Physical and Mental Health-Related Quality of Life Trajectories Among People With Multiple Sclerosis

Author(s):
Julia O’Mahony, Ph.D; Amber Salter, PhD; Beyza Ciftci, MD, MSc; Robert J Fox, MD; Gary R. Cutter, PhD; Ruth Ann Marrie, MD, PhD

Corresponding Author:
Julia O’Mahony, julia.omahony@mail.utoronto.ca

Affiliation Information for All Authors: 1. Department of Internal Medicine, University of Manitoba, Winnipeg, MB, Canada; 2. Department of Biostatistics, The University of Texas Southwestern Medical Center, Dallas, TX, United States; 3. Departments of Medicine and Community Health Sciences, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada; 4. Mellen Center for Multiple Sclerosis, Neurological Institute, Cleveland Clinic, Cleveland, OH, United States; 5. Department of Biostatistics, University of Alabama at Birmingham, Birmingham, AL, United States.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND), which permits downloading and sharing the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Neurology® Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.
Equal Author Contribution:

Contributions:
Julia O'Mahony: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data
Amber Salter: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Beyza Ciftci: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data
Robert J Fox: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Gary R. Cutter: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Ruth Ann Marrie: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data

Figure Count:
2

Table Count:
5

Search Terms:

Acknowledgment:
NARCOMS is a project of the Consortium of Multiple Sclerosis Centers (CMSC). NARCOMS is funded in part by the CMSC and the Foundation of the CMSC.

Study Funding:
This study was funded by Consortium of Multiple Sclerosis Centers (CMSC).

Disclosures:
J. O’Mahony receives research funding from: Multiple Sclerosis Society of Canada, Multiple Sclerosis Scientific Foundation, and CMSC; A. Salter receives research funding from Multiple Sclerosis Society of Canada, National Multiple Sclerosis Society, CMSC and the US Department of Defense and is a member of editorial advisory board for Neurology. R.A. Marrie receives research funding from CIHR, Research Manitoba, Multiple Sclerosis Society of Canada, Multiple Sclerosis Scientific Foundation, Crohn’s and Colitis Canada, National Multiple Sclerosis Society, CMSC and the US Department of Defense, and is a co-investigator on studies receiving funding from Biogen Idec and Roche Canada. G.R. Cutter data/safety monitoring committees for AMO, BioLineRx, BrainStorm Cell Therapeutics, Galmed, Horizon, Hisun, Merck, Merck/Pfizer, OPKO Biologics, Neurim, Novartis, Orphazyme, Sanofi, Reata, Receptos/Celgene, Teva, NHLBI (Protocol Review Committee), NICHD (OPRU oversight committee); consulting/advisory boards for Biogen, Click Therapeutics, Genzyme, Genentech, GW, Klein Buendel, MedImmune, MedDay, Novartis, Osmotica, Perception Neuroscience, Recursion, Roche, Somahlution, and TG Therapeutics. R.J. Fox has received personal consulting fees from AB Science, Biogen, Celgene, EMD Serono, Genentech, Genzyme, Immunic, Janssen, Novartis, Sanofi, and TG Therapeutics; has served on advisory committees for AB Science, Biogen, Genzyme, Immunic, Janssen, Novartis, Sanofi, and TG Therapeutics; and received clinical trial contract and research grant funding from Biogen, Novartis, and Sanofi. The other author reports no relevant disclosures.
Abstract

Background and Objectives: Most studies of health-related quality of life (HRQoL) in multiple sclerosis (MS) have been cross-sectional. The few longitudinal studies have not accounted for potential heterogeneity in HRQOL trajectories. There may be groups of individuals with common physical and mental HRQoL trajectories over time. Identification of early risk factors for membership in trajectories with poor HRQoL would inform on those at risk. We aimed to identify physical and mental HRQoL trajectories among people with MS and early risk factors for membership in the trajectory groups with the worst HRQoL.

Methods: Between 2004 and 2020, we queried NARCOMS participants regarding HRQoL using the RAND-12, demographics, fatigue, and physical impairments (using Patient Determined Disease Steps). We included participants who were enrolled in the NARCOMS registry within three years of MS diagnosis, lived in the United States, reported physician-confirmed MS, and had ≥3 HRQoL observations. We used group-based trajectory modelling to determine whether there were distinct clusters of individuals who followed similar HRQoL trajectories over time. We evaluated whether baseline participant characteristics associated with the probability of trajectory group membership using a multinomial logit model.

Results: We included 4,888 participants who completed 57,564 HRQoL questionnaires between one and 27 years after MS diagnosis. Participants had a mean (SD) age of 41.7 (9.5) years at diagnosis, and 3,978 participants (81%) were women. We identified five distinct physical HRQoL trajectories and four distinct mental HRQoL trajectories. Older age at diagnosis, worse physical impairments, and worse fatigue were associated with increased odds of being in the group with the worst physical HRQoL when compared to the four other groups. Income ≤$50,000 and no post-secondary education were associated with increased odds of membership in the group with the lowest mental HRQoL when compared to the other three groups.

Discussion: We identified groups of people with MS who reported similar physical and mental HRQoL trajectories over time. There are early risk factors for membership in the groups with the worst HRQoL that are easily identifiable by clinicians, providing an opportunity for early interventions.

