

Journal Pre-proof

Comparative Responsiveness of Preference-Based Health-Related Quality of Life, Social Care and Wellbeing Measures in the Context of Multiple Sclerosis

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PII: S1098-3015(25)05620-7

DOI: <https://doi.org/10.1016/j.jval.2025.09.3063>

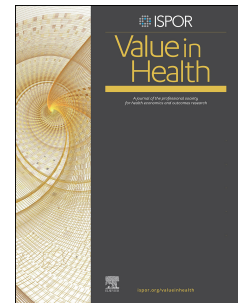
Reference: JVAL 4483

To appear in: *Value in Health*

Received Date: 9 April 2025

Revised Date: 26 August 2025

Accepted Date: 26 September 2025



Please cite this article as: Goodwin E, Heather A, Morrish N, Freeman J, Boddy K, Thomas S, Chataway J, Middleton R, Hawton A, Comparative Responsiveness of Preference-Based Health-Related Quality of Life, Social Care and Wellbeing Measures in the Context of Multiple Sclerosis, *Value in Health* (2025), doi: <https://doi.org/10.1016/j.jval.2025.09.3063>.

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Précis: Condition-specific and non-health preference-based measures showed greater responsiveness than the EQ-5D-3L when assessed using standardised values, but not absolute values, in people with multiple sclerosis.

Word Count: 3999

Number of Pages: 27

Number of Figures: 0

Number of Tables: 6

Supplementary materials:

Pages: 31

Figures: 0

Tables: 3

Authorship Confirmation: All authors certify that they meet the ICMJE criteria for authorship.

Funding/Support: This work was supported by Grant 82 from the UK Multiple Sclerosis Society.

Role of the Funders/Sponsors: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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Acknowledgements: The research reported in this paper was funded by the Multiple Sclerosis Society of Great Britain (Grant Code 82). The data were collected by the UK MS Register Project (Ref: 16/SW/0194); we would like to acknowledge the contribution of all Members of the UK MS Register Team based at Swansea University Medical School. We also thank the Members of the HEMS Patient Involvement Group, and the Members of the MS Register who provided the data used in this study.

Comparative responsiveness of preference-based health-related quality of life, social care and wellbeing measures in the context of multiple sclerosis

Abstract

Objectives

To provide evidence on the responsiveness of social care and wellbeing preference-based measures (PBMs) compared to health-related quality of life PBMs in the context of multiple sclerosis (MS).

Methods

The ICEpop CAPability measure for Adults (ICECAP-A) and Adult Social Care Outcomes Toolkit (ASCOT) were completed online in September 2019, March 2020, September 2020, via the UK MS Register. Responses were linked to EQ-5D-3L and MS Impact Scale–Eight Dimensions (MSIS-8D) values, and to MS Walking Scale-12 (MSWS-12), Hospital Anxiety and Depression Scale (HADS) and Fatigue Severity Scale (FSS) scores. Responsiveness was assessed in relation to minimal important differences on MSWS-12, HADS and FSS between timepoints, using mean change scores, t-tests, standardised effect sizes, standardised response means and multivariable regression analyses.

Results

Data from 1,742 people with MS were available for analysis. When using standardised values, MSIS-8D showed the greatest responsiveness and EQ-5D-3L the least. In contrast, when absolute utility values were used, EQ-5D-3L performed similarly to MSIS-8D and

better than ICECAP-A and ASCOT. Standardised regression analyses indicated the MSIS-8Ds to be the most responsive, followed by the ASCOT, ICECAP-A, and EQ-5D-3L.

Conclusions

The ICECAP-A, ASCOT and MSIS-8D were more responsive than the EQ-5D-3L in the context of MS when compared using standardised scores. The increased responsiveness of EQ-5D-3L when absolute values were used seems an artefact of the wide-ranging scale of this measure. This illustrates how the maximum potential range of values for a given PBM tariff could influence whether an intervention is found to be cost-effective.

Keywords:

Preference-based measures, Responsiveness, EQ-5D, Wellbeing measures, Social care related quality of life measures, Health-related quality of life measures, QALY measures

Highlights

What methods or evidence gap does your paper address?

- Evidence is limited for the responsiveness of preference-based measures (PBMs) of health-related quality of life, wellbeing or social care related quality of life in the context of multiple sclerosis.

What are the key findings from your research?

- This paper provides evidence for the comparative responsiveness of five PBMs: EQ-5D-3L, MSIS-8D, MSIS-8D-P, ICECAP-A and ASCOT. When values were standardised, MSIS-8D and MSIS-8D-P showed the greatest responsiveness, while EQ-5D-3L showed the least. When absolute values were compared, EQ-5D-3L showed greater responsiveness than ICECAP-A and ASCOT, equal to the MSIS-8D measures.

What are the implications of your findings for healthcare decision making or the practice of HEOR?

- The comparative responsiveness of different PBMs depends upon the PBMs under consideration and the metric(s) used to judge responsiveness. These findings illustrate how the maximum range of values for a PBM could influence whether an intervention is found to be cost-effective and suggest that careful interpretation and presentation are required to ensure that non-health impacts are not eclipsed by “larger” health impacts when assessing health and social care interventions.

Introduction and background

The funding of health and social care treatments in the UK largely depends on demonstrating their cost-effectiveness,¹ which is typically assessed by weighing up the costs of treatments against the benefits they provide.^{2,3} Concerns have been raised, however, about the ability of the outcome measures typically used in cost-effectiveness analysis to capture all the benefits of interventions that are experienced by people with multiple sclerosis (MS).⁴⁻⁹ This highlights the importance of *responsiveness*, i.e. the ability of a measurement tool to accurately detect and quantify a change over time in the construct of interest when it has occurred.¹⁰ If scores on an outcome measure do not sufficiently alter as a result of significant events, important treatment effects may be missed. Such issues have hampered funding decisions¹¹⁻¹³ and may have limited the services that are available to people with MS. Consequently, in 2012, the National Institute for Health and Care Excellence (NICE) called for improvements to the framework for assessing the cost-effectiveness of treatments for MS.¹³

Much of the research in this area has focused on measures of health-related quality of life (HRQL).¹⁴ In the UK, the National Institute for Health and Care Excellence (NICE)¹⁵ recommends the EQ-5D, a generic preference-based measure (PBM) of HRQL with five dimensions: mobility; self-care; usual activities; pain/discomfort; anxiety/depression.¹⁶ Concerns regarding the responsiveness of generic PBMs to MS treatment effects⁴⁻⁹ led to the development of a condition-specific PBM of HRQL: the Multiple Sclerosis Impact Scale (MSIS-8D), which is derived from the Multiple Sclerosis Impact Scale-29 (MSIS-29)¹⁷ and includes HRQL dimensions of particular importance to people with MS: physical; social; mobility; daily activities; fatigue; emotion; cognition; depression.¹⁸ Both measures have a

tariff of utility values based on the preferences of a UK general population sample, enabling the calculation of quality-adjusted life-years (QALYs).^{16,19} In addition, the MSIS-8D-P provides a tariff based on the preferences of a UK sample of people with MS, for the same descriptive system.²⁰

