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Self-Perceived Quality of Life Among Patients with Alzheimer's Disease: Two Longitudinal Models of Analysis

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Abstract. The objective was to analyze the factors that influence self-perceived quality of life (QoL) in patients with Alzheimer's disease (AD), contrasting two different longitudinal models. A total of 127 patients were followed up over 24 months. The instruments applied were: Quality of Life in Alzheimer's Disease scale (QoL-AD), Geriatric Depression Scale-15, Anosognosia Questionnaire-Dementia, Disability Assessment in Dementia, Neuropsychiatric Inventory, and the Mini-Mental State Examination. Two models for grouping patients were tested: 1) Baseline score on the QoL-AD (QoL-Baseline), and 2) Difference in QoL-AD score between baseline and follow-up (QoL-Change). Generalized estimating equations were used to analyze longitudinal data, and multinomial regression analyses were performed. Over the follow-up period the QoL-Baseline model showed greater variability between groups (Wald $\chi^2 = 172.3$, $p < 0.001$) than did the QoL-Change model (Wald $\chi^2 = 1.7$, $p = 0.427$). In the QoL-Baseline model the predictive factors were greater depression (odds ratio [OR] = 1.20; 95% CI: 1.00–1.45) and lower functional ability (OR = 0.92; 95% CI: 0.85–0.99) for the Low QoL group (< 33 QoL-AD), and less depression (OR = 0.68; 95% CI: 0.52–0.88), more anosognosia (OR = 1.07; 95% CI: 1.01–1.13), and fewer neuropsychiatric symptoms (OR = 0.95; 95% CI: 0.91–0.99) for the High-QoL group (>37 QoL-AD). The model based on baseline scores (QoL-Baseline) was better than the QoL-Change model in terms of identifying trajectories and predictors of QoL in AD.

Keywords: Alzheimer's disease, analytic models, anosognosia, depression, longitudinal study, quality of life

INTRODUCTION

In its report, *Dementia: A Public Health Priority*, the World Health Organization [1] highlights the need to develop programs that can improve the social wellbeing and quality of life (QoL) of people with dementia. Consequently, it is important to identify the factors that influence QoL so as to design interventions that might improve it.

Among research that has examined predictors of change in the QoL of patients with dementia, longitudinal studies are of particular interest. The majority of these studies have found, when considering samples

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as a whole, that mean QoL scores remain relatively stable over time [2–14], although some research conducted in residential settings has reported a decrease [15–17].

The factors associated with perceived QoL are consistent across some studies. Greater depression appears to be the most relevant aspect and it is associated with a deteriorating QoL over time [2, 6–8, 18]. A greater number of neuropsychiatric symptoms (higher scores on the NPI) is also associated with poorer perceived QoL [5, 11, 17], whereas better functional ability correlates with higher QoL scores [3, 6] Cognitive changes appear to have only a weak or no effect [12, 19].

Many longitudinal studies also distinguish subgroups of patients according to whether their perceived QoL deteriorates, remains stable, or improves over time. The combined data of five community studies [3, 7–9, 13], with a total sample of 417 people, indicate that QoL scores deteriorated in 28.2%, remained stable in 35.9%, and improved in 35.7%. Across six studies carried out in residential care settings [2, 4, 14–17], with a total sample of 906 elders, QoL scores deteriorated in 41%, remained stable in 27.2%, and improved in 31.7%.

Analyzing the self-perceived QoL of patients is, however, a complex task [15] due to the considerable individual variability and small effect sizes involved. It should also be noted that the severity of dementia does not seem to affect QoL scores [12, 13]. Baseline QoL appears to have a predictive value, although studies report contrasting results as regards the direction of the effect: While some studies have found that higher QoL at baseline was associated with better QoL at follow-up [2, 6, 7, 9, 15, 16], others, mostly in residential settings, report a reduction in perceived QoL among those with higher baseline QoL scores [4, 14, 17].

Despite this evidence, most studies aimed at analyzing the evolution of QoL have used the total QoL score or have defined groups based on how their scores changed (QoL-Change: Deterioration/stability/improvement). However, given the predictive capacity of baseline QoL and the stability of scores over time, it might be more useful to define groups on the basis of their baseline score (Low, Medium, and High QoL), to analyze how these scores change, and to identify predictive factors for each group at the time of the baseline assessment. This distribution of groups could then be compared with that used by the majority of studies (i.e., QoL-Change: Decreased, No change, Increased).

