (i.e., partners, cohabiting/married) with a PwMS, but another frequent definition acknowledged in the literature is one where the HRQL or burden of care rests with family members of the affected person such as children, siblings or parents. However, the life situation and also HRQL might be different depending on the caregiver being a partner or a child of the PwMS, and it is not fully known what proportion of partners is giving informal care and to what extent from a population-based perspective. Since there is knowledge that HRQL might be affected in both persons and because of differences in cultures, healthcare systems, populations under study, and methods of collecting data, there is a need to describe HRQL in partners.
in Sweden, for the overall purpose of planning healthcare and social care for PwMS together with their partners.

In Stockholm, a population-based study has been carried out using a sample of PwMS who were tested and interviewed in their homes, and a 10-year follow-up study of this cohort of persons has been performed. In the same study, partners of PwMS were invited to participate, independent of whether they were caregivers or not, in order to collect information regarding their HRQoL. The aim of the present study was thus to describe and analyse HRQoL in partners of PwMS in Sweden, at baseline and also in a 10-year follow-up, in comparison with a reference population based on the age group, and with regard to personal factors, functioning, and disease-related factors of PwMS.

**METHODS AND MATERIAL**

**Identification of partners of PwMS and data collection**

Partners were identified through a population-based study of PwMS in Stockholm, Sweden. Information on the case finding procedure of the population-based sample of PwMS has been presented elsewhere. The study protocol applied was part of a larger protocol for the survey of PwMS in Stockholm used at home visits with structured face-to-face interviews and tests. These home visits were conducted from 1999 to 2002 for the baseline study and from 2009 to 2012 for the follow-up study. Partners—defined as a spouse or a partner living together with the PwMS—were asked to participate during the home visit or, if not possible, to fill in the questionnaires in connection with the home visit and return these by post. In total, three samples of partners were identified throughout the 10-year period of time: (1) partners at the baseline study, (2) partners at the 10-year follow-up study and (3) partners who were the same persons both at baseline and at 10-year follow-up.

**Questionnaires on HRQoL in partners**

HRQoL was assessed using the Sickness Impact Profile (SIP), which is a measure of possible health-related limitations in a person’s daily life in 12 categories, comprising altogether 136 statements. A total score is calculated as well as scores on the physical and psychosocial dimensions. The scores range from 0 to 100 where 0 reflects no impact on perceived function in health. The scores of the partners of PwMS were compared with age group-matched scores from the general population living in Stockholm.

**Personal factors and caregiver status of partners**

Information on age, sex, level of education, and work status was collected by a protocol during the home visits or returned by post if the partners were not present at the time. Through the protocol, the partners were also asked how many hours per week they spent on informal care for PwMS—meaning helping with personal or instrumental activities of daily living (ADL) or other informal care such as spending more time on household and family activities. A total number of hours per week was calculated from this information. Partners who responded that they spent >1 h/week on informal care were categorised as caregivers.

**Personal factors and disease-specific factors and functioning of PwMS**

Information on age, sex, level of education, and work status was collected by a protocol during the home visits. Coping capacity and functioning were assessed by tests and structured face-to-face interviews which included the following variables and classifications: coping capacity by the Sense Of Coherence (SOC) scale categorised as weak or moderate/strong according to a reference population, depressive symptoms by the Beck Depression Inventory (BDI) categorised as below 10 indicating no signs of depression or >10 points indicating mild-to-more severe depression, cognitive function by the Symbol Digit Modalities Test (SDMT) categorised as performance below normal or normal (age-related norms, written or oral reply—1.5 SD), walking capacity by walking speed on 2×5 m categorised as cannot walk/walk at lower speed or normal speed (age-related/gender-related norms, 1.5 SD), manual dexterity by the Nine-Hole-Peg Test (NHPT) categorised as < or >0.5 pegs/s, dependency in activities of daily living by the Katz Extended ADL Index categorised as independent (full score) or dependent (dependent in one or more items), and frequency of social/lifestyle activities by the Frenchay Activities Index categorised with regard to age-related/sex-related norms, <lower quartile.

Information on disease-specific factors were assessed and collected during the home visits and were verified by a senior neurologist (SF); information on disease severity by the Expanded Disability Status Scale (EDSS) was categorised as mild-to-moderate (EDSS 0–5.5 points) or severe (EDSS 6–9.5 points), and information on type of MS was categorised as relapsing (benign or relapsing) or progressive (primary or secondary progressive).