HRQL measures are designed to assess interventions that aim primarily to improve health. However, there is increasing interest in broadening the evaluative space to incorporate ‘benefits beyond health’.²¹ A key development in the UK was the extension of the remit of NICE in 2013 to include social care. NICE recommends two instruments to capture the non-health effects of social care interventions.¹⁵ These generic measures each have a tariff of values, based on the preferences of a UK general population sample, enabling the calculation of equivalents to the health-related QALY.^{22,23}

For interventions with social care outcomes, NICE recommends the Adult Social Care Outcomes Toolkit (ASCOT).²² The ASCOT measures social care-related quality of life (SCRQL) and includes the following dimensions: control over daily life; personal cleanliness and comfort; food and drink; personal safety; social participation and involvement; occupation; accommodation cleanliness and comfort; dignity.

For interventions with wellbeing outcomes, NICE recommends the ICEpop CAPability measure for Adults (ICECAP-A).²³ The ICECAP-A measures ‘capability wellbeing’, i.e. being able to do and be the things in life that matter to individuals.²⁴ Its attributes cover: attachment; security; role; enjoyment; control.

The symptoms of MS, and the variety of interventions and services used by people with MS, have meaningful impacts on people with MS beyond their health and HRQL, including role functioning, employment, self-efficacy and independence.²⁵⁻²⁹ PBMs of HRQL do not directly capture beneficial effects of interventions and services on these factors.^{6,29} This suggests that instruments designed to measure broader aspects of quality of life and wellbeing may be more responsive to these non-health effects. This research aimed to explore whether social care and wellbeing PBMs (SCW-PBMs) are more responsive than HRQL-PBMs in the context of MS by assessing and comparing the responsiveness of the ICECAP-A, ASCOT, EQ-5D-3L and MSIS-8D, using data from the UK MS Register (UKMSR).

Methods

Patient-reported outcome measures and minimal important differences

The responsiveness of the PBMs was assessed in relation to minimal important differences (MIDs) on three patient-reported outcome measures (PROMs): the Multiple Sclerosis Walking Scale-12 (MSWS-12),³⁰ the Hospital Anxiety and Depression Scale (HADS)³¹ and the Fatigue Severity Scale (FSS).³² These measures form part of the UKMSR's routine data collection and represent frequently experienced MS symptoms that impact upon HRQL^{27,28} and broader aspects of wellbeing.²⁹ Higher scores on these measures indicate greater symptom severity, therefore a positive change indicates a deterioration and a negative change indicates an improvement. Published MIDs for each PROM were sourced from the literature. When there was more than one possible MID, the MID for use in the analysis was agreed through discussion among the research team.

The MSWS-12 version 2.0 is a validated measure of walking ability, consisting of three items with three response levels and nine items with five response levels. Raw scores are recalibrated to a 0–100 point scale. The MID of ≥ 8 points was used for analyses.³³⁻³⁵

The HADS is a validated measure with separate subscales for depression and anxiety.³¹ Each subscale comprises seven items with four response levels, giving a total subscale score range of 0–21. Estimates of the MID range from 1.5 to 2.5 points.³⁶⁻³⁸ A MID of 2.0 was used for analysis of each HADS subscale.

The FSS is a nine-item measure of the severity and impact of fatigue. Total scores are expressed as the average score across the items, giving a range from 1 to 7 points. Estimates for FSS MID range from 0.45 to 1.1 points.^{39,40} A MID of 1.0 was used for this analysis.

Survey of people with MS

The UKMSR administers an online survey every six months, which is completed by approximately 5,000 people with MS. The survey includes PROMs alongside sociodemographic and clinical information. It can also host study-specific questionnaires, which can be anonymously linked to its existing data.⁴¹

The ICECAP-A and the ASCOT were administered three times over an 18-month period (September 2019, March 2020 and September 2020). This was alongside the UKMSR's regular surveys at the same timepoints, which collected data on: EQ-5D-3L, MSIS-29, MSWS-12, HADS, FSS, age, gender, type of MS and date of diagnosis. Values for the PBMs were estimated using published UK tariffs: EQ-5D-3L,¹⁶ MSIS-8D based on general population preferences,¹⁹ MSIS-8D-P based on preferences of people with MS,²⁰ ICECAP-A,²³ ASCOT.²²

Following their standard procedures, the UKMSR emailed all members of the register, inviting them to take part and providing them with a link to the additional questionnaires. Previous surveys hosted by the UKMSR suggested that we could expect a sample of approximately 2,000 at each timepoint.

No personal data were collected that could identify individuals. All data were accessed via an encrypted secure desktop connection. Data were analysed using Stata17, with do-files

available on GitHub (https://github.com/exeterhems/hums_responsiveness) and Zenodo.⁴²

Ethical approval for the UKMSR has been provided by the South West Central Bristol Research Ethics Council 21/SW/0085.

Responsiveness analysis

The responsiveness of the PBMs was assessed in relation to MIDs on each of the PROMs (MSWS-12, HADS depression, HADS anxiety and FSS). A series of complete case analyses was undertaken using data from all respondents who provided at least two consecutive responses to at least one of the PBMs over the three timepoints.

Based on MIDs in the total or subscale score of each PROM compared to the previous timepoint, the following groups were identified:

1. individuals with a *MID indicative of an improvement*
2. individuals with a *MID indicative of a worsening*
3. individuals with *no MID*

Hypotheses regarding these groups, *ceteris paribus*, were that there would be:

1. a *significant increase* in PBM values
2. a *significant decrease* in PBM values
3. *no significant change* in PBM values.

This gave a total of 16 groups in which a change in PBM values was hypothesised: one improvement group and one deterioration group for each of the four PROMs (eight groups), for Timepoint 1 to 2 and for Timepoint 2 to 3 (16 groups).