The hypothesis underlying the present study is that a model in which groups are defined according to their baseline QoL score would be better at identifying the trajectories and predictive factors of QoL, and that these factors (e.g., depression, neuropsychiatric symptoms, anosognosia, and functional ability) would not be the same for each group.

Given the wide range of factors that are potentially involved and the various models that have been used to study changes in the perceived QoL of patients with dementia, the present study had the following objectives: 1) to analyze the factors that influence self-perceived QoL when the total sample of patients is considered; 2) to analyze the factors associated with self-perceived QoL when three subgroups are established on the basis of the baseline QoL score (QoL-Baseline model) and according to the change in score over time (QoL-Change model); and 3) to assess which of these models is best in terms of identifying the trajectory and predictors of QoL scores over time.

METHODS

Design and study population

This was a longitudinal study involving a 24-month follow-up of a consecutive sample of outpatients seen at the Dementia Unit (Department of Neurology) of Bellvitge University Hospital (Hospitalet de Llobregat, Barcelona). They were all diagnosed as either AD according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [20] or probable AD according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke / Alzheimer's Disease and Related Disorders Associations [21]. In addition, they all scored between 10 and 28 on the Mini-Mental State Examination (MMSE) [22], thereby enabling a quality-of-life scale (QoL-AD) [23] to be administered. The main caregiver was defined as the person with ongoing responsibility for helping the patient with activities of daily living (ADL). All the caregivers were relatives of the patients.

Patients were excluded if they presented vascular or traumatic events, alcohol or substance dependence or abuse, and if they had severe communication problems that prevented them from responding adequately to the assessment instruments. Informed consent was obtained for all participants. The study was approved by the hospital's Clinical Research Ethics Committee (ref. PR162/10).

Instruments

Socio-demographic data for patients were gathered using a structured questionnaire designed by the researchers.

- Quality of life. The Quality of Life in Alzheimer's Disease (QoL-AD) scale [23] was used to explore patients' own views regarding their quality of life. This instrument comprises 13 items that refer to different aspects of the patient's wellbeing. Each item is scored on a Likert-type scale ranging from 1 (poor) to 4 (excellent), yielding a total score between 13 and 52 (the higher the score the better the perceived quality of life).
- Behavioral and psychological symptoms of dementia. This aspect was evaluated by means of the Neuropsychiatric Inventory (NPI) [24], which comprises 12 subscales that assess the frequency and severity of 12 neuropsychiatric symptoms, based on information provided by caregivers. Scores range from 0 to 144, and the higher the score the greater the frequency and severity of neuropsychiatric symptoms.
- Anosognosia. The Anosognosia Questionnaire-Dementia (AQ-D) [25] was administered to patients and caregivers. It comprises 30 items referring to cognitive/functional deficits and changes in the patient's behavior, with each item being rated according to the frequency of occurrence, from 0 (never) to 3 (always). The total score therefore ranges from 0 to 90. The degree of anosognosia is estimated on the basis of the difference between patient and caregiver scores; the greater the difference the greater the anosognosia.
- Cognitive assessment of the patient. This was based on the MMSE [22], a brief cognitive assessment tool whose score ranges from 0 to 30 (the lower the score the greater the cognitive deterioration). Patients' scores were corrected for age and level of education [26].
- Depression in the patient. This was assessed using the Geriatric Depression Scale (GDS), in its 15-item format [27]. The cut-off score for probable depression is 6, while a score of 10 or higher is indicative of depression. The 15-item version of the GDS has been previously used to assess depression in patients with AD [28, 29].
- Functional assessment of the patient. The Disability Assessment for Dementia (DAD) [30] is a measure of basic and instrumental ADL and it was administered to the main caregiver. The DAD comprises 40 items and its total score ranges from 40 to 80 (the higher the score the greater the patient's functional ability).
- Severity of dementia. This was based on the criteria of the Global Deterioration Scale (GDS) [31], a tool designed to determine the stage of a patient's dementia. Patients were excluded if they were classified as either GDS 7, due to the severity of their dementia, or GDS 3, due to the possible confusion with mild cognitive impairment.