Introduction
Multiple sclerosis (MS) is a chronic immune-mediated inflammatory disease with heterogeneous outcomes. People with MS report lower health-related quality of life (HRQoL) when compared to individuals in the general population or those living with other chronic diseases.\textsuperscript{1-3} Most studies of HRQoL in MS have been cross-sectional. The few longitudinal studies have focused on population average changes in HRQoL over time and have not accounted for potential heterogeneity in the evolution of HRQoL within the MS population. Herein, we call the evolution of HRQoL over time a trajectory.\textsuperscript{4}

Group-based trajectory modeling (GBTM) employs finite mixture modelling to identify subgroups of people within a population with similar changes in a phenomenon over time.\textsuperscript{4} GBTM differs from linear regression, which assumes a single underlying population with a single average probability trajectory and an associated set of variance parameters measuring the population variability about a single mean trajectory.\textsuperscript{5} Therefore, GBTM is particularly valuable when modelling outcomes in diseases with heterogeneous outcomes, such as MS, where subpopulations with different behaviors may exist. Prior studies among people experiencing other chronic disorders have used GBTM to identify distinct HRQoL trajectories and factors associated with membership in those trajectories. A study of 817 prostate cancer survivors identified three physical HRQoL and three mental HRQoL trajectories.\textsuperscript{6} Comorbidity was associated with membership in those trajectories. Three HRQoL trajectories were identified among 213 people with early rheumatoid arthritis.\textsuperscript{7} Gender was associated with trajectory membership. Five HRQoL trajectories were identified among 452 people with axial spondyloarthritis.\textsuperscript{8} Sex, age, and disease duration were associated with trajectory membership.

In cross-sectional studies, HRQoL in MS is adversely influenced by physical impairments, fatigue, and comorbidities.\textsuperscript{9-12} It is not known whether assessment of these factors early in the disease course can predict long-term trajectories of HRQoL. However, identification of individuals at risk for poor outcomes early in their disease may allow clinicians to target clinical and pharmacological interventions more effectively.

Using GBTM, we aimed to identify physical and mental HRQoL trajectories among people with MS and early risk factors for membership in the trajectory groups with the worst HRQoL. We hypothesized that there would be distinct physical and mental HRQoL trajectory groups and that membership in the groups with the worst HRQoL would be associated with greater physical impairments and fatigue at diagnosis.

**Methods**

**Study Population**
The North American Research Committee on Multiple Sclerosis (NARCOMS) registry is a self-report registry for individuals with MS that has collected demographic and clinical information since 1996. Information is collected at enrollment, and updated semi-annually thereafter. Extensive efforts have validated diagnoses of MS and outcomes used.\textsuperscript{13-16}

**Standard Protocols, Approvals, and Consents**
Participants permit use of their de-identified information for research purposes. At the time of this analysis, the NARCOMS registry was approved by the Institutional Review Board of Washington University at St. Louis.

We included participants in this study who were enrolled in the NARCOMS Registry within three years of MS diagnosis, lived in the United States, reported physician-confirmed MS, and reported HRQoL at ≥3 time points. Restricting this analysis to participants who were enrolled in the NARCOMS Registry within three years of MS diagnosis enabled us to create a virtual inception cohort, reflecting the common clinical situation when people with MS first engage in MS-specific care and may be evaluated for risk factors for membership in poor HRQoL trajectories. Most participants in the NARCOMS Registry reside in the US; inclusion in this analysis was restricted to US inhabitants because HRQoL varies between countries and we did not have enough participants from non-US countries to account for between-country heterogeneity. At least three HRQoL observations were needed to ascertain non-linear trajectories (e.g., three observations needed for quadratic).

### Demographic and clinical characteristics

At enrollment in the NARCOMS registry, participants reported sex, date of birth, race, education, income, year of MS diagnosis, age at MS diagnosis, year of MS symptom onset, Patient Determined Disease Steps (PDDS), MS disease course, fatigue, and comorbidities. Race was collected because it is a social determinant of health associated with outcomes among people with MS. The PDDS is a single-item measure of disability with response options ranging from 0 (normal) to 8 (bedridden). It correlates highly with the physician-scored Expanded Disability Status Scale score. Participants reported fatigue using the Performance Scales; the fatigue domain was assessed using a single-item measure with responses ranging from 0 (normal) to 5 (total fatigue). Diagnostic lag was calculated as the difference in years between the reported age at MS diagnosis and the age at MS symptom onset. Participants reported HRQoL using the RAND-12. Duration of RAND-12 observation was calculated as the difference in years between the first and last RAND-12 observations. Comorbidities were queried at enrollment and updates as of 2006 using the following question format: “Has a doctor ever told you that you have...?” Participants indicated the presence or absence of comorbidities and, if present, the year of diagnosis. Queried comorbidities varied from update to update. Overall, these included blood disorders, cancer, hypercholesterolemia, diabetes, epilepsy, gastrointestinal disorders, cardiac disorders including valvular disease, HIV, kidney disorders, mental health disorders, migraine, musculoskeletal disorders, skin disorders, sleep disorders, thyroid and parathyroid disorders, and visual disorders. Participants were also asked to specify diagnoses conferred to them that were not queried; chronic disorders known to negatively affect HRQoL were included (e.g., endometriosis, Parkinson’s disease). We excluded disorders that are signs or symptoms of MS. Participants were categorized as having any mental health comorbidity if they reported the presence of any of the following mental health disorders: anxiety, depression, bipolar disorder, psychosis, posttraumatic stress disorder, schizophrenia, anorexia, or bulimia. Participants were categorized as having any physical comorbidity if they reported the presence of any comorbidity that was not a mental health disorder.