Paired t-tests were undertaken to assess the statistical significance ($p < 0.05$) of differences between PBM values from Timepoint 1 to Timepoint 2, and from Timepoint 2 to Timepoint 3, for each respondent group. Results were adjusted for multiple testing using Bonferroni correction. The magnitude of changes in PBM values between timepoints was assessed using the absolute size of the change, as well as standardised effect sizes (SES) and standardised response means (SRM) to enable comparison across measures on a standardised scale. SES were calculated as the mean change divided by the standard deviation of the earlier mean score (Cohen's d statistic), and interpreted as no (< 0.2), small (0.2), moderate (0.5) or large (0.8) effect⁴³. SRMs were calculated by dividing the mean change by the standard deviation of the mean change score,⁴⁴ and were directly compared between PBMs.⁴⁵ The five PBMs were ranked for each respondent group according to the absolute size of the SRM. The mean and modal average ranks across all respondent groups were then calculated for each PBM. The PBMs were also ranked for each respondent group according to the absolute size of the non-standardised mean change score, and their mean and modal average ranks across all groups were calculated.

The comparison of changes in PBM values was undertaken using the following metrics:

- Number of respondent groups in which there was a statistically significant difference in PBM values between timepoints.
- Number of respondent groups in which there was at least a small effect size.
- Average rank in terms of the absolute size of the SRM.
- Average rank in terms of the absolute size of the mean change score.

Regression responsiveness analyses

Multivariable regression analyses were used to compare the responsiveness of the PBMs by exploring independent relationships between change on each PROM and change on each PBM. A separate regression model was run for each PBM.

Two sets of regression analyses were undertaken using: i) change scores on the continuous scale of the PROMs and; ii) changes on the PROMs coded as '*no MID*' (reference case), '*MID indicative of an improvement*', and '*MID indicative of a worsening*'. Continuous scores on the PROMs and the PBMs were standardised to a mean of zero and a standard deviation of one to enable direct comparison.

Since panel data were used, the appropriateness of fixed-effect and random-effects models was investigated. The Hausman test indicated that random-effects should be used over fixed-effects. However, the Breusch-Pagan Lagrange multiplier test found no evidence of significant differences across timepoints, indicating that random effects was inappropriate. Therefore, a multivariable pooled OLS regression was run with standard errors clustered by respondent. The data failed the assumption of normality of residuals, requiring a choice between conducting a robust regression or a regression with clustered standard errors. The latter was chosen, supported by the observation that the p-values were larger and less significant when clustering, indicating this was the more conservative choice.

Illness-related events

The relevance of the PROMs for assessing the responsiveness of SCW-PBMs is questionable. The PROMs were designed to measure individual symptoms, which are more closely related to health status than SCRQL or wellbeing. The types of interventions for which the SCW-PBMs are recommended are unlikely to directly impact specific symptoms. Therefore, an

Illness-Related Events (IRE) questionnaire was designed for completion by people with MS. Significant IREs, which people with MS describe as affecting their quality of life and wellbeing, were identified via a systematic ‘review of reviews’ of the relevant literature. This resulted in a ‘longlist’ of IREs. The Health Economics and Multiple Sclerosis (HEMS) Patient Involvement Group⁴⁶ worked with the researchers to reduce this to a shortlist of the most impactful events, amenable for assessing PBM responsiveness and for inclusion in the UKMSR surveys. The resulting IRE questionnaire was discussed in detail with the co-applicant team, explored in cognitive interviews with people with MS, and piloted online with 50 members of the UKMSR. The questionnaire was administered alongside the UKMSR surveys in September 2019, March 2020 and September 2020, and asked people with MS to report whether or not they had experienced each of the specific IREs over the previous six months (Table 1). The responsiveness of the PBMs in relation to these IREs was analysed using the same methods as with the PROMs, with groups of respondents determined by whether they had experienced a particular IRE.

Public and patient involvement (PPI)

The HEMS Patient Involvement Group⁴⁶ were integral to this research, meeting with the project team six times over the life of the study, with multiple additional contacts via email. The Group’s involvement included, but was not limited to, shaping the focus of the research and the application, helping the project team to understand the relevance of the research from the perspective of people with MS, giving their views on the study materials, interpreting the findings, considering the implications for the MS community, and guiding next steps in terms of policy, practice and research.

Results

Participants

Table 2 presents demographic and clinical data for the 1,742 people with MS who provided at least two consecutive responses to at least one PBM over the three timepoints, as well as mean (SD) PBM values and PROM scores at all timepoints. At Timepoint 1, mean (SD) health state values were somewhat lower for the EQ-5D-3L (0.567 (0.310)) compared to the MSIS-8D (0.617 (0.189)) and MSIS-8D-P (0.655 (0.181)). Mean capability wellbeing according to the ICECAP-A value was 0.767 (0.199) and mean SCRQL according to the ASCOT value was 0.771 (0.199).

Responsiveness

Table 3 presents the results of the t-tests, the SRM and SES, and rankings of SRM and mean change scores, by PBM, for each of the 16 groups (i.e. eight respondent groups in which an effect was hypothesised from Timepoint 1 to 2 and from Timepoint 2 to 3, based on MIDs for the MSWS-12, HADS Depression, HADS Anxiety and FSS). A summary of the responsiveness results for each PBM is given in Table 4.

Bonferroni correction produced a new threshold for significance of 9.804×10^{-5} . Across the 16 groups for which an effect was hypothesised, the number of groups with a statistically significant change in PBM values ranged from three for the EQ-5D-3L to 13 for the MSIS-8D. The MSIS-8D-P was responsive to change in 11 groups, and the ICECAP-A and ASCOT were each responsive to change in six groups. No statistically significant changes in PBM values were observed in respondents whose PROM scores differed by less than the corresponding MID between timepoints (results available on request from authors).

In terms of effect sizes, none met the threshold for a moderate or large effect size. Small effects were detected by the EQ-5D-3L in one group, the MSIS-8D-P in 13 groups, and the MSIS-8D in 12. The ICECAP-A detected small effects in five groups, and the ASCOT in two.

With regard to SRMs, the EQ-5D-3L had the lowest mean (4.50) and modal (5) average ranked SRM across all the groups and was ranked last (5/5) in 11 groups. The MSIS-8D had the highest mean (1.56) and modal (1) average ranked SRM, with only one ranking below 2/5. The mean and modal average rank for the MSIS-8D-P SRMs were 1.75 and 2 respectively, with two rankings below 2/5. The ICECAP-A SRMs had a mean and modal average rank of 3.31 and 3 respectively, while the SRMs for the ASCOT had a mean rank of 3.75 and mode of 4.

Based on mean change scores, the modal average rank (1) for the EQ-5D-3L was the joint-highest of the five PBMs, alongside the MSIS-8D. Its mean average rank (2.63) was the third highest, behind the MSIS-8D (1.69) and MSIS-8D-P (2.25); this was primarily due to the EQ-5D-3L having the smallest mean change score in four groups. The MSIS-8D mean change score only ranked below 2/5 in two groups. The comparative responsiveness of the MSIS-8D, MSIS-8D-P, ICECAP-A and ASCOT relative to each other remained consistent with the analyses using standardised values.