Procedure

Neurologists from the Dementia Unit of Bellvitge University Hospital selected eligible patients according to the inclusion criteria and then determined their stage of dementia using the GDS. The initial sample was recruited between January and December 2011, with a 24-month follow-up assessment being conducted in May 2014. The baseline sample comprised 221 patients, of whom 127 were able to be re-assessed at 24 months. Regarding the 94 (42.5%) patients lost to follow-up, 27 (28.7%) had entered residential care, 31 (32.9%) decided not to participate any further, 2 (2.1%) had changed address, and 34 (36.1%) had died. The present study only uses data from the 127 participants who completed the 24-month follow-up.

The aims of the study were explained to all participants prior to the baseline interview, and informed consent was obtained from both patients and caregivers before proceeding. Patients and their caregivers were then interviewed separately by two clinical psychologists trained in the administration of the respective tests.

Models of longitudinal analysis

In order to study the factors associated with changes in perceived QoL, we designed two models for grouping the scores obtained by patients on the QoL-AD. The first was based on their score at baseline (QoL-Baseline) and yielded three groups that were comparable in terms of the number of subjects in each: Low-QoL (< 33, $n = 40$), Medium-QoL (33–37, $n = 43$), and High-QoL (> 37, $n = 44$). The second model was based on the difference between QoL-AD scores at baseline and 24-month follow-up (QoL-Change), and here we established three groups

based on the cut-off points that have generally been used in previous studies [2, 4, 9, 14]: Decreased QoL (≤ 3, $n = 25$), No change (± 2, $n = 44$), and Increased QoL (≥ 3, $n = 58$). The number of groups was the same at all the assessment points and in both models.

Statistical analysis

For the longitudinal analysis of data we applied generalized estimating equations (GEE) and the Wald χ^2 statistic [32], in conjunction with a first-order autoregressive working correlation matrix (AR1). This approach enabled us to examine the general effects of the independent variables on the dependent variable (QoL-AD), with respect to the factors time, patient group, and the interaction between the two (Time*Group), as well as the simple effects of differences between the groups and the assessment points.

The effect size of the difference between several means was assessed using eta squared (η^2), the value of which was interpreted according to the following criteria: <0.06, weak effect; 0.06–0.13, moderate effect; >0.13, strong effect [33].

A multivariate analysis was first performed for the whole sample, taking the QoL-AD score as the dependent variable and patient factors (introduced simultaneously) as independent variables, and specifying the parameter estimates at each of the three measurement points (baseline, 12 months, and 24 months).

In order to detect the factors that predicted patients' group assignment in the two models we performed multinomial regression analyses at baseline, using the 'Main effects' option.

For hypothesis contrasts the level of statistical significance was set at 0.05. All data processing and analysis was performed using SPSS, v22.0 para Windows (SPSS Inc.; Chicago).

RESULTS

Comparison of the study sample with the baseline sample lost to follow-up

The study sample comprised the 127 patients and caregivers who, from among the 221 initially recruited, completed the full 24-month follow-up. At baseline, the cases lost to follow-up ($n = 94$) were older than those in the study sample (79.4 ± 6.9 versus 76.6 ± 7.3; $z = 3.0$, $p = 0.002$), and they were also more impaired, presenting a poorer cognitive status (MMSE = 17.2 ± 5.5 versus 19.1 ± 5.2; $z = 2.4$, $p = 0.014$), lower functional ability (DAD = 54.7 ± 9.5 versus 60.6 ± 10.0; $z = 4.2$, $p < 0.001$), greater anosognosia (AQ-D = 38.9 ± 18.2 versus 30.2 ± 18.2; $t = 3.4$, $p = 0.001$), and more neuropsychiatric symptoms (NPI = 31.2 ± 21.9 versus 20.9 ± 16.4; $z = 3.9$, $p < 0.001$).

Self-perceived QoL at baseline did not differ significantly between lost cases and those who were followed up (QoL-AD = 35.2 ± 4.9 versus 34.9 ± 4.7; $z = 0.8$, $p = 0.402$). Neither did the QoL-AD scores of lost cases vary according to the severity of dementia (GDS stage, $\chi^2 = 4.0$, $p = 0.131$).

Sociodemographic and clinical characteristics of the study sample

At baseline, patients had a mean age of 76.6 ± 7.3 years, 82 of them (64.6%) were women, and 43 (33.9%) had received five or more years of formal education.

