Patient-Reported Outcomes

Quality of Life and Utility Measurement in a Large Clinical Trial Sample of Patients with Mild to Moderate Alzheimer’s Disease: Determinants and Level of Changes Observed

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A B S T R A C T

Objective: To evaluate the performance (in terms of responsiveness to change, associations with other criterion standards, and indicators of Alzheimer’s disease [AD] severity) of a quality-of-life measure (Quality of Life in Alzheimer’s Disease [QOL-AD]) and a health utility measure (Health Utilities Index Mark 3 [HUI-3]) from two recently completed clinical trials of a new drug for AD. Methods: Change from baseline scores was calculated, and treatment effects were analyzed using mixed models for repeated measures. Three separate models were then estimated to examine the association between the quality-of-life/utility end points and the clinical and other health outcome end points measured during the trials, including cognition, function, behavior, and dependence. Results: The performance of the two measures differed. Subject-assessed QOL-AD was found to be weakly associated with clinical measures of cognition, and with caregiver reports of function, behavior, and dependence, and showed little movement over time and did not appear to differ by baseline AD severity. Proxy-assessed QOL-AD scores were consistently lower than subject-assessed scores, and the level of decline in QOL-AD was greater using proxy-assessed QOL-AD. Proxy-assessed HUI-3 scores were more strongly associated with clinical measures of cognition, function, behavior, and dependence than the subject- and proxy-assessed QOL-AD scores. Larger proportionate changes over 78 weeks were observed with HUI-3 scores and greater separation in HUI-3 scores by baseline severity. Conclusions: Subject-assessed QOL-AD is less likely than proxy-assessed QOL-AD to respond to changes in clinical measures used to track progression in clinical trials of subjects with mild to moderate AD. Proxy-assessed HUI-3 assessments were more in line with other outcome assessments and could therefore be better outcome measures to evaluate clinical progression in mild to moderate AD. Keywords: Alzheimer’s disease, Health Utility Index (HUI), patient-reported outcomes, Quality of Life in Alzheimer’s Disease (QOL-AD).

Introduction

Quality-of-life (QOL) assessment is increasingly important in the regulatory assessment of new drugs [1,2]. Equally, utility is important as part of health technology assessments surrounding funding decisions [3]. There has been much debate about how best to measure health-related QOL and utility in Alzheimer’s disease (AD) because of challenges of changing cognitive performance and patient insight over the course of a study and concerns about bias among family caregivers who provide proxy assessments [4]. There have been a number of reviews on QOL assessment in AD [5,6]. The Quality of Life in Alzheimer’s Disease (QOL-AD) is one of the most frequently used QOL measures in AD and offers both patient-assessed and proxy-assessed options [7].

The QOL-AD has been widely used in cross-sectional [8–15] and longitudinal observation studies [16–18], in a clinical trial examining long-term follow-up strategies for patients with AD [19], and in a 6-month study examining the efficacy of Ginko Biloba [20]. These studies have already provided useful information about determinants of QOL-AD scores assessed by the patient and the proxy: in general, depression, anxiety, insight, and use of antidementia treatment have been shown to be associated with patient-assessed QOL-AD while proxy-assessed QOL-AD is determined by many factors including patient impaired function, neuropsychiatric symptoms, cognition, dependency, and caregiver characteristics. On the basis of these findings, researchers have argued that the patient and proxy ratings should be considered complementary and not combined.

Conflict of interest: Loretto Lacey and Chris Leibman were full-time employees of Janssen Alzheimer Immunotherapy Research & Development, LLC, at the time the work was conducted. Joel Bobula, Katja Rüdell, and Jose Alvir are employees of Pfizer, Inc. * Address correspondence to: Joel Bobula, Pfizer, Inc., 500 Arcola Road, Collegeville, PA 19426.
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in a composite score. A European consensus panel recommended the QOL-AD as a measure of choice for evaluating psychosocial interventions research in dementia care, having reviewed the literature on a number of QOL outcome measures [21].

Recent long-term observational studies have shown that larger mean changes might be expected in the proxy-assessed QOL-AD than in the patient-assessed QOL-AD. In a 2-year follow-up study, patient-assessed QOL-AD scores did not change significantly but proxy-assessed QOL-AD scores did change significantly [17]. In a 3-year follow-up observational study, there was a significant decline in mean scores for proxy-assessed QOL-AD at 12 and 36 months, but vast individual differences in QOL-AD scores [16]. The authors noted that “the wide variation in changes from baseline may affect the validity of using QOL measures as efficacy parameters because improvements in QOL cannot with certainty be appraised as an effect of the intervention.”