Regression analyses

Table 5 shows the results of the regression analyses in which standardised change scores on each of the PBMs (the dependent variable) were regressed against standardised changes in all

PROMs scores (continuous, independent variables). The MSIS-8D measures were the most responsive, showing strong relationships ($p \leq 0.001$) with all four PROMs and standardised beta coefficients ranging from -0.081 to -0.253. ICECAP-A and EQ-5D-3L values were significantly but less strongly related to all PROMs (coefficient ranges: -0.044 to -0.204 and -0.053 to -0.162 respectively). ASCOT values were not significantly related to FSS scores (range of significant coefficients: -0.056 to -0.175).

Table 6 shows the results of the regression analyses in which standardised change scores on each of the PBMs (the dependent variable) were regressed against changes in all PROMs scores categorised according to no change (the baseline level), improvement, or deterioration. Again, the MSIS-8D measures were the most responsive, showing strong or moderate relationships with improvement and deterioration on all PROMs (coefficient range: -0.143 to -0.327). The EQ-5D-3L was the least responsive, showing no significant relationship ($p > 0.05$) with improvement or deterioration on the MSWS-12 or deterioration on the FSS, and weaker relationships with improvement or deterioration on HADS-D scores or improvement on the FSS (range of significant coefficients: -0.129 to -0.216).

Illness-related events

Results of the IRE analysis are presented in Supplementary Materials. No associations between IREs and PBM values reached significance across timepoints. Of the 25 mean change scores with $SES \geq 0.2$, 13 were in the opposite direction to that hypothesised. Across all the PBMs in the regression analyses, only five variables were significant. In all these analyses, results were not consistent across the timepoints.

Discussion

This appears to be the first investigation into the responsiveness of PBMs recommended by NICE for use in the economic evaluation of interventions with a social care element, when used with people with MS. The comparison between these and two HRQL-PBMs, one generic and one condition-specific, provides evidence to inform the selection of outcome measures for economic evaluations of MS interventions.

Summary of findings

A clear pattern emerged across the standardised analyses. The EQ-5D-3L was consistently the least responsive of the PBMs. The most responsive were the MSIS-8D and MSIS-8D-P, which performed either best or second-best in the t-tests, SES and SRM analyses, and equal-best in the regression analyses. The ICECAP-A exhibited slightly better responsiveness than the ASCOT in the SES and SRM analyses but slightly worse in the second regression analyses, and these instruments showed equal responsiveness according to the t-tests and first regression analysis.

This pattern shifted when absolute, rather than standardised, metrics were used. Here, the EQ-5D-3L appeared substantially more responsive than the SCW-PBMs, performing similarly to the MSIS-8D and MSIS-8D-P. This finding may be an artefact of differences in scale length. EQ-5D-3L values can range from -0.594 to 1,¹⁶ a much greater range of scores than the other PBMs (MSIS-8D: 0.079 to 0.882; MSIS-8D-P: 0.138 to 0.893; ICECAP-A: 0 to 1; ASCOT -0.17 to 1).^{19, 20, 22, 23} The standardisation inherent in the SRM and SES controls for these differences in scale, whereas the mean change scores do not.

The MS-specific MSIS-8D measures were clearly the most responsive of the PBMs, even when absolute (rather than standardised) mean changes were assessed. This may be unsurprising given that the MSIS-8D descriptive system is condition-specific, designed to include content of particular relevance to people with MS, whereas the other PBMs are generic. This implies that the *relevance of the descriptive system* of a PBM can affect its responsiveness. It may also hold that the *relevance of the preference weights* of a PBM may affect its responsiveness. Qualitative research suggests differences in the rationales of people with MS and the general public for their health state preferences,⁴⁷ and significant differences have been identified between QALY weights derived from people with MS and from the general population.⁴⁸ However, the comparison between the MSIS-8D, with preference weights elicited from the general population, and the MSIS-8D-P, with preference weights elicited from people with MS, showed no consistent differences between the measures in terms of responsiveness.

Strengths and limitations

Using data from the UKMSR is a significant strength of this research. The UKMSR is the largest ongoing cohort study of people with MS in the UK. It has been described as a representative population of people with MS,⁴⁹ and the data have been used in a variety of research studies.

There are limitations to the analysis described in this paper. Firstly, at the time of data collection, the UKMSR was using the EQ-5D-3L, rather than the EQ-5D-5L. The increased number of response levels per dimension on the latter is intended to increase its sensitivity to differences and responsiveness to changes in HRQL.⁵⁰ The UKMSR has since replaced the EQ-5D-3L with the EQ-5D-5L, and future analyses of UKMSR data could usefully explore

whether this new version of the instrument demonstrates improved responsiveness in the context of MS.

The lack of any consistent pattern of responsiveness of the PBMs to MS illness-related events may be due to limitations in how the events were described, defined, and/or captured.

However, great methodological care was taken in developing the IRE questionnaire including drawing on the relevant literature, multiple patient involvement sessions, cognitive interviews, and piloting via the UKMSR. Limited responsiveness of PBMs to key events that impact the quality of life and wellbeing of people with MS is of concern.

Consequently, the responsiveness of the PBMs discussed here is based on changes in PROMs which assess symptoms commonly experienced by people with MS. The constructs measured by these PROMs (walking ability, depression, anxiety, fatigue) are of greater relevance to the HRQL-PBMs than to the SCW-PBMs, and as such may underestimate the responsiveness of the latter, particularly given that SCW-PBMs are recommended for use in social care interventions that are unlikely to impact directly on symptoms.

It is not yet known *what* drives the differences in responsiveness of the PBMs.⁵¹ The conceptualisation of HRQL used in relation to PBMs differs from its broader conceptualisation in health and quality of life research. HRQL in a wider context has been defined as, ‘the patient’s subjective perception of the impact of his [*sic*] disease and its treatment(s) on his [*sic*] daily life, physical, psychological and social functioning and well-being’.⁵² In the PBM framework, HRQL is operationalised as the preference weight assigned to an individual’s health state based (usually) on general population preferences for that health state. A change in a HRQL-PBM value indicates a change in health status, represented

by the associated change in preference weight. Likewise, for the SCW-PBMs, the construct being considered is the preference weight assigned to an individual's 'wellbeing state' or 'SCRQL state'. A change in a SCW-PBM value indicates a change in wellbeing or SCRQL state, represented by the associated change in preference weight. Therefore, the descriptive systems of the PBMs may be responsive to change, but it is ultimately the overlying preference weights associated with these underlying states that will dictate the responsiveness of the measure. These components of PBMs and how to investigate their psychometric properties require further consideration and exploration.