### HRQoL

Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology.
HRQoL was queried in select updates between 2004 and 2020 using the RAND-12, which is a validated measure of health status, known to be responsive to changes in disability and employment status in MS populations. The RAND-12 captures the following eight concepts: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality (energy and fatigue), social functioning, role limitations due to emotional problems, and mental health (psychological distress and psychological well-being). The RAND-12 can be scored to produce two aggregate scores: one that summarizes physical HRQoL (Physical Component Score, PCS-12) and a separate aggregate score that summarizes mental HRQoL (Mental Component Score, MCS-12). Alternatively, the RAND-12 can be scored to produce eight subscale scores for each of the concepts evaluated. The aggregate and subscale scores all range from 0 to 100 with higher scores indicating better HRQoL. Each score has a mean of 50 and standard deviation (SD) of 10.

**Analysis**

We summarized characteristics of the study population using mean (SD), median (interquartile range (IQR)), and frequency (percentage). We performed bivariate analyses between the first physical and mental HRQoL observations of participants and individual characteristics included in the multivariable models described herein.

We identified two sets of trajectories using group-based trajectory modelling (GBTM): One set for physical HRQoL and a second set for mental HRQoL. We assumed a normal distribution censored at zero to accommodate the continuous outcomes (PCS-12 and MCS-12). We evaluated multiple models with varying numbers of groups and trajectory shapes (polynomial orders). Participants with missing data were included, but only available data were used. The preferred models were chosen based on a combination of the Bayesian information criterion (BIC) index of model-fit, Akaike Information Criterion (AIC), parsimony, theoretical justification, research questions, and clinical interpretability. Meaningful differences in the BIC were evaluated using the Bayes factor. Trajectory model fit was evaluated using the average posterior probability, odds of correct classification, and the confidence intervals around estimated group membership probabilities. An average posterior probability ≥0.7 (with 1 being no ambiguity in group assignment) was considered a good fit. Each participant was assigned to the group to which they had the highest probability of membership. We present the summary statistics that profile the characteristics of individuals following each of the identified physical and mental HRQoL trajectories. We report the number and percentage of participants who are in the lowest physical and lowest mental HRQoL trajectory groups. We also report the number and percentage of participants who are in the highest physical and highest mental HRQoL trajectory groups. As a complementary analysis, we generated unadjusted trajectories for the eight RAND-12 subscales.

To identify risk factors for membership in the trajectory groups with the lowest mental or physical HRQoL, we evaluated the association of baseline participant characteristics with the probability of group membership using a multinomial logit model. Modeling the probability of trajectory group membership accounts for uncertainty in group membership. This modeling extension is incorporated into the trajectory estimation and allows for simultaneous estimation of the parameters determining trajectory shapes and the multinomial logit parameters that predict probabilities of trajectory group membership as a function of individual-level covariates. We
report the coefficient estimates of the parameters of the multinomial logit function. The coefficients were estimated jointly with the parameter estimates of the trajectories.

We evaluated the following baseline characteristics: female sex (male sex as reference group, binary), age at MS diagnosis (years, continuous), diagnostic lag (years, continuous), year of MS diagnosis (years, continuous), progressive disease course (relapsing remitting disease course as the reference group, binary), PDDS (ordinal), white race (non-white race as reference group, binary), education > high school diploma or GED (education ≤ high school diploma or GED reference group, binary), income >$50,000 annually (income ≤$50,000 annually reference group, binary), the presence of any physical comorbidity (no physical comorbidity as the reference group, binary) and the presence of any mental comorbidity (no mental comorbidity as the reference group, binary). Race was evaluated as white versus non-white because this was the only configuration that would allow our model to converge due to small cell sizes. We also adjusted for baseline fatigue (ordinal) in the model for membership in the physical HRQoL trajectory groups; we did not adjust for fatigue in the model for mental HRQoL, because the mental HRQoL score (MCS-12) accounts for vitality (defined as energy and fatigue). Variable selection was informed by literature review and factors accessible to clinicians at the time of initial encounter to inform on clinically relevant predictors of trajectory membership.

We used k-fold cross-validation (k=5) to validate the stability of the latent classes identified in the GBTM.\textsuperscript{31} We report the root-mean squared errors (RMSE, which measure the average prediction error for the model) as measures of model fit. Similar RMSE among the model using the full dataset and after cross-validation would indicate that performance of the model should perform consistently when applied to an external dataset.

Statistical analyses were conducted using Stata 17.0.\textsuperscript{32}

**Data Availability Statement**
The data sets generated and analyzed during this study are held by the NARCOMS registry (narcoms.org).