Shearer et al. [22] reviewed the literature on the use of the Health Utility Index Mark 3 (HUI-3) in AD and concluded that the “validity of the HUI3 for caregiver reports was supported in two studies[23,24] although the validity of the HUI3 for use in AD patients (i.e., patient completed) has been queried due to poor correlations with patient self-assessments of functional status” [23]. For self-completion by patients with mild dementia and for proxy completion, the reliability of the HUI-3, using test-retest reliability (intraclass correlation coefficients), has been reported to be 0.70 or more [23].

Two recently completed randomized clinical trials of bapineuzumab, despite failing to show significant efficacy on the primary outcomes of cognition and function [25], provide a rich data set to investigate the performance of the subject- and proxy-assessed QOL-AD as well as the performance of the proxy-assessed HUI-3 as a measure of utility and its interrelationships with multiple symptoms, including measures of cognition, function, behavior, and dependence. The primary objective of Study ELN15727-301 and Study ELN15727-302 (hereafter referred to as Study 301 and Study 302, respectively) was to demonstrate the safety and efficacy of multiple doses of intravenously administered bapineuzumab in patients with mild to moderate AD compared with placebo (Study 301: NCT00667810 and Study 302: NCT00676143).

This article presents a comprehensive evaluation of the performance of subject- and proxy-assessed QOL-AD and the proxy-based HUI-3 based on pooled data from these two placebo-controlled randomized clinical trials investigating the efficacy of bapineuzumab. These analyses could inform decisions about the usefulness of QOL-AD and HUI-3 in future clinical trials in those with mild to moderate AD. Moreover, the multitude of other instruments and indicators of health status in this trial allows for a better understanding of the determinants of QOL. This may help other evaluations of interventions to improve both patient- and proxy-assessed QOL in patients with mild to moderate AD.

Methods

Study Design

Study 301 and Study 302 were multicenter, randomized, double-blind, placebo-controlled, parallel-group outpatient studies in male and female subjects aged 50 years to younger than 89 years with mild to moderate AD (Study 301: ClinicalTrials.gov identifier NCT00667810 and Study 302: ClinicalTrials.gov identifier NCT00676143). Study 302 was conducted at 170 sites in the United States from December 2007 through April 2012 and included participants who were carriers of the apolipoprotein E (apoE) ε4 allele, a genetic risk factor for AD. Study 301 was conducted at 218 sites in the United States (195 sites), Canada (17), Germany (4), and Austria (2) from December 2007 through June 2012 and included participants who were noncarriers [26]. Bapineuzumab or placebo was administered via an intravenous infusion every 13 weeks for a total of six infusions over the course of the 78-week study. Informed consent was obtained from all participants, or, if not capable of providing informed consent, from their legally acceptable representative. The studies were conducted according to the Declaration of Helsinki and were approved by independent review boards.

Full inclusion and exclusion criteria are described elsewhere (Study 301: NCT00667810 and Study 302: NCT00676143). Briefly, subjects were enrolled in the study if they were aged 50 years to younger than 89; had a diagnosis of probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer’s Disease and Related Disorders Association criteria and a screening visit brain magnetic resonance imaging scan consistent with a diagnosis of AD; a Mini-Mental State Examination (MMSE) score of 16 to 26 inclusive; a Rosen Modified Hachinski Ischemic score [27] of 4 or less; and lived at home or independently in a community dwelling and had a caregiver who consented to participate in the study, could accompany the subject on all clinic visits, and was a reliable informant in the opinion of the investigator. Subjects were excluded if they had clinically significant neurological disease other than AD; a major psychiatric disorder; history of stroke or seizures; a brain magnetic resonance imaging scan indicative of significant non-AD abnormality; or history or evidence of any clinically significant autoimmune disease or chronic illness that was likely to result in deterioration affecting the subject’s safety during the study.