Implications and conclusions

The relative responsiveness of SCW-PBMs versus HRQL-PBMs in the context of MS appears to depend on which PBMs are being considered and the metric(s) used to judge responsiveness.

These findings indicate that a condition-specific HRQL-PBM was more responsive to changes in walking ability, anxiety, depression and fatigue compared to the SCW-PBMs. Compared to a generic HRQL-PBM, the SCW-PBMs demonstrated greater responsiveness.

However, this is only if the responsiveness of the measures is compared using standardised scores; the wide range of EQ-5D-3L tariff values without standardisation tends towards eclipsing the apparent responsiveness of other PBMs. This is an important consideration in the selection of PBMs for use in economic evaluation: it is the magnitude of change in absolute values that determines the effectiveness side of the cost-effectiveness equation, therefore the scale-range of a PBM could influence whether an intervention is found to be cost-effective. NICE currently recommend the use of SCW-PBMs as a complement to

HRQL-PBMs to capture non-health effects of interventions.¹⁵ These findings suggest that SCW-PBM analyses require careful interpretation and presentation to ensure that non-health impacts are not eclipsed by “larger” health impacts when the two are used together to inform health and social care decision-making.

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Table 1: Illness-related events

Change in treatments and services since previous timepoint	Response category
Receiving any treatments for MS	Yes/No
Receiving a new drug treatment for MS symptoms	Yes/No/NA
Stopping a drug treatment for MS symptoms	Yes/No/NA
Did you stop the medicine/drug treatment because ...	It made things worse? It made no difference? Symptoms improved? Other reason
Receiving a new or existing disease-modifying treatment	Yes/No/NA
Did you ...	Take a DMT throughout? Start a DMT? Stop a DMT? Switch DMTs?
Receiving a new non-drug treatment or therapy for MS	Yes/No/NA
Stopping a non-drug treatment or therapy for MS	Yes/No/NA
Did you stop the treatment/therapy because ...	It made things worse? It made no difference? Symptoms improved? Other reason
Change in NHS or social care services	Yes/No/NA
Overall are the services you receive now better, the same or worse?	Better Same Worse
Changed in self-funded services or support	Yes/No/NA
Overall are the services you receive now better, the same or worse?	Better Same Worse

Changes in employment since previous timepoint	Response category
Been in paid work at any point in the last six months	Yes/No
Permanently left employment due to MS	Yes/No/NA
Did you want to leave your job?	Yes No
Changed job due to MS?	Yes/No/NA
Did you want to change your job?	Yes No
Reduced working hours due to MS	Yes/No/NA
Did you want to reduce your hours?	Yes No
Returned to work after having been off for more than 4 weeks due to MS	Yes/No/NA
Did you go back to work because ...	You needed to You wanted to
Experiences of MS since previous timepoint	Response category
Change of diagnosis from RRMS to SPMS	Yes/No/NA
Experiencing new MS symptoms	Yes/No
Experiencing new complications or side-effects due to MS treatment	Yes/No/Don't know/NA
Experiencing an MS relapse	Yes/No/NA
Additional questions on relapses	Response category
How many relapses have you had in the last 6 months?	One Two Three or more
How long did the first relapse last? By this we mean how long was it until the symptoms settled down or disappeared?	48 hours 1 week 1 month Over 1 month Ongoing
Were you admitted to hospital as a result of this relapse?	Yes/No

Did you spend any time off work as a result of having this relapse?	Yes/No/NA
Did having this relapse limit any other everyday activities?	Yes/No
Did you have a second relapse in the last 6 months?	Yes/No

Table 2: Descriptive statistics for all respondents who provided at least two consecutive responses to at least one PBM (N=1742) and Spearman correlations between measures at Timepoint 1 to assess suitability for anchor-based responsiveness analysis

	N	%	Mean	SD	Observed range	Theoretical range	UK general population
Timepoint 1							
Gender - Female	1288	74.07	-	-	-	-	51.67%
Gender - Male	451	25.93	-	-	-	-	48.33%
MS type - RRMS	745	49.24	-	-	-	-	NA
MS type - SPMS	296	19.56	-	-	-	-	NA
MS type - PPMS	328	21.68	-	-	-	-	NA
MS type - Benign	26	1.72	-	-	-	-	NA
MS type - Unknown	118	7.80	-	-	-	-	NA
Age	1740	-	54.630	11.053	21 to 85	-	49.143
MSWS-12	1717	-	61.905	37.763	0 to 100	0 to 100	NA
HADS depression score	1717	-	6.893	4.569	0 to 21	0 to 21	3.68
HADS anxiety score	1717	-	6.710	4.621	0 to 21	0 to 21	6.14
FSS score	1713	-	4.956	1.505	1 to 7	1 to 7	NA
EQ-5D value	1725	-	0.567	0.310	-0.594 to 1	-0.594 to 1	0.856
MSIS-8D value	1722	-	0.617	0.189	0.079 to 0.882	0.079 to 0.882	NA
MSIS-8D-P value	1722	-	0.655	0.181	0.138 to 0.893	0.138 to 0.893	NA
ICECAP-A value	1693	-	0.767	0.199	0.071 to 1	0 to 1	0.83
ASCOT value	1670	-	0.771	0.199	-0.062 to 1	-0.171 to 1	0.86
Timepoint 2							
MSWS-12	1608	-	61.530	37.897	0 to 100	0 to 100	
HADS depression score	1618	-	6.985	4.589	0 to 21	0 to 21	
HADS anxiety score	1618	-	6.682	4.629	0 to 21	0 to 21	
FSS score	1663	-	4.942	1.468	1 to 7	1 to 7	
EQ-5D value	1712	-	0.577	0.305	-0.594 to 1	-0.594 to 1	
MSIS-8D value	1660	-	0.618	0.187	0.079 to 0.882	0.079 to 0.882	
MSIS-8D-P value	1660	-	0.655	0.180	0.138 to 0.893	0.138 to 0.893	
ICECAP-A value	1537	-	0.767	0.197	0 to 1	0 to 1	
ASCOT value	1512	-	0.775	0.201	-0.171 to 1	-0.171 to 1	