**Results**

**Participants**
After application of the inclusion criteria, 4,888 participants were eligible for the current analysis (Figure 1). Participants completed 57,564 HRQoL questionnaires within 27 years after MS diagnosis, with a mean (SD) of 12 (7) RAND-12 responses per participant over time. Half of the participants were older than age 42 years at the time of MS diagnosis and most participants were women (Table 1).

**Physical HRQoL Trajectories**
We identified five distinct physical HRQoL trajectories (Figure 2). Group 1 (26.4%) reported consistently low and stable physical HRQoL; Group 2 (29.2%) reported moderately low and stable physical HRQoL; Group 3 (13.4%) reported moderate to low physical HRQoL within the first ten years after diagnosis followed by normal physical HRQoL thereafter; Group 4 (17.1%) experienced an early decline in physical HRQoL within the first eight years after diagnosis and then an increase to moderate/normal HRQoL thereafter; and Group 5 (13.9%) reported
persistently normal physical HRQoL for the first 20 years after diagnosis and then a decline. The RMSE for the physical HRQoL model was 8.89.

**Characteristics associated with Physical HRQoL Trajectories**

On univariate logistic regression, several participant characteristics were associated with increased odds of being in the group with the lowest physical HRQoL (Group 1) when compared to all other groups, including older age at MS diagnosis, longer diagnostic lag, progressive disease course, worse physical impairments, worse fatigue, and annual income ≤$50,000 (Table 2). The group with the lowest physical HRQoL differed from all other groups in terms of year of MS diagnosis; however, the direction of this relationship differed across groups. The group with the lowest HRQoL (Group 1) had an earlier year of MS diagnosis when compared to the group with the persistently normal then late decline (Group 5). Male sex and no post-secondary education were associated with increased odds of being in the group with the lowest physical HRQoL (Group 1) when compared to three of the four other groups (Groups 3-5). The presence of any comorbid physical disorder was associated with increased odds of being in the group with the lowest physical HRQoL (Group 1) when compared to Groups 2, 4, and 5. The presence of any comorbid mental disorder was associated with increased odds of being in the group with the lowest physical HRQoL (Group 1) when compared to Groups 2, 3, and 5.

On multivariable logistic regression, older age at MS diagnosis, worse physical impairments, and worse fatigue were associated with increased odds of being in the group with the lowest physical HRQoL (Group 1) when compared to all other groups (Table 3). More recent year of MS diagnosis was associated with increased odds of being in the group with the lowest physical HRQoL (Group 1) when compared to three of the other groups (Groups 2, 3, and 4) and decreased odds of being in the group with persistently normal physical HRQoL followed by a late decline (Group 5). A longer diagnostic lag, annual income ≤$50,000, and the presence of a comorbid physical disorder were associated with increased odds of being in the group with the lowest physical HRQoL (Group 1) compared to all other groups. However, not all of these associations were statistically significant. No post-secondary education was consistently associated with increased odds of being in the group with the lowest physical HRQoL (Group 1) when compared to three of the other groups, but this was statistically significant only for Group 2. Similarly, male sex was associated with increased odds of being in the group with the lowest physical HRQoL (Group 1) when compared to all other groups, but this was only statistically significant for Group 4. Race and disease course were not associated with group membership.

**Mental HRQoL Trajectories**

We identified four distinct mental HRQoL trajectories (Figure 2A): Group 1 (18.6%) reported chronically low mental HRQoL; Group 2 (32.9%) reported moderately low and stable mental HRQoL; Group 3 (22.2%) reported moderately low mental HRQoL with a late decline (Group 5). The group with the lowest mental HRQoL (Group 1) reported chronically normal mental HRQoL. The RMSE for the mental HRQoL model was 9.36.

**Characteristics associated with mental HRQoL trajectories**

On univariate logistic regression, non-white race, annual income ≤$50,000, and the presence of any comorbid mental health disorder were associated with increased odds of being in the group with the lowest mental HRQoL (Group 1; Table 4) compared to the other three groups. Greater
diagnostic delay, worse physical impairments, and no post-secondary education were associated with increased odds of being the group with the lowest mental HRQoL (Group 1) compared to Groups 3 and 4. More recent year of MS diagnosis was associated with increased odds of being in the group with the lowest mental HRQoL (Group 1) compared to Groups 2 and 3. Younger age at MS diagnosis was associated with increased odds of being in the group with the lowest mental HRQoL (Group 1) compared to the group with chronically normal mental HRQoL (Group 4). Sex, disease course, and the presence of any comorbid physical disorder were not associated with group membership.

On multivariable logistic regression, annual income ≤$50,000 and no post-secondary education were associated with increased odds of membership in the group with the lowest mental HRQoL (Group 1; Table 5) when compared to the three other groups. Younger age at MS diagnosis and non-white race were associated with increased odds of membership in the group with the lowest mental HRQoL (Group 1) compared to Group 4. Worse physical impairments were associated with increased odds of membership in the group with the lowest mental HRQoL (Group 1) compared to Groups 3 and 4. More recent year of MS diagnosis was associated with increased odds of membership in the group with the lowest mental HRQoL (Group 1) compared to Groups 2 and 3. The presence of a mental comorbidity was associated with increased odds of membership in the group with the lowest mental HRQoL (Group 1) compared to Groups 2 and 4. Sex, disease course, and the presence of any comorbid physical disorder were not associated with group membership.