The QOL-AD and HUI-3 [28] were administered at baseline, week 26, week 52, and week 78. Both caregivers and patients completed the QOL-AD, but only the caregivers completed the self-administered proxy version of the HUI-3. The QOL-AD is a 13-item questionnaire designed to provide both a subject report and a caregiver report of the subject’s QOL. Points are assigned to each item as follows: poor = 1, fair = 2, good = 3, and excellent = 4. The total score is the sum of all the 13 items and the total range of possible scores is 13 to 52 (higher scores indicate better QOL). The proxy version of HUI-3 is a generic, preference-weighted, health status assessment system completed by the caregiver. The proxy version encompasses 16 questions (one additional item than the self-reported version to identify the relationship of the respondent) that are used to obtain data about patients so that their health status can be described using HUI-3 health states, and ultimately a preference-based utility score for their health. Possible HUI-3 utility values can range from −0.36 (worse than death) to 1 (perfect health), with 0 representing death.

At baseline, week 26, week 52, and week 78, cognitive function was assessed using the Alzheimer’s Disease Assessment Scale-Cognitive Subscale (ADAS-COG; range 0–70) [29], global disability was assessed using the Clinical Dementia Rating Scale-Sum of Boxes [32]. GMSE (0–30) [34] assessments were also made at baseline and at weeks 19, 32, 45, 58, and 78. To estimate MMSE levels at weeks 26 and 52, the mean of two assessments (19 and 32; 45 and 58) was calculated.

Analysis

Level of Change Analysis Using Individual Study Data

For the individual studies, change from baseline scores were calculated for the subject-assessed QOL-AD scores and the proxy-assessed QOL-AD scores at week 78 and treatment effects were analyzed using a restricted maximum likelihood-based mixed model for repeated measures, similar to that used for
primary efficacy measures in both studies. Only descriptive statistics were prespecified for the analysis of HUI-3 utility scores in the different treatment groups.

Analysis Using Pooled Data Set

Using the pooled data set from both studies, mean changes in the QOL-AD and HUI-3 scores at week 78 were determined for three subgroups of patients with the following baseline severity: very mild (MMSE score ≥ 24), mild (MMSE score ≥ 21), and moderate (MMSE score < 21).

Pearson correlations between the QOL-AD and utility measures and the other clinical measures were determined for each of the four assessment times: baseline, week 26, week 52, and week 78. A priori, the strength of the correlation coefficient to establish concurrent validity between the QOL-AD and the other scales was considered: 0 to 0.25 = little if any correlation, 0.26 to 0.49 = low correlation, 0.50 to 0.69 = moderate correlation, 0.70 to 0.89 = high correlation, and 0.90 to 1.0 = very high correlation. Moderate correlation would be considered useful because this would mean that the scales were associated, but not redundant.

Using restricted maximum likelihood–based mixed models for repeated measures, three separate models were estimated: Model 1 examined the association between QOL/utility and the DS; model 2 examined independent associations between AQDAS-COG, DAD, and NPI and QOL/utility; and model 3 examined independent associations between MMSE, DAD, and NPI and QOL/utility. MMSE and AQDAS-COG were not included in the same model because of concerns about multicollinearity. All models also controlled for patient age, sex, and assessment time.

Results

Demographic and Baseline Characteristics

Patients’ demographic and baseline characteristics for patients participating in studies 301 and 302 and for the pooled data set are presented in Table 1. In study 301, 493 and 621 patients received placebo and bapineuzumab (0.5 and 1 mg/kg), respectively, while 432 and 658 patients received placebo and bapineuzumab (0.5 mg/kg), respectively, in study 302. The two treatment groups were similar at baseline with very mild and mild AD.

Changes in QOL-AD and HUI-3 Over Time

The QOL-AD subject and caregiver baseline scores and adjusted least squares (LS) mean (standard error) change scores at week 78 are presented in Table 2. Change in subject-assessed QOL-AD was small, with LS mean changes of −0.6 versus −0.2 and −0.3 versus −0.6 for placebo and bapineuzumab for studies 301 and 302, respectively. No significant differences across treatments were observed. The average baseline scores for QOL-AD proxy were consistently lower, by approximately 3 points, than the corresponding subject-assessed QOL-AD scores. Change in caregiver proxy-assessed QOL-AD was larger at week 78, with LS mean changes of −2.3 versus −2.7 and −2.3 versus −2.6 for placebo and bapineuzumab for study 301 and study 302, respectively. No significant differences across treatments were observed.

The HUI-3 baseline and unadjusted mean change in scores at week 78 is presented in Table 3. No statistical testing of changes was conducted because the study protocol had prespecified descriptive statistics.