Across the follow-up period we observed a moderate deterioration in cognitive status (MMSE, $\eta^2 = 0.10$), a notable decrease in functional ability (DAD, $\eta^2 = 0.16$), and an increased presence of both neuropsychiatric symptoms (NPI, $\eta^2 = 0.03$) and anosognosia (AQ-D, $\eta^2 = 0.02$), with a small effect size. Patients' ratings of their own QoL did not change significantly during follow-up ($p = 0.247$). Complete data shown in Table 1.

Factors affecting QoL ratings during follow-up in the whole sample

The multivariate analysis (Table 2) showed that depression had an important negative effect on self-perceived QoL at all three assessment points. Greater anosognosia had a positive effect on QoL-AD scores that likewise continued across the follow-up period. The positive effect of greater functional ability was only significant at 12 and 24 months. Neuropsychiatric symptoms and cognitive status had no significant effect on QoL scores.

The severity of dementia (assessed by GDS stage) had little effect on QoL-AD scores, and the differences between severity groups (GDS stages 4, 5, and 6) were not significant at baseline (Wald $\chi^2 = 1.0$, $p = 0.585$), at 12 months (Wald $\chi^2 = 0.8$, $p = 0.661$), or at 24 months (Wald $\chi^2 = 0.3$, $p = 0.836$). With respect to the general effects of the model, only Time was significant (Wald $\chi^2 = 6.4$, $p = 0.040$), there being a slight increase in QoL-AD scores at

Table 1
Sociodemographic and clinical data of patients

	Baseline	12 months	24 months	Differences			
	1 ($n=127$)	2 ($n=127$)	3 ($n=127$)	Test	*df*	*p*	η^2
Age, mean (SD)	76.6 (7.3)	77.8 (7.2)	79.0 (7.2)[b]	7.1[1]	2	**0.025**	
Women, *n* (%)	82 (64.6)	82 (64.6)	82 (64.6)	0.0[2]	2	1.000	
Marital status (widowed), *n* (%)	37 (30.1)	38 (30.9)	40 (32.0)	0.1[2]	2	0.948	
Schooling (>5 years), *n* (%)	43 (33.9)	43 (33.9)	43 (33.9)	0.0[2]	2	1.000	
Cognition (MMSE), mean (SE)	19.1 (0.4)	16.8 (0.5)[a]	13.9 (0.6)[b,c]	106.1[3]	2	**<0.001**	0.10
Function (DAD), mean (SE)	60.6 (0.8)	55.5 (0.8)[a]	50.0 (0.8)[b,c]	201.4[3]	2	**<0.001**	0.16
Behavior (NPI), mean (SE)	20.9 (1.4)	23.4 (1.4)	28.6 (1.5)[b,c]	25.5[3]	2	**<0.001**	0.03
Anosognosia (AQ-D), mean (SE)	30.2 (1.6)	34.5 (1.7)	37.9 (1.6)[b]	44.4[3]	2	**<0.001**	0.02
Depression (GDS), mean (SE)	3.3 (0.2)	3.4 (0.2)	3.1 (0.2)	3.9[3]	2	0.137	0.00
Quality of life (QoL-AD), mean (SE)	34.9 (0.4)	35.1 (0.4)	35.9 (0.4)[b,c]	16.9[3]	2	**<0.001**	0.000
GDS stage, *n* (%)							
GDS 4	68 (53.5)	33 (26.0)	12 (9.4)	83.6[2]	4	**<0.001**	
GDS 5	43 (33.9)	52 (40.9)	40 (31.5)	V = 0.33			
GDS 6	16 (12.6)	42 (33.1)	75 (59.1)				
Family caregivers, *n* (%)							
Spouse	72 (56.7)	72 (56.7)	70 (55.2)	0.2[2]	4	0.992	
Adult-child	51 (40.2)	52 (40.9)	53 (41.7)	V = 0.01			
Other	4 (3.1)	3 (2.4)	4 (3.1)				
Living with caregiver, *n* (%)							
Yes	101 (79.5)	100 (78.7)	97 (76.4)	0.4[2]	2	0.819	
No	26 (20.5)	27 (21.3)	30 (23.6)	*V* = 0.03			

[1]Kruskal-Wallis; [2]Chi square test for categorical variables; V, Cramer's V; [3]Generalized estimating equations, Wald χ^2, for time. Means, estimated marginal; SE, standard error; Significant with Bonferroni *post hoc* contrasts: [a]1-2, [b]1-3, [c]2-3; η^2 = Eta-squared (effect size); *p*-values < 0.05 are shown in bold. MMSE, Mini-Mental State Examination; DAD, Disability Assessment in Dementia; NPI, Neuropsychiatric Inventory; AQ-D, Anosognosia Questionnaire-Dementia; GDS, Geriatric Depression Scale; GDS stage, Global Deterioration Scale; QoL-AD, Quality of Life in Alzheimer's Disease scale.