Overlap between Physical and Mental HRQoL Trajectories
We did not observe a pattern of overlap between membership in the worst or best HRQoL physical and mental trajectories. Overall, 415 (8%) participants were members in both the worst physical HRQoL trajectory (Group 1) and the worst mental HRQoL trajectory (Group 1). By comparison 388 (8%) participants were members in both the best physical HRQoL trajectory (Group 5) and the best mental HRQoL trajectory (Group 4).

Subscale Trajectories
In the complementary analysis of the unadjusted trajectories of the eight RAND-12 subscales, we identified five distinct trajectories for the physical functioning, role limitations (physical), bodily pain, and general health subscales and four distinct trajectories for the vitality, role limitations (emotional), social functioning, and mental health subscales (eFigure 1). As shown, the general trajectory patterns of the former four subscales are overall similar to the five trajectories generated from the physical HRQoL aggregate score and the general trajectory patterns of the latter four subscales are overall similar to the four trajectories generated from the mental HRQoL aggregate score.

Cross-Validation
We found substantial overlap between the trajectories estimated using cross-validation and those estimated using our original dataset, suggesting that the latent classes identified using our original dataset are stable (eFigure 2). The RMSE of the physical HRQoL model (8.98) and of the mental HRQoL model (9.52) were similar to those reported for the initial model using the entire dataset.
Discussion

Using a large virtual inception cohort of participants with MS residing in the US, we investigated whether there are clusters of people who followed similar physical and mental HRQoL trajectories. We identified five clusters of participants who followed similar physical HRQoL trajectories, and four clusters of participants who followed similar mental HRQoL trajectories for up to 27 years following MS diagnosis. Specifically, there were clusters of individuals with MS who had chronically low and stable physical HRQoL, moderately low but stable physical HRQoL, low physical HRQoL soon after MS diagnosis followed by persistently normal physical HRQoL, an early decline in physical HRQoL followed by a rebound to normal physical HRQoL, and persistently normal physical HRQoL followed by a decline 20 years after MS diagnosis. Older age at diagnosis, worse physical impairments as measured using the PDDS, and worse fatigue within three years of diagnosis were associated with increased odds of being in the group with the worst physical HRQoL trajectory as compared to being in the other four physical HRQoL trajectories. With respect to mental HRQoL, we observed individuals with chronically low mental HRQoL, moderately low and stable mental HRQoL, low mental HRQoL soon after MS diagnosis followed by persistently normal mental HRQoL, and chronically normal mental HRQoL. Annual household incomes ≤$50,000 and no post-secondary education were associated with increased odds of being in the group with the worst mental HRQoL as compared to being in the other three mental HRQoL trajectories (see eFigure 3 summary).

We identified distinct HRQoL trajectories among people with MS. The GBTM approach highlights the heterogeneity in the MS population and illustrates the importance of longitudinal datasets to delineate groups of people who follow similar trajectories. Our finding of different long-term HRQoL trajectories among people with MS may help to explain some of the discrepant findings reported among prior studies that have evaluated HRQoL trends among people with MS using a single average for the entire population. A study of 204 veterans with MS reported worsening in physical functioning over three years using the 36-Item Short Form Health Survey for Veterans, but no change in mental health. A study of 288 people with MS found a decline in self-reported physical functioning over a two-year period using the SF-36, but no change in the other domains of that instrument. A study of 3,779 people found that most of the participants reported stable HRQoL over a five year period, but that 40% of participants experienced clinically significant declines in their physical HRQoL and 36% experienced clinically significant declines in their mental HRQoL. A longitudinal Phase 3 study of RRMS patients treated with interferon-beta reported declines in physical and total scores on the Sickness Impact Profile questionnaire and no change in the psychosocial domain. The findings of some of these studies contrasted with ours possibly due to methodological differences in the study populations, instruments used, duration of observation (all five years or less), or analytic approaches. Traditional regression methods model the average outcome in the population, and may fail to detect meaningful heterogeneity within the population, whereas we modelled heterogeneity explicitly. Our finding of distinct clusters of people with MS who report similar physical or mental HRQoL trajectories is consistent with prior studies that found distinct trajectories among people with MS for outcomes such as cost of illness, work productivity, disability progression, and health care use prior to nursing home entry. Collectively, this highlights the importance of accounting for heterogeneity when evaluating MS outcomes.
The factors that we identified as associated with membership in the trajectory groups with the worst HRQoL are consistent with findings from prior cross-sectional and longitudinal studies. People who are younger at the time of MS diagnosis have better physical HRQoL, but worse mental HRQoL. Worse physical impairments and fatigue are associated with worse physical HRQoL. Less income and lower education is associated with worse mental HRQoL. The presence of comorbidities is associated with worse physical and mental HRQoL.