Changes in mean scores for placebo and bapineuzumab were −0.123 versus −0.123 and −0.123 versus −0.137 for studies 301 and 302, respectively. The proportionate change was considerably larger than that observed for the QOL-AD. HUI-3 utility values can range from −0.36 (worse than death) to 1.00 (perfect health); hence, a decline of between −0.123 and −0.137 is a proportionate change of between 9.0% and 10.0%. QOL-AD total scores range from 13 (worse QOL) to 52 (better QOL); hence, a decline of between −0.2 and −0.6 in the QOL-AD subject total score is a proportionate change of between 0.05% and 1.5%. A decline of −2.3 and −2.7 in the QOL-AD caregiver proxy total score is a proportionate change of between 5.9% and 6.9%.

Changes in QOL-AD and HUI-3 by Baseline Severity

Table 4 presents the mean baseline QOL-AD and HUI-3 scores for patients in different subgroups based on their baseline MMSE score, in addition to the mean change in scores at week 78. Baseline subject-assessed QOL-AD varied little by severity level, with an average score of 40.1 in subjects with very mild AD and 40.1 in subjects with moderate AD. Change scores were small but tended to be larger in patients with moderate AD than in those with very mild and mild AD.

At baseline, caregiver proxy-assessed QOL-AD tended to be lower in subjects with moderate AD than in subjects with less severe AD, but the difference was not statistically significant.
severe AD and changes in the QOL-AD score tended to be higher for the moderate group. HUI-3 scores showed a wider separation than did the QOL-AD scores across the severity subgroups, with a mean baseline level of 0.543 for subjects with very mild AD and 0.409 for subjects with moderate AD. Change scores showed the same trend, with severe AD having an average change score of 0.157 compared with 0.157 for subjects with moderate AD. Change scores showed the same trend, with a mean baseline level for the moderate group.

**Bivariate and Covariate-Adjusted Associations**

Correlations between subject-assessed QOL-AD, proxy-assessed QOL-AD, and HUI-3 and other clinical variables are presented in Figure 1. Results of the mixed models are presented in Table 5.

Subject-assessed QOL-AD was highly correlated with caregiver proxy-assessed QOL-AD. There were weak but significant correlations with clinical measures of cognition (AQDAS-COG and MMSE), function (DAD), behavior (NPI), dependence (DS), and global disability (Clinical Dementia Rating Scale-Sum of Boxes) (Fig. 1A). The associations, indicated by beta coefficients in models 1 to 3 for subject-assessed QOL-AD, were relatively small but statistically significant for AQDAS-COG, DAD, NPI, and DS, but not for MMSE, in agreement with the weak correlations observed above (Table 5).

Proxy-assessed QOL-AD was weakly correlated with other clinical measures. There were higher correlations with other proxy-reported measures (DAD, NPI, DS, and Clinical Dementia Rating) and lower correlations with clinician-reported measures (MMSE and AQDAS-COG). There was a moderate correlation with

<table>
<thead>
<tr>
<th>Table 2 – Subject- and caregiver proxy-assessed QOL-AD total scores: Observed values and change from baseline to week 78.</th>
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</thead>
<tbody>
<tr>
<td>QOL-AD total score</td>
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<tr>
<td><strong>Subject-assessed QOL-AD</strong></td>
</tr>
<tr>
<td>Baseline, mean ± SD</td>
</tr>
<tr>
<td>Change from baseline at week 78, N</td>
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<tr>
<td>Change from baseline at week 78, mean (SE)†</td>
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<tr>
<td>Difference in means (95%)</td>
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<td>P-value</td>
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<tr>
<td><strong>Caregiver-proxy QOL-AD</strong></td>
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<tr>
<td>Baseline, mean ± SD</td>
</tr>
<tr>
<td>Change from baseline at week 78, N</td>
</tr>
<tr>
<td>Change from baseline at week 78, mean (SE)†</td>
</tr>
<tr>
<td>Difference in means (95%)</td>
</tr>
<tr>
<td>P-value</td>
</tr>
</tbody>
</table>

**Note.** MMSE, Mini-Mental State Examination; QOL, quality of life; QOL-AD, Quality of Life in Alzheimer’s Disease; SE, standard error.

* Bapineuzumab 0.5 mg/kg and 1.0 mg/kg pooled.