**Statistical analyses**

All data were analysed using SPSS V.20.0. The significance of differences between groups in the two cross-sectional parts of the study (HRQoL at baseline and at 10-year follow-up) was examined by the Wilcoxon-Mann-Whitney test for data on ordinal level and a χ² test for difference in proportions. The Sign test was applied for the purpose of comparing results from partners of PwMS with already published data on the reference population grouped according to age (<41, 41–55 and >56 years). Probability values less than 0.05 were considered statistically significant. For the purpose of logistic regression analyses, SIP scores of partners were dichotomised into low and high impact on HRQoL according to > median SIP score of the group at baseline. The association between potential predictors and the outcome...
variable (≥ median SIP) was initially assessed using a χ2 test or Fisher’s exact test. Significant results from these univariate analyses (p<0.05) allowed potential predictors to enter a forward, stepwise, logistic regression analysis in order to identify the most important predicting factors. For the stepwise selection, we used as the criterion for entry a probability value less than 0.10, and as the criterion for removal a probability value greater than 0.15. For the purpose of examining change of HRQL in partners, the McNemar test was used for change in proportions of the two dependent groups, and the Wilcoxon SIGN Rank Test was used for data on an ordinal level.

RESULTS

**HRQL of partners at baseline**

In the population-based study of PwMS (n=166), 102 (61%) were living with a partner at baseline. Of those, 64 (63%) agreed to participate in the interview together with PwMS during a home visit, or by returning questionnaires by post. The majority of partners were men (68%), the mean age was 53 years and 73% were working (table 1).

Some 67% were caregivers to their partner with MS, spending at least 1 h of informal help per week, and the mean (SD) and range hours per week were 22 (25) and 1–116, respectively. Information on personal factors, functioning and disease-specific factors of PwMS cohabiting with partners at baseline is presented in table 2.

At baseline, 64 partners agreed to fill in the SIP. The total SIP score, the physical and psychosocial and dimension scores, as well as the 12 category SIP scores of partners of PwMS are shown in table 3. In comparison with a Swedish reference population, partners of PwMS in Stockholm had higher SIP scores (meaning a worse HRQL) in the categories Sleep and rest, Emotional behaviour, Social interaction, and Alertness behaviour (p=0.001–0.031). In addition, partners had higher SIP scores in the categories Work (p=0.016), and Recreation and pastimes (p=0.002) than in reference group aged 41–55 years, and in the category Ambulation (p=0.008) in comparison with the older reference group aged ≥56 years.

In univariate analyses, higher SIP scores in partners were associated with living with PwMS who had depressive symptoms (<0.001), were dependent on ADL (p=0.026), had low frequency of social/lifestyle activities (p=0.017) and were not working (p=0.042). In the multivariate logistic regression analysis, the final model included two variables independently associated with higher SIP scores in partners: depressive symptoms in PwMS (OR 7.4, 95% CI 2.3 to 24.1, R2=0.31, p=0.001) and living with a PwMS not working (n.s.; table 4).

**HRQL of partners at the 10-year follow-up**

In the 10-year follow-up study, 54 of 118 PwMS (46%) lived with a partner. A total of 40 of 54 eligible partners (74%) agreed to participate. The mean age was 61, and 65% were men (table 1). At this point, some 72% were caregivers, spending a mean (SD) of 15 (14) h/week on informal caregiving for their partner with MS (range 1–70 h).

Forty partners filled in the SIP (table 3). Similarly, as in the baseline study, the most affected category was Recreation and pastimes with a mean (SD) SIP score of 13 (16; table 3). In comparison with a Swedish reference population, partners of PwMS in Stockholm aged >40 years (only 2 partners aged <40) had higher SIP scores in the categories Alertness Behaviour, Social interaction, Sleep and rest, and Recreation and pastimes (p-values <0.001–0.031). Partners aged ≥56 years had higher SIP scores in the category Emotional behaviour (p=0.031). Subgroup analyses of SIP scores with regard to personal factors and disease-specific factors and functioning of PwMS were not applicable due to the small number of participating partners.