Strengths of our study include the large sample size, long average duration of follow-up, emphasis on information accessible to clinicians, and use of a valid measure of HRQoL. Study limitations should also be considered. Participants in the NARCOMS registry are volunteers, which may limit the generalizability of our findings. Due to small cell sizes, we were unable to evaluate whether there is a relationship between the number of comorbidities and trajectory group membership. Prior studies suggest that increasing number of comorbidities is associated with lower physical HRQoL. We were unable to differentiate the severity and relative importance of individual comorbidities on HRQoL. Prior studies suggest that some comorbidities such as headache and musculoskeletal disorders have a stronger association with HRQoL than others. We were unable to fully evaluate the relationship between race and HRQoL due to minimal variability in race among study participants. We did not account for changes in clinical status or health behaviors over time because we were specifically interested in identifying factors associated with long-term HRQOL outcome that are measurable at baseline that may prompt intervention. Future studies should examine the role of changes in disability, fatigue, health behaviors, comorbidity and disease-modifying therapy on HRQoL trajectories. Future studies should also examine whether interventions targeted at supporting those with low socioeconomic status improve mental HRQoL among people with MS.

There are clusters of people with MS who follow similar physical and mental HRQoL trajectories over time. There are early risk factors for membership in the groups with the worst HRQoL that are easily identifiable by clinicians and potentially amenable to change, providing an opportunity for early targeted interventions for those at risk of poor long-term HRQoL. Risk factors for membership in the group with the lowest physical HRQoL, including greater physical impairments and greater fatigue are often captured during routine neurological examinations or through self-report assessments. Both physical impairments and fatigue are responsive to disease modifying MS therapies, emphasizing the need for early initiation of treatments among those with these risk factors. The socioeconomic risk factors for membership in the group with the lowest mental HRQoL, including less education and income, may be easily identified using brief self-report assessments. Interventions that target social determinants of mental health have been shown to be effective at the individual, system (e.g., health, education), and macro (e.g., political, economic) levels. Income supplements have been associated with reductions in food insecurity, which is associated with worse mental health. Expansion of the Earned Income Tax Credit generated improvements in well-being among recipients, including decreased depression, increased happiness, and increased self-esteem. Greater access to green spaces around homes, schools, and workplaces is associated with fewer depressive symptoms. Prior studies have shown that supported education might be beneficial for young adults experiencing mental illness, although these benefits weaken with age.

**eFigure 1** --http://links.lww.com/WNL/C205

Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology.
References

31. Mosteller F, Tukey JW. Data analysis, including statistics. 1968.
### Table 1 Baseline Participant Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>3,978</td>
</tr>
<tr>
<td>Age at MS Symptom Onset, median (IQR)</td>
<td>34</td>
</tr>
<tr>
<td>Age at MS Diagnosis, median (IQR)</td>
<td>42</td>
</tr>
<tr>
<td>Diagnostic Lag, median (IQR)</td>
<td>5</td>
</tr>
<tr>
<td>Disease Duration at First RAND-12 Observation, median (IQR)</td>
<td>4.25</td>
</tr>
<tr>
<td>Age at First RAND-12 Observation, median (IQR)</td>
<td>46.3</td>
</tr>
<tr>
<td>Year of MS Diagnosis, median (IQR)</td>
<td>2001</td>
</tr>
<tr>
<td>Progressive Disease Course, n (%)</td>
<td>387</td>
</tr>
<tr>
<td>PDDS, median (IQR)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Fatigue, median (IQR)</td>
<td>Mild</td>
</tr>
<tr>
<td>Race White, n (%)</td>
<td>4,274</td>
</tr>
<tr>
<td>Education &gt; than High School Diploma or GED, n (%)</td>
<td>3,358</td>
</tr>
<tr>
<td>Income &gt;$50,000, n (%)</td>
<td>2,261</td>
</tr>
<tr>
<td>Presence of Any Comorbid Physical Disorder, n (%)</td>
<td>2,669</td>
</tr>
<tr>
<td>Presence of Any Comorbid Mental Health Disorder, n (%)</td>
<td>1,414</td>
</tr>
</tbody>
</table>
Table 2: Physical Health Trajectory Group Descriptives