† Mixed model for repeated measures with change from baseline as the response variable and the fixed-effect model terms for treatment, visit (scheduled week), treatment-by-visit interaction, baseline value, baseline value-by-visit interaction, MMSE total score stratum, cholinesterase inhibitor or memantine use stratum, APOE*E4 allele copy number stratum, and baseline age. Treatment differences (bapineuzumab minus placebo) are estimated using least squares means with factor levels weighted according to overall baseline sample proportions. A positive difference (bapineuzumab minus placebo) favors bapineuzumab. Total scores range from 13 (worse QOL) to 52 (better QOL); a positive change from baseline indicates improved QOL.

<table>
<thead>
<tr>
<th>Table 3 – HUI-3 total score: Observed values and changes from baseline.</th>
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<tbody>
<tr>
<td><strong>HUI-3 total score</strong></td>
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<tr>
<td><strong>Plac</strong></td>
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<tr>
<td>Baseline, N (N = 493)</td>
</tr>
<tr>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Change from baseline week 78, N</td>
</tr>
<tr>
<td>Mean ± SD</td>
</tr>
</tbody>
</table>

**Note.** The HUI-3 total score anchor points range from 0.00 (dead) to 1.00 (perfect health); a positive change from baseline indicates improved utility.

HUI-3, Health Utility Index Mark 3.

* Bapineuzumab 0.5 mg/kg and 1.0 mg/kg pooled.
The associations, indicated by beta coefficients in models 1 to 3, were larger than for the subject-assessed QOL-AD and statistically significant for MMSE, DAD, NPI, and DS but not for AQDAS-COG (Table 5).

Our results suggest that subject-assessed QOL-AD is less likely than proxy-assessed QOL-AD to respond to changes in clinical measures that are frequently used to assess disease progression and efficacy in clinical trials in those with mild to moderate AD. Subject-assessed QOL-AD was found to be weakly associated with clinical measures of cognition (MMSE and AQDAS-COG), and with caregiver reports of function (DAD), behavior (NPI), and dependence (DS), and, in our sample, showed little movement over time and did not appear to differ by baseline AD severity. This is consistent with other research indicating that, in general, depression, insight, and use of antidementia treatment have been shown to be associated with patient-assessed QOL-AD and not other clinical measures [35,36].

Our observations that proxy-assessed QOL-AD scores were consistently lower than subject-assessed scores and level of decline in QOL-AD greater using proxy-assessed QOL-AD are consistent with the findings of others [17]. This was further supported by the larger changes observed at week 78 in the individual 301 and 302 studies. It is important to note, however, that although such changes were greater than for subject-assessed QOL-AD, they were relatively small. For example, the LS mean changes after 78 weeks did not exceed 3 points, a change that is frequently used to define the "minimal clinically important difference," for the QOL-AD proxy [19]. Our analysis of changes across subjects with different baseline severity did show that patients with moderate AD had a mean change of 3.0 at week 78. This suggests that the rate of change in proxy-assessed QOL-AD may be sufficient to detect minimal clinically important differences in QOL in 18-month studies in subjects with moderate AD. But the smaller changes observed in patients with milder AD at week 78 suggest that it may be difficult to detect differences in such patients over an 18-month period on the basis of a definition of a 3-point minimal important difference. Despite some overlap between proxy and subject data, the patients consistently reported less change over this time period.

Our results further suggest that proxy-assessed HUI-3 scores are more strongly associated with clinical measures of cognition, function, behavior, and dependence than subject- and proxy-assessed QOL-AD scores. Consistent with this finding, we observed larger proportionate changes over 78 weeks with HUI-3 and greater separation in HUI-3 scores by baseline severity. HUI-3 domains include eight health dimensions: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. The inclusion of the cognition domain has been used to support the inclusion of HUI-3 in AD clinical trials over an alternative utility measure, the EuroQol five-dimensional questionnaire, which lacks a cognition dimension. Based on these findings, the proxy-assessed HUI-3 would appear to be a useful measure for inclusion in clinical trials investigating disease-modifying treatments in those with mild to moderate AD. The mixed-models analysis shows that HUI-3 utility scores are independently associated with measures of cognition (MMSE and AQDAS-COG), function (DAD), and behavior (NPI) and beta coefficients provide quantitative estimates for changes in HUI-3 that might be expected per unit changes in these clinical measures. As noted, however, HUI-3 includes (in addition to cognition and emotion) items related to general age-related disability or to progression in other chronic illnesses; thus, changes in HUI-3 that were observed in our sample over the 78-week follow-up period may be inflated because of decline in vision, hearing, or other physical changes that affect performance on cognitive and clinical measures but that might not respond to treatment of dementia.