### Table 1  Personal factors and informal caregiving of partners of persons with multiple sclerosis at baseline (n=64) and at 10-year follow-up (n=40), and of the cohort of partners who participated on both occasions (n=24) in the Sickness Impact Profile interview

<table>
<thead>
<tr>
<th>Personal factors of partners and caregiver status</th>
<th>Sample of partners at baseline</th>
<th>Sample of partners at 10-year follow-up</th>
<th>Cohort of partners participating on both occasions, baseline</th>
<th>Cohort of partners participating on both occasions, at 10-year follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>53 (13), 29–81</td>
<td>61 (10), 39–85</td>
<td>51 (11), 29–75*</td>
<td>60 (12), 39–85</td>
</tr>
<tr>
<td>Men</td>
<td>40 (63)</td>
<td>26 (65)</td>
<td>14 (58)</td>
<td></td>
</tr>
<tr>
<td>University education</td>
<td>18 (29)†</td>
<td>10 (25)</td>
<td>7 (30)†</td>
<td></td>
</tr>
<tr>
<td>Working</td>
<td>46 (73)†</td>
<td>24 (60)</td>
<td>20 (87)‡</td>
<td>17 (71)</td>
</tr>
<tr>
<td>Informal caregiver</td>
<td>42 (67)†</td>
<td>28 (72)§</td>
<td>16 (67)</td>
<td>18 (75)</td>
</tr>
</tbody>
</table>

*n=21.
†n=63.
‡n=23.
§n=39.
Change in HRQL in the cohort of partners from baseline to 10-year follow-up

A cohort of 24 of the same partners of PwMS filled in the SIP both at baseline and at 10-year follow-up, and there were no significant changes of SIP scores between these two time points.

DISCUSSION

In our population-based study of PwMS in Stockholm at baseline, 61% had a partner who they were cohabiting with, and 10 years later, this proportion was 46%. The clinical picture of MS affecting not only the person themselves but also their partner is supported by the results shown in this study. In partners identified at the two time points over 10 years, HRQL was significantly worse than in the general population. Partners had continuously impacted HRQL in several areas at both time points. More than half of the partners were described as caregivers at both time points. Besides the impact in areas such as emotional behaviour and alertness behaviour, partners also had an impact on their HRQL in terms of social interaction and recreation and pastime. HRQL in partners was independently associated with depressive symptoms in PwMS, taking into account a range of personal-related and disease-related factors and functioning of PwMS. No significant changes regarding the impact on HRQL from baseline to 10 year follow-up were identified in the cohort of same partners at the two time points. However, the longitudinal change of HRQL in partners who did not live anymore in a relationship with the PwMS at 10 years remains unknown since they were not identified for the follow-up study.

Regarding the progressive nature of MS, the continuous impact on partners’ HRQL is expected.14 It was, however, somewhat surprising that HRQL scores were not significantly worse at the 10-year follow-up. The stable levels of impact on HRQL of partners may be explained by the existence of a response shift,28 where partners who have stayed in the relationship with PwMS revise their prior values and the relative impact of MS. However, the impact on partner’s HRQL did not decrease over time, which implies the need for continuous MS care efforts including focus on partners.29

The presence of depressive symptoms in PwMS was independently associated with the greater impact on HRQL in partners. Other studies confirm that depression in people with MS is related to the impact on HRQL in caregivers.4 Clinical implications may be that when depressive symptoms are identified in PwMS, it is particularly important to also involve the partners since they will most likely be affected as well. Other factors

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Table 2  Personal factors, functioning and disease-specific factors of persons with MS, cohabiting with partners participating in the baseline study (n=64) and at 10-year follow-up (n=40), and in the cohort of persons cohabiting with the same partner on both occasions (n=24)