<table>
<thead>
<tr>
<th>Variable</th>
<th>Physical Health Five Groups</th>
<th>Chronically Lowest (n=1,313)</th>
<th>Chronically low (n=1,463)</th>
<th>Early low then Normal (n=634)</th>
<th>Early Decline then Late Rebound (n=803)</th>
<th>Persistently Normal then Late Decline (n=675)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Female, n (%)</td>
<td>Age at MS Diagnosis, median (IQR)</td>
<td>Diagnostic Lag, median (IQR)</td>
<td>Year of MS Diagnosis, median (IQR)</td>
<td>Duration of RAND-12 Observation, median (IQR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1,016 (77%)</td>
<td>46 (39, 52)</td>
<td>8 (3, 15)</td>
<td>2002 (1999, 2007)</td>
<td>7 (4-12)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1,136 (78%)</td>
<td>44* (36, 49)</td>
<td>6* (2, 12)</td>
<td>2000* (1998, 2003)</td>
<td>8* (4-14)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>543* (86%)</td>
<td>38* (31, 44)</td>
<td>3* (1, 8)</td>
<td>1999* (1997, 2003)</td>
<td>10* (5-15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>708* (88%)</td>
<td>40* (33, 46)</td>
<td>4* (2, 10)</td>
<td>1997* (1994, 1999)</td>
<td>9* (5-16)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>575* (85%)</td>
<td>38* (31, 45)</td>
<td>3* (1, 8)</td>
<td>2004* (2001, 2007)</td>
<td>6* (4-10)</td>
</tr>
<tr>
<td>Predictor</td>
<td>Chronically Lowest</td>
<td>Chronically Low</td>
<td>Early low then Normal</td>
<td>Early Decline then Late Rebound</td>
<td>Persistently Normal then Late Decline</td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>--------------------</td>
<td>---------------------</td>
<td>-----------------------</td>
<td>---------------------------------</td>
<td>--------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.05 (0.83, 1.33)</td>
<td>1.37 (0.97, 1.95)</td>
<td>2.03* (1.42, 2.89)</td>
<td>1.27 (0.85, 1.88)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at MS Diagnosis</td>
<td>0.98* (0.97, 0.99)</td>
<td>0.94* (0.93, 0.96)</td>
<td>0.97* (0.96, 0.99)</td>
<td>0.93* (0.92, 0.95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnostic Lag</td>
<td>0.99 (0.98, 1.00)</td>
<td>0.98* (0.96, 0.99)</td>
<td>0.98</td>
<td>0.98 (0.96, 1.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosed Year</td>
<td>0.89* (0.86, 0.92)</td>
<td>0.95* (0.91, 0.99)</td>
<td>0.74* (0.70, 0.78)</td>
<td>1.24* (1.18, 1.29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressive Disease Course</td>
<td>0.83 (0.58, 1.17)</td>
<td>1.26</td>
<td>0.74</td>
<td>1.07 (0.62, 1.86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDDS</td>
<td>0.85* (0.79, 0.90)</td>
<td>0.55* (0.49, 0.61)</td>
<td>0.57* (0.51, 0.63)</td>
<td>0.41* (0.35, 0.48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.72* (0.66, 0.80)</td>
<td>0.51* (0.45, 0.58)</td>
<td>0.60* (0.53, 0.67)</td>
<td>0.44* (0.38, 0.51)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race White</td>
<td>0.78 (0.57, 1.06)</td>
<td>0.98</td>
<td>1.02</td>
<td>0.90 (0.60, 1.35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education &gt; than High School Diploma or GED</td>
<td>0.95 (0.77, 1.18)</td>
<td>1.55* (1.13, 2.12)</td>
<td>1.24</td>
<td>1.73 (1.21, 2.47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Income &gt;$50,000</td>
<td>1.21 (0.97, 1.51)</td>
<td>1.26</td>
<td>1.15</td>
<td>1.85* (1.32, 2.59)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of Any Comorbid Physical Disorder</td>
<td>0.71* (0.57, 0.87)</td>
<td>0.91</td>
<td>0.79</td>
<td>0.55* (0.41, 0.75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of Any Comorbid Mental Health Disorder</td>
<td>1.05 (0.84, 1.32)</td>
<td>1.07</td>
<td>1.26</td>
<td>0.90 (0.65, 1.24)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4: Mental Health Trajectory Group Descriptives

<table>
<thead>
<tr>
<th>Variable</th>
<th>Chronically Lowest (n=957)</th>
<th>Chronically Low (n=1,634)</th>
<th>Early Low then Normal (n=999)</th>
<th>Chronically Normal (n=1,298)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>797 (83%)</td>
<td>1,324 (81%)</td>
<td>801 (80%)</td>
<td>1,056 (81%)</td>
</tr>
<tr>
<td>Age at MS Diagnosis, median (IQR)</td>
<td>42 (34, 49)</td>
<td>41* (34, 47)</td>
<td>42 (34, 48)</td>
<td>44* (37, 50)</td>
</tr>
<tr>
<td>Diagnostic Lag, median (IQR)</td>
<td>6 (2, 13)</td>
<td>5 (2, 12)</td>
<td>5* (2, 11)</td>
<td>4* (1, 10)</td>
</tr>
<tr>
<td>Duration of RAND-12 Observation, median (IQR)</td>
<td>5 (3-9)</td>
<td>8* (4-14)</td>
<td>12* (7-16)</td>
<td>8* (4-13)</td>
</tr>
<tr>
<td>Progressive Disease Course, n (%)</td>
<td>70 (41%)</td>
<td>89 (9%)</td>
<td>82 (11%)</td>
<td>146 (14%)</td>
</tr>
<tr>
<td>PDDS, median (IQR, min-max)</td>
<td>Moderate (Mild, Early Cane)</td>
<td>Gait Disability (Mild, Early Cane)</td>
<td>Mild* (Normal, Gait Disability)</td>
<td>Mild* (Normal, Gait Disability)</td>
</tr>
<tr>
<td>Race White, n (%)</td>
<td>780 (82%)</td>
<td>1,445* (88%)</td>
<td>929* (93%)</td>
<td>1,120* (86%)</td>
</tr>
<tr>
<td>Education &gt; than High School Diploma or GED, n (%)</td>
<td>595 (62%)</td>
<td>1,055 (65%)</td>
<td>692 (69%)</td>
<td>1,016* (78%)</td>
</tr>
<tr>
<td>Income &gt;$50,000, n (%)</td>
<td>366 (38%)</td>
<td>717* (44%)</td>
<td>449* (45%)</td>
<td>729* (56%)</td>
</tr>
<tr>
<td>Any Comorbid Physical Disorder, n (%)</td>
<td>529 (60%)</td>
<td>858 (57%)</td>
<td>571 (61%)</td>
<td>711* (56%)</td>
</tr>
<tr>
<td>Any Comorbid Mental Health Disorder, n (%)</td>
<td>403 (50%)</td>
<td>406* (29%)</td>
<td>337* (36%)</td>
<td>268* (21%)</td>
</tr>
</tbody>
</table>