### Strengths and Limitations

By pooling data from two large randomized clinical trials, this study provided a robust study design for the comparison of...
Correlations between proxy-assessed HUI-3 and other end points at specific time points in the trials. Notes. All correlations with the exception of those marked with an asterisk are statistically significant (P < 0.05). Sign of correlations: age (−); sex (−); AQDAS-COG (−); MMSE (−); DAD (−); NPI (−); DS (−); CDR (−); QOL-AD pt (−); QOL-AD cg (−). AQDAS-COG, Alzheimer’s Disease Assessment Scale-Cognition; CDR, Clinical Dementia Rating; DAD, Disability Assessment for Dementia; DS, dependence scale; HUI-3, Health Utilities Index Mark 3; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; QOL-AD cg, Quality of Life in Alzheimer’s Disease-caregiver assessed; QOL-AD pt, Quality of Life in Alzheimer’s Disease-patient-assessed.

Further Research

Further work is required to understand QOL and the relationship between cognitive, functional, behavioral, and caregiver factors that influence QOL in AD. Based on current findings, the most effective treatment approaches in mild to moderate AD may need to be multifactorial, including treatment not only specifically targeting cognitive change but also recognizing and treating mood, behavioral, and caregiver characteristics that also influence QOL. Both the QOL-AD and HUI-3 provide information that may be helpful in developing and evaluating such interventions, but additional work is needed to refine and strengthen the measurement of QOL in AD.

Conclusions

In this clinical trial population it appears that HUI-3 has preferential psychometric properties. Subject-assessed QOL-AD is less likely than proxy-assessed QOL-AD to respond to changes in clinical measures used to track the progression of subjects with mild to moderate AD in clinical trials. The proxy-assessed HUI-3 assessment is likely to respond to changes in these clinical progression measures in mild to moderate AD, but the changes may not be specific to AD-related factors. More work is required to understand what drives subject-assessed QOL and how to best evaluate time- and treatment-related QOL changes in individuals with AD.

Acknowledgments

We thank and acknowledge all the patients and the caregivers for their participation in the clinical trials and for providing us with valuable information about their quality of life. We also acknowledge the advice and guidance of Rebecca Logsdon, PhD, the developer of the QOL-AD.
### Table 5 – Associations (regression coefficients) between clinical variables and QOL-AD (patient- and proxy-assessed) and HUI-3 using mixed-effects models for repeated measures.

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Subject-assessed QOL-AD</th>
<th>Proxy-assessed QOL-AD</th>
<th>HUI-3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1</td>
<td>Model 2</td>
<td>Model 3</td>
</tr>
<tr>
<td>AQDAS-COG</td>
<td>-0.00977*</td>
<td>-0.02044</td>
<td>0.00192</td>
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<tr>
<td>MMSE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAD</td>
<td>0.01982†</td>
<td>0.0253³</td>
<td>0.08627†</td>
</tr>
<tr>
<td>NPI</td>
<td>-0.04906†</td>
<td>-0.04909–</td>
<td>-0.1477–</td>
</tr>
<tr>
<td>DS</td>
<td>-0.22908‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>38.23</td>
<td>37.70†</td>
<td>39.75¹</td>
</tr>
<tr>
<td>No. of observations</td>
<td>7706</td>
<td>7586</td>
<td>8005</td>
</tr>
</tbody>
</table>

Notes. All models controlled for age, sex, and assessment week; for patient-assessed QOL-AD, week was significant for models 1 and 3 (P < 0.05); for proxy-assessed QOL-AD, week was significant for all models (P < 0.0001); for HUI-3, age and week were significant for all models (P < 0.0001) and sex for models 2 and 3.

AQDAS-COG, Alzheimer’s Disease Assessment Scale-Cognition; DAD, Disability Assessment for Dementia; DS, dependence scale; HUI-3, Health Utilities Index Mark 3; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; QOL-AD, Quality of Life in Alzheimer’s Disease.

* P = 0.0005;
† P < 0.0001;
‡ P = 0.005.

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### References