<table>
<thead>
<tr>
<th>Personal factors, functioning and disease-specific factors of persons with MS</th>
<th>Sample of persons with MS at baseline n=64</th>
<th>Sample of persons with MS at 10-year follow-up n=40</th>
<th>Cohort of persons with MS cohabiting with partner on both occasions, baseline n=24</th>
<th>Cohort of persons with MS cohabiting with partner at 10-year follow-up n=24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>40 (63)</td>
<td>26 (65)</td>
<td>13 (54)</td>
<td>61 (11), 37–89</td>
</tr>
<tr>
<td>Age, mean (SD), range 51 (12), 26–79</td>
<td>60 (10), 37–89</td>
<td>10 (42)</td>
<td>7 (29)</td>
<td></td>
</tr>
<tr>
<td>University education</td>
<td>28 (44)</td>
<td>19 (47)</td>
<td>11 (46)</td>
<td>3 (16)</td>
</tr>
<tr>
<td>Working</td>
<td>26 (41)</td>
<td>12 (30)</td>
<td>11 (46)</td>
<td>7 (29)</td>
</tr>
<tr>
<td>Weak SOC</td>
<td>6 (10)n=60</td>
<td>4 (13)n=31</td>
<td>3 (13)</td>
<td>3 (16)</td>
</tr>
<tr>
<td>Depressive symptoms &gt;10 BDI</td>
<td>26 (43)n=60</td>
<td>11 (30)n=37</td>
<td>9 (38)</td>
<td>8 (35)</td>
</tr>
<tr>
<td>SDMT below normal</td>
<td>28 (47)n=60</td>
<td>15 (43)n=35</td>
<td>12 (52)n=23</td>
<td>7 (35)</td>
</tr>
<tr>
<td>NHPT below normal</td>
<td>46 (72)</td>
<td>25 (63)</td>
<td>17 (71)</td>
<td>18 (75)</td>
</tr>
<tr>
<td>Cannot walk or walks below normal speed</td>
<td>56 (88)</td>
<td>36 (92)n=39</td>
<td>19 (79)</td>
<td>21 (91)n=23</td>
</tr>
<tr>
<td>Katz dependent total</td>
<td>46 (72)</td>
<td>30 (75)</td>
<td>16 (67)</td>
<td>17 (71)</td>
</tr>
<tr>
<td>Low frequency of lifestyle activities</td>
<td>43 (67)</td>
<td>25 (63)</td>
<td>14 (58)</td>
<td>15 (63)</td>
</tr>
<tr>
<td>EDSS</td>
<td>19 (30)</td>
<td>4 (10)</td>
<td>7 (29)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Mild, 0–3</td>
<td>7 (11)</td>
<td>13 (32)</td>
<td>4 (17)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Moderate, 3.5–5.5</td>
<td>25 (39)</td>
<td>9 (23)</td>
<td>8 (33)</td>
<td>5 (21)</td>
</tr>
<tr>
<td>Severe, 6–6.5</td>
<td>13 (20)</td>
<td>14 (35)</td>
<td>5 (21)</td>
<td>12 (50)</td>
</tr>
<tr>
<td>Very severe 7–9.5</td>
<td>23 (36)</td>
<td>9 (23)</td>
<td>6 (25)</td>
<td>4 (17)</td>
</tr>
</tbody>
</table>

BDI, Beck depression Inventory; EDSS, Expanded disability Status Scale; MS, multiple sclerosis; NHPT, Nine-Hole-Peg Test; SDMT, Symbol Digit Modalities Test; SOC, Sense Of Coherence scale.
that were associated with a greater impact on HRQL in partners in univariate analyses are living with a PwMS who is not working, and their ADL dependency. These results may be interpreted in the light of the International Classification of Functioning, disability and health (ICF)\(^{30}\) such that participation restrictions in PwMS are associated with a greater impact on partners’ HRQL. Therefore, care efforts that facilitate activity and participation for PwMS and their partners are warranted and the effect of such interventions on partners’ HRQL should be scientifically evaluated.\(^{29} 31 32\) Rehabilitation of PwMS with a focus on performing activities, for the purpose of recreation and pastime and social interaction, with and without partners is of particular interest, according to the results of this study.

Of the group of partners of PwMS in this study, the majority (67–75%) was classified as caregivers. However, the remaining partners did state that they used less than 1 h/week to help with informal care or other, highlighting the difficulties with classifying partners as ‘caregivers’. In a Cochrane review of interventions for caregivers of stroke survivors, it was concluded that a limitation across all studies was the lack of definition for the informal caregiver population.\(^{30}\) The caregiver concept may, however, be up for discussion since being a caregiver is sometimes restricted to helping with predominantly physical needs, while psychosocial support or simply ‘being there’ with loving care and engagement for their partner with MS is not accounted for. Further studies with a qualitative design\(^{33}\) may add knowledge to the literature of the life situation of partners of PwMS. Such studies would make it possible to also capture the positive impact,\(^{34} 35\) rather than only the negative impact of the MS disease on partners of afflicted persons. In this study and in another Scandinavian study,\(^7\) there were higher proportions of men compared with studies of Solari \textit{et al}\(^4\) and Giordano \textit{et al},\(^8\) which might be due to cultural differences regarding informal caregiving or differences regarding other sample characteristics, that is, other caregivers than partners of PwMS who participated (parents/children).\(^4 5\)

Limitations to consider when interpreting the results are the low number of partners in the cohort at follow-up, and the lack of a validated HRQL instrument that captures the impact on partners more specifically than the SIP.\(^{35}\) In addition, the relatively large proportion of severely disabled PwMS in this population-based study should be considered. In a Swedish longitudinal cohort study of PwMS, use of informal care was more common in PwMS with fatigue.\(^{36}\) In this study, fatigue was not studied in PwMS, and nor was the presence of depressive symptoms in the partners themselves, which may be regarded as limitations, as both these disabilities may potentially affect HRQL in partners.\(^1\) Further studies with larger population-based samples of partners of PwMS are warranted in order to explore the impact on their HRQL, taking depression, fatigue and other potential aspects into account. Future studies should also explore partners’ specific needs and experiences from supporting a PwMS beyond the concept of HRQL, and care programmes need to be developed and evaluated, keeping in mind the mean of informal care hours (15–22 h/week) for the majority of partners in this study.