	N	%	Mean	SD	Observed range	Theoretical range
Timepoint 3						
MSWS-12	1366	-	63.472	37.605	0 to 100	0 to 100
HADS depression score	1367	-	6.822	4.632	0 to 21	0 to 21
HADS anxiety score	1367	-	6.328	4.736	0 to 21	0 to 21
FSS score	1205	-	4.989	1.441	1 to 7	1 to 7
EQ-5D value	1396	-	0.577	0.304	-0.429 to 1	-0.594 to 1
MSIS-8D value	1382	-	0.622	0.189	0.079 to 0.882	0.079 to 0.882
MSIS-8D-P value	1382	-	0.660	0.182	0.138 to 0.893	0.138 to 0.893
ICECAP-A value	1012	-	0.762	0.202	0 to 1	0 to 1
ASCOT value	1003	-	0.778	0.193	-0.056 to 1	-0.171 to 1
Spearman's rho	EQ-5D-3L		MSIS-8D		MSIS-8D-P	ICECAP-A
MSWS-12	-0.584		-0.708		-0.713	-0.568
HADS-D	-0.681		-0.771		-0.762	-0.803
HADS-A	-0.501		-0.581		-0.570	-0.587
FSS	-0.685		-0.650		-0.653	-0.561

N, number of observations; PPMS, primary progressive multiple sclerosis; RRMS, relapsing remitting multiple sclerosis; SD, standard deviation; SPMS, secondary progressive multiple sclerosis.

Sources for UK general population norms:

Norms are provided for the UK adult general population.

Gender and age: Office for National Statistics: Census-based statistics UK 2021.
<https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/censusbasedstatisticsuk2021>

- The figure reported here is the mean average age of people aged 18 or over. Note that people aged 85 years and older were combined into a single category in the published Census-based statistics report. For the purposes of calculating an estimated mean age for this table, the age for this group was assumed to be 90 years.

HADS depression and anxiety scores: Crawford JR, Henry JD, Crombie C, Taylor EP. Brief report: Normative data for the HADS from a large non-clinical sample. *British Journal of Clinical Psychology* (2001), 40, 429–434.

EQ-5D value: Janssen B, Szende A. Population Norms for the EQ-5D. 2013 Sep 26. In: Szende A, Janssen B, Cabases J, editors. *Self-Reported Population Health: An International Perspective based on EQ-5D*. Dordrecht (NL): Springer; 2014

ICECAP-A value: Mitchell, P.M., Al-Janabi, H., Byford, S. et al. Assessing the validity of the ICECAP-A capability measure for adults with depression. BMC Psychiatry 17, 46 (2017). <https://doi.org/10.1186/s12888-017-1211-8>

ASCOT value: Netten A, Burge P, Malley J, Potoglou D, Towers AM, Brazier J, Flynn T, Forder J, Wall B. Outcomes of social care for adults: developing a preference-weighted measure. Health Technol Assess. 2012;16(16):1-166. doi: 10.3310/hta16160.

The MSWS-12, MSIS-8D and MSIS-8D-P are specific to multiple sclerosis, therefore general population values are not relevant. No UK general population norms could be sourced for the FSS.

Table 3: Results of t-tests, standardised response means and effect sizes, grouped by changes in PROM score

Timepoint 1 to 2											
Measure	Obs	Mean (SD) Timepoint 1	Mean (SD) Timepoint 2	Mean (SD) change score	t-stat	p- unadj	p-adj sig ^a	SRM	SES	SRM rank	Change score rank
Respondent groups based on change in MSWS-12 scores											
Improvement											
EQ-5D	274	0.590 (0.251)	0.628 (0.240)	0.038 (0.207)	-3.028	0.003	No	0.183	0.154	5	2
MSIS-8D*	275	0.617 (0.168)	0.656 (0.159)	0.039 (0.132)	-4.927	<0.001	Yes	0.297	0.240	1	1
MSIS-8D-P*	275	0.657 (0.163)	0.692 (0.155)	0.035 (0.125)	-4.681	<0.001	Yes	0.282	0.222	2	3
ICECAP-A	260	0.788 (0.182)	0.815 (0.163)	0.027 (0.102)	-4.250	<0.001	Yes	0.264	0.156	4	5
ASCOT	250	0.785 (0.173)	0.816 (0.155)	0.032 (0.112)	-4.456	<0.001	Yes	0.282	0.193	2	4
Deterioration											
EQ-5D	242	0.585 (0.264)	0.571 (0.260)	-0.014 (0.197)	1.113	0.267	No	-0.072	-0.054	5	5
MSIS-8D	241	0.626 (0.171)	0.601 (0.174)	-0.024 (0.123)	3.079	0.002	No	-0.198	-0.142	2	2
MSIS-8D-P	241	0.668 (0.166)	0.641 (0.172)	-0.028 (0.121)	3.584	<0.001	No	-0.231	-0.165	1	1
ICECAP-A	230	0.761 (0.207)	0.739 (0.207)	-0.021 (0.111)	2.941	0.004	No	-0.194	-0.104	3	4
ASCOT	223	0.758 (0.213)	0.736 (0.223)	-0.022 (0.115)	2.838	0.005	No	-0.190	-0.101	4	3
Respondent groups based on change in HADS-D scores											
Improvement											
EQ-5D	331	0.479 (0.318)	0.537 (0.309)	0.058 (0.217)	-4.816	<0.001	Yes	0.265	0.184	5	2
MSIS-8D*	335	0.543 (0.189)	0.606 (0.179)	0.062 (0.135)	-8.477	<0.001	Yes	0.463	0.339	1	1
MSIS-8D-P*	335	0.586 (0.185)	0.644 (0.173)	0.058 (0.132)	-8.09	<0.001	Yes	0.442	0.325	2	2
ICECAP-A*	305	0.708 (0.205)	0.750 (0.194)	0.042 (0.125)	-5.908	<0.001	Yes	0.338	0.212	3	5
ASCOT*	300	0.710 (0.205)	0.753 (0.197)	0.043 (0.135)	-5.571	<0.001	Yes	0.322	0.216	4	4
Deterioration											
EQ-5D	386	0.551 (0.301)	0.518 (0.308)	-0.033 (0.213)	3.05	0.002	No	-0.155	-0.108	5	5
MSIS-8D*	384	0.610 (0.173)	0.562 (0.188)	-0.048 (0.132)	7.123	<0.001	Yes	-0.363	-0.265	2	2
MSIS-8D-P*	384	0.650 (0.166)	0.600 (0.184)	-0.049 (0.128)	7.558	<0.001	Yes	-0.386	-0.283	1	1
ICECAP-A	353	0.756 (0.194)	0.719 (0.204)	-0.037 (0.127)	5.482	<0.001	Yes	-0.292	-0.186	3	3
ASCOT	345	0.763 (0.202)	0.729 (0.213)	-0.034 (0.128)	4.9	<0.001	Yes	-0.264	-0.162	4	4