*p<0.05 when Group 1 is the reference group bivariate analyses
<table>
<thead>
<tr>
<th>Predictor</th>
<th>Chronically Lowest</th>
<th>Chronically Low</th>
<th>Early Low then Normal</th>
<th>Chronically Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.92 (0.68, 1.25)</td>
<td>0.89 (0.63, 1.25)</td>
<td>0.82 (0.61, 1.09)</td>
<td></td>
</tr>
<tr>
<td>Age at MS Diagnosis</td>
<td>0.99 (0.98, 1.01)</td>
<td>1.01 (0.99, 1.03)</td>
<td>1.04* (1.02, 1.05)</td>
<td></td>
</tr>
<tr>
<td>Diagnostic Lag</td>
<td>0.997 (0.98, 1.01)</td>
<td>0.99 (0.97, 1.01)</td>
<td>0.97* (0.96, 0.99)</td>
<td></td>
</tr>
<tr>
<td>Diagnosed Year</td>
<td>0.83* (0.80, 0.86)</td>
<td>0.73* (0.70, 0.77)</td>
<td>0.97 (0.95, 1.00)</td>
<td></td>
</tr>
<tr>
<td>Progressive Disease Course</td>
<td>0.91 (0.58, 1.43)</td>
<td>1.33 (0.82, 2.16)</td>
<td>1.24 (0.84, 1.82)</td>
<td></td>
</tr>
<tr>
<td>PDDS</td>
<td>1.01 (0.94, 1.08)</td>
<td>0.87* (0.81, 0.94)</td>
<td>0.82* (0.76, 0.87)</td>
<td></td>
</tr>
<tr>
<td>Race White</td>
<td>1.15 (0.82, 1.63)</td>
<td>1.41 (0.90, 2.20)</td>
<td>1.36* (1.01, 1.85)</td>
<td></td>
</tr>
<tr>
<td>Education &gt; than High School Diploma or GED</td>
<td>1.31* (1.02, 1.69)</td>
<td>1.37* (1.03, 1.82)</td>
<td>1.70* (1.33, 2.18)</td>
<td></td>
</tr>
<tr>
<td>Income &gt;$50,000</td>
<td>1.43* (1.10, 1.85)</td>
<td>1.49* (1.11, 2.00)</td>
<td>1.59* (1.25, 2.03)</td>
<td></td>
</tr>
<tr>
<td>Presence of Any Comorbid Physical Disorder</td>
<td>1.07 (0.83, 1.37)</td>
<td>1.08 (0.82, 1.43)</td>
<td>1.07 (0.85, 1.35)</td>
<td></td>
</tr>
<tr>
<td>Presence of Any Comorbid Mental Health Disorder</td>
<td>0.50* (0.39, 0.65)</td>
<td>0.77 (0.58, 1.02)</td>
<td>0.28* (0.22, 0.36)</td>
<td></td>
</tr>
</tbody>
</table>
US participants enrolled in the NARCOMS registry as of 2021 (N = 40,122)

Diagnosed with MS (n = 37,242)

Enrolled in NARCOMS within 3 years of MS diagnosis (n = 12,609)

Year of MS diagnosis ≥ 1993 (n = 12,603)

Offered RAND-12 questionnaire (n = 5,628)

Provided RAND-12 response (n = 5,626; 65,479 responses)

Provided ≥ 3 RAND-12 responses (n = 5,478; 44,710 responses)

Have complete covariate data (n = 4,888; 57,564 responses)

A. Physical

B. Mental
Physical and Mental Health-Related Quality of Life Trajectories Among People With Multiple Sclerosis
Julia O’Mahony, Amber Salter, Beyza Ciftci, et al.
Neurology published online August 10, 2022
DOI 10.1212/WNL.0000000000200931

This information is current as of August 10, 2022

Updated Information & Services
including high resolution figures, can be found at:
http://n.neurology.org/content/early/2022/08/10/WNL.0000000000200931.full

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Autonomic diseases
http://n.neurology.org/cgi/collection/autonomic_diseases
Multiple sclerosis
http://n.neurology.org/cgi/collection/multiple_sclerosis
Outcome research
http://n.neurology.org/cgi/collection/outcome_research
Quality of life
http://n.neurology.org/cgi/collection/quality_of_life

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.neurology.org/about/about_the_journal#permissions

Reprints
Information about ordering reprints can be found online:
http://n.neurology.org/subscribers/advertise