In conclusion, this is the first Swedish study to describe HRQL in partners of PwMS, taking into account personal factors and disease-specific factors and functioning in PwMS. Depressive symptoms in PwMS were associated with worse HRQL in their partners, which implies the need for further attention to this disability in MS care. HRQL of partners was continuously impacted in the longitudinal perspective, in areas such as emotional

### Table 3

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline n=64 mean (SD)</th>
<th>10-Year follow-up n=40 mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Summary scores</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total SIP score</td>
<td>4 (7)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Physical dimension</td>
<td>3 (9)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Psychosocial dimension</td>
<td>5 (8)</td>
<td>5 (7)</td>
</tr>
<tr>
<td><strong>Physical categories</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body care and movement</td>
<td>2 (7)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Mobility</td>
<td>3 (9)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Ambulation</td>
<td>4 (13)*</td>
<td>4 (11)</td>
</tr>
<tr>
<td><strong>Psychosocial categories</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional behaviour</td>
<td>5 (10)*†</td>
<td>7 (13)*</td>
</tr>
<tr>
<td>Alertness behaviour</td>
<td>6 (14)*†</td>
<td>7 (12)†</td>
</tr>
<tr>
<td>Social interaction</td>
<td>6 (10)*†</td>
<td>5 (7)†</td>
</tr>
<tr>
<td>Communication</td>
<td>0 (2)</td>
<td>1 (3)</td>
</tr>
<tr>
<td><strong>Independent categories</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep and rest</td>
<td>5 (8)*†</td>
<td>8 (12)†</td>
</tr>
<tr>
<td>Home management</td>
<td>3 (12)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Work</td>
<td>5 (15)†</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Recreation and pastimes</td>
<td>14 (18)†</td>
<td>13 (16)†</td>
</tr>
<tr>
<td>Eating</td>
<td>1 (2)</td>
<td>0 (1)</td>
</tr>
</tbody>
</table>

*Significant difference (worse HRQL) in comparison with the Swedish reference population aged >56 years (p<0.05).
†Significant difference (worse HRQL) in comparison with the age group 41–55 years (p<0.05).
HRQL, health-related quality of life; MS, multiple sclerosis; SIP, Sickness Impact Profile.

### Table 4

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressive symptoms in persons with MS</td>
<td>7.4 (2.3 to 24.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Person with MS not working</td>
<td>3.0 (0.8 to 11.4)</td>
<td>0.107</td>
</tr>
</tbody>
</table>

Prediction model characteristics: R²=0.31; overall classification correct=73.3%.
*Model based on 60 partners of persons with MS. MS, multiple sclerosis.
behaviour, social interaction and recreation and pastime. This knowledge needs to be accounted for in the planning of MS care, together with the development of specific evidence-based support for both the emotional burden of depressive symptoms and engagement in recreational life in both partners and PwMS.

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Contributors KG was involved in the designing, planning and conduct of the study; participated in the collection of baseline data, performed analyses of partners’ QoL at baseline to 10-year follow-up in relation that is disability of persons with MS, and contributed in the writing of the manuscript. CC was involved in collection of data at 10-year follow-up, analyses of disability data of persons with MS at 10-year follow-up, gave valuable comments on the manuscript and performed interpretation of results. UE was involved in collection of data at baseline, analyses of disability data of persons with MS at baseline, gave valuable comments on the manuscript and performed interpretation of results. SF gave valuable comments on the manuscript and performed interpretation of results; also contributed as the senior advisor on data collection and was involved in the management of disease-related information of persons with MS. SJ was involved in collection of data at 10-year follow-up, acted as the advisor on analyses of 10-year disability data of persons with MS, gave valuable comments on the manuscript and performed interpretation of results. LWH acted as a senior advisor on designing and planning of the study, gave valuable comments on the manuscript and performed interpretation of results.

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Competing interests None.

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Data sharing statement No additional data are available.

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