Measure	Obs	Mean (SD) Timepoint 1	Mean (SD) Timepoint 2	Mean (SD) change score	t-stat	p- unadj	p-adj sig ^a	SRM	SES	SRM rank	Change score rank
Respondent groups based on change in HADS-A scores											
Improvement											
EQ-5D	405	0.508 (0.312)	0.567 (0.295)	0.059 (0.219)	-5.42	<0.001	Yes	0.269	0.194	5	1
MSIS-8D*	408	0.548 (0.198)	0.605 (0.183)	0.057 (0.134)	-8.617	<0.001	Yes	0.427	0.300	1	2
MSIS-8D-P*	408	0.591 (0.191)	0.643 (0.175)	0.052 (0.130)	-8.005	<0.001	Yes	0.396	0.282	3	3
ICECAP-A*	375	0.707 (0.214)	0.756 (0.190)	0.049 (0.119)	-8.015	<0.001	Yes	0.414	0.244	2	4
ASCOT	366	0.719 (0.211)	0.759 (0.201)	0.041 (0.133)	-5.848	<0.001	Yes	0.306	0.197	4	5
Deterioration											
EQ-5D	376	0.591 (0.295)	0.539 (0.312)	-0.051 (0.184)	5.432	<0.001	Yes	-0.280	-0.170	5	2
MSIS-8D*	378	0.631 (0.176)	0.580 (0.196)	-0.052 (0.131)	7.636	<0.001	Yes	-0.393	-0.277	2	1
MSIS-8D-P*	378	0.669 (0.170)	0.618 (0.192)	-0.051 (0.128)	7.742	<0.001	Yes	-0.398	-0.282	1	2
ICECAP-A*	356	0.768 (0.193)	0.725 (0.209)	-0.044 (0.121)	6.822	<0.001	Yes	-0.362	-0.218	3	4
ASCOT	346	0.782 (0.190)	0.745 (0.210)	-0.037 (0.123)	5.528	<0.001	Yes	-0.297	-0.183	4	5
Respondent groups based on change in FSS scores											
Improvement											
EQ-5D	160	0.585 (0.275)	0.644 (0.245)	0.058 (0.195)	-3.782	<0.001	No	0.299	0.224	3	1
MSIS-8D*	160	0.621 (0.181)	0.671 (0.164)	0.050 (0.108)	-5.894	<0.001	Yes	0.466	0.290	1	2
MSIS-8D-P*	160	0.658 (0.175)	0.704 (0.161)	0.046 (0.109)	-5.35	<0.001	Yes	0.423	0.275	2	3
ICECAP-A	147	0.782 (0.186)	0.810 (0.175)	0.028 (0.110)	-3.106	0.002	No	0.256	0.156	4	4
ASCOT	141	0.795 (0.185)	0.812 (0.186)	0.018 (0.128)	-1.631	0.105	No	0.137	0.095	5	5
Deterioration											
EQ-5D	160	0.619 (0.300)	0.602 (0.306)	-0.016 (0.195)	1.066	0.288	No	-0.084	-0.054	5	4
MSIS-8D	158	0.666 (0.165)	0.640 (0.176)	-0.026 (0.107)	3.005	0.003	No	-0.239	-0.150	1	1
MSIS-8D-P	158	0.701 (0.159)	0.677 (0.171)	-0.024 (0.107)	2.86	0.005	No	-0.228	-0.148	2	2
ICECAP-A	143	0.814 (0.176)	0.796 (0.190)	-0.018 (0.107)	1.978	0.050	No	-0.165	-0.097	3	3
ASCOT	135	0.816 (0.163)	0.800 (0.188)	-0.015 (0.118)	1.494	0.138	No	-0.129	-0.086	4	5

Timepoint 2 to 3											
Measure	Obs	Mean (SD) Timepoint 2	Mean (SD) Timepoint 3	Mean (SD) change score	t-stat	p- unadj	p-adj sig ^a	SRM	SES	SRM rank	Change score rank
Respondent groups based on change in MSWS-12 scores											
Improvement											
EQ-5D	170	0.601 (0.241)	0.645 (0.227)	0.043 (0.157)	-3.583	<0.001	No	0.275	0.184	3	1
MSIS-8D*	171	0.627 (0.158)	0.666 (0.152)	0.038 (0.112)	-4.471	<0.001	Yes	0.342	0.247	2	3
MSIS-8D-P*	171	0.661 (0.157)	0.701 (0.149)	0.040 (0.111)	-4.750	<0.001	Yes	0.363	0.264	1	2
ICECAP-A	125	0.781 (0.175)	0.789 (0.189)	0.008 (0.108)	-0.867	0.388	No	0.078	0.046	5	5
ASCOT	124	0.784 (0.173)	0.796 (0.166)	0.012 (0.105)	-1.257	0.211	No	0.113	0.070	4	4
Deterioration											
EQ-5D	224	0.624 (0.236)	0.587 (0.229)	-0.036 (0.196)	2.756	0.006	No	-0.184	-0.155	4	1
MSIS-8D*	222	0.661 (0.148)	0.626 (0.158)	-0.035 (0.120)	4.392	<0.001	Yes	-0.295	-0.232	1	2
MSIS-8D-P*	222	0.700 (0.143)	0.666 (0.156)	-0.034 (0.117)	4.344	<0.001	Yes	-0.292	-0.229	2	3
ICECAP-A	157	0.805 (0.176)	0.787 (0.169)	-0.019 (0.123)	1.892	0.060	No	-0.151	-0.107	5	5
ASCOT	156	0.809 (0.159)	0.777 (0.169)	-0.031 (0.120)	3.264	0.001	No	-0.261	-0.192	3	4
Respondent groups based on change in HADS-D scores											
Improvement											
EQ-5D	292	0.533 (0.316)	0.560 (0.303)	0.027 (0.196)	-2.363	0.019	No	0.138	0.087	5	5
MSIS-8D*	291	0.585 (0.183)	0.630 (0.179)	0.044 (0.112)	-6.76	<0.001	Yes	0.396	0.246	1	1
MSIS-8D-P*	291	0.626 (0.179)	0.669 (0.174)	0.043 (0.113)	-6.511	<0.001	Yes	0.382	0.244	2	2
ICECAP-A	216	0.741 (0.191)	0.770 (0.181)	0.028 (0.125)	-3.354	0.001	No	0.228	0.153	4	4
ASCOT	213	0.754 (0.184)	0.784 (0.178)	0.030 (0.112)	-3.875	<0.001	No	0.265	0.163	3	3
Deterioration											
EQ-5D	273	0.538 (0.291)	0.492 (0.300)	-0.046 (0.208)	3.663	<0.001	No	-0.222	-0.156	5	5
MSIS-8D*	273	0.596 (0.175)	0.544 (0.198)	-0.052 (0.143)	5.973	<0.001	Yes	-0.361	-0.276	4	3
MSIS-8D-P*	273	0.635 (0.170)	0.583 (0.192)	-0.052 (0.139)	6.201	<0.001	Yes	-0.375	-0.288	3	3
ICECAP-A*	188	0.752 (0.185)	0.687 (0.211)	-0.065 (0.111)	8.012	<0.001	Yes	-0.584	-0.327	1	1
ASCOT*	187	0.774 (0.185)	0.710 (0.214)	-0.064 (0.140)	6.238	<0.001	Yes	-0.456	-0.319	2	2

[illegible]

The following are highlighted in bold: significant results following Bonferroni correction, $SES \geq 0.2$, highest ranked SRMs and mean change scores.

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Table 4: Summary of responsiveness results

	Number of groups (total N=16)		Ranked SRM*		Ranked mean change score	
	With a statistically significant change	With an SES > 0.2	Mean average rank	Modal average rank	Mean average rank	Modal average rank
EQ-5D-3L	3	1	4.50	5	2.63	1
MSIS-8D	13	12	1.56	1	1.69	1
MSIS-8D-P	11	13	1.75	2	2.25	3
ICECAP-A	6	5	3.31	3	4.00	4
ASCOT	6	2	3.75	4	4.13	5

SRMs and mean change scores ranked from 1 for the largest absolute value to 5 for the smallest.

Table 5: Multivariable regression analyses between change in score on the PROMs and the PBMs (N=2226, n=1458)

	EQ-5D-3L	MSIS-8D	MSIS-8D-P	ICECAP-A	ASCOT
MSWS-12	-0.053* (0.020) [-0.093,-0.013]	-0.081*** (0.021) [-0.123,-0.040]	-0.081*** (0.022) [-0.123,-0.038]	-0.053** (0.020) [-0.093,-0.013]	-0.056** (0.020) [-0.095,-0.017]
HADS depression	-0.074** (0.027) [-0.127,-0.022]	-0.187*** (0.026) [-0.238,-0.137]	-0.192*** (0.026) [-0.242,-0.142]	-0.204*** (0.025) [-0.254,-0.155]	-0.175*** (0.024) [-0.223,-0.127]
HADS anxiety	-0.162*** (0.029) [-0.219,-0.105]	-0.253*** (0.026) [-0.304,-0.202]	-0.248*** (0.026) [-0.300,-0.197]	-0.195*** (0.024) [-0.243,-0.147]	-0.170*** (0.024) [-0.217,-0.122]
FSS	-0.063* (0.025) [-0.112,-0.013]	-0.131*** (0.019) [-0.169,-0.094]	-0.132*** (0.019) [-0.170,-0.094]	-0.044* (0.022) [-0.087,0.000]	-0.044 (0.030) [-0.102,0.014]
Constant	-0.004 (0.017) [-0.038,0.030]	0.019 (0.016) [-0.012,0.051]	0.016 (0.016) [-0.015,0.048]	0.008 (0.017) [-0.025,0.040]	0.000 (0.017) [-0.034,0.034]
R-squared	0.0533	0.1812	0.1811	0.1266	0.0947

* P <= 0.05, ** P <= 0.01, *** P <= 0.001
N, number of responses; n, number of participants.
Darker shading illustrates a stronger relationship in terms of p-value

Table 6: Multivariable regression analyses between change in score on the PROMs, as indicated by whether an MID occurred indicating an improvement or deterioration in health, and change in score on the PBM (N=2226, n=1458)

	N (n)	EQ-5D-3L	MSIS-8D	MSIS-8D-P	ICECAP-A	ASCOT
MSWS-12	1518 (1072)					
Improvement	349 (346)	0.114 (0.058) [0.000,0.228]	0.228*** (0.057) [0.117,0.340]	0.218*** (0.056) [0.109,0.328]	0.202*** (0.055) [0.093,0.310]	0.149** (0.053) [0.044,0.253]
Deterioration	359 (341)	-0.073 (0.056) [-0.182,0.037]	-0.143** (0.053) [-0.248,-0.039]	-0.159** (0.054) [-0.265,-0.053]	-0.052 (0.053) [-0.155,0.051]	-0.163** (0.055) [-0.270,-0.056]
HADS-D	1249 (958)					
Improvement	479 (465)	0.129* (0.058) [0.016,0.242]	0.292*** (0.054) [0.185,0.398]	0.292*** (0.054) [0.186,0.399]	0.237*** (0.053) [0.133,0.340]	0.204*** (0.054) [0.097,0.310]
Deterioration	498 (483)	-0.129* (0.057) [-0.241,-0.017]	-0.306*** (0.053) [-0.409,-0.202]	-0.330*** (0.053) [-0.433,-0.226]	-0.325*** (0.054) [-0.430,-0.219]	-0.303*** (0.055) [-0.410,-0.196]
HADS-A	1150 (873)					
Improvement	568 (545)	0.195*** (0.055) [0.087,0.302]	0.327*** (0.050) [0.228,0.425]	0.310*** (0.050) [0.212,0.408]	0.348*** (0.051) [0.248,0.448]	0.237*** (0.050) [0.139,0.335]
Deterioration	508 (493)	-0.216*** (0.053) [-0.320,-0.111]	-0.278*** (0.051) [-0.379,-0.177]	-0.273*** (0.051) [-0.373,-0.173]	-0.148** (0.051) [-0.248,-0.049]	-0.214*** (0.054) [-0.319,-0.108]
FSS	1810 (1263)					
Improvement	199 (199)	0.201* (0.081) [0.043,0.360]	0.271*** (0.067) [0.139,0.403]	0.258*** (0.067) [0.126,0.390]	0.103 (0.073) [-0.041,0.247]	-0.004 (0.075) [-0.152,0.143]
Deterioration	217 (216)	-0.108 (0.071) [-0.247,0.031]	-0.224*** (0.067) [-0.355,-0.092]	-0.212** (0.068) [-0.346,-0.078]	-0.125 (0.065) [-0.254,0.003]	-0.071 (0.070) [-0.209,0.068]
Constant		-0.015 (0.032) [-0.077,0.047]	-0.007 (0.029) [-0.064,0.051]	0.003 (0.029) [-0.054,0.060]	-0.044 (0.028) [-0.098,0.011]	0.025 (0.031) [-0.037,0.086]
R-squared		0.0470	0.1482	0.1471	0.1070	0.0839

* P <= 0.05, ** P <= 0.01, *** P <= 0.001

N, number of responses; n, number of participants.

Darker shading illustrates a stronger relationship in terms of p-value