Table 2
Multivariate analysis. QoL-AD, Time & Factors, in the overall sample

	Parameter estimates											
	Model effects			Baseline			12 months			24 months		
	χ^2	*df*	*p*	B (SE)	χ^2	*p*	B (SE)	χ^2	*p*	B (SE)	χ^2	*p*
Time*												
Depression (GDS)	71.8	3	**<0.001**	–0.66 (0.10)	43.1	**<0.001**	–0.72 (0.11)	42.8	**<0.001**	–0.80 (0.11)	53.2	**<0.001**
Anosognosia (AQ-D)	43.0	3	**<0.001**	0.07 (0.01)	26.7	**<0.001**	0.07 (0.01)	26.3	**<0.001**	0.09 (0.01)	37.6	**<0.001**
Function (DAD)	8.0	3	**0.044**	0.02 (0.02)	1.3	0.247	0.06 (0.02)	5.8	**0.015**	0.06 (0.02)	4.7	**0.029**
Behavior (NPI)	5.6	3	0.130	–0.04 (0.02)	3.7	0.054	–0.02 (0.01)	3.3	0.068	–0.01 (0.00)	1.2	0.262
Cognition (MMSE)	5.8	3	0.120	0.09 (0.05)	2.7	0.095	–0.02 (0.04)	0.2	0.618	0.00 (0.03)	0.0	0.822

Method: Dependent variable = QoL-AD; Independent variables = introduced simultaneously. Generalized estimating equations, Wald χ^2; B, beta coefficient; SE, standard error; *p*-values < 0.05 are shown in bold. MMSE, Mini-Mental State Examination; DAD, Disability Assessment in Dementia; NPI, Neuropsychiatric Inventory; AQ-D, Anosognosia Questionnaire-Dementia; GDS, Geriatric Depression Scale; QoL-AD, Quality of Life in Alzheimer's Disease scale.

24 months among patients in the GDS 6 group ($\eta^2 = 0.007$). Neither the between-groups difference (Wald $\chi^2 = 1.1$, $p = 0.553$) or the Time*Group interaction (Wald $\chi^2 = 0.6$, $p = 0.960$) were significant.

Regarding sociodemographic variables, men scored slightly higher than women in the model (Wald $\chi^2 = 3.9$, $p = 0.046$), although the differences were only significant at 24 months. Participants with >5 years of schooling also scored higher (Wald $\chi^2 = 6.4$, $p = 0.011$), with differences being significant at 12 and 24 months. In both cases the effect sizes were small ($d < 0.5$). Age, relationship to the caregiver (spouse/adult child), and living with the caregiver were associated with no significant differences between the groups, although scores did increase slightly over the follow-up period for younger participants ($\eta^2 = 0.00$), those who lived with the caregiver ($\eta^2 = 0.01$), and those who were cared for by a spouse ($\eta^2 = 0.00$), the corresponding effect sizes being very small.

Table 3
Quality of life scores (QoL-AD) for the groups created in the two models

	1. Baseline	2. 12 months	3. 24 months	Simple effects		
	Mean (SE)	Mean (SE)	Mean (SE)	χ^2	*df*	*p*
A. Groups QoL-Baseline						
A1. Low-QoL	29.4 (0.4)	30.9 (0.7)[a]	31.7 (0.7)[b]	21.1	2	**<0.001**
A2. Medium	35.3 (0.2)[d]	35.5 (0.4)[d]	36.3 (0.4)[d]	5.5	2	0.064
A3 High-QoL	39.6 (0.3)[e,f]	38.6 (0.3)[a,e,f]	39.3 (0.4)[e,f]	9.5	2	**0.008**
Simple effects χ^2 *(df) p*	341.8 (2)**<0.001**	95.2 (2) **<0.001**	79.0 (2) **<0.001**			
• Model χ^2 *(df) p*	Time: 18.1 (2) **<0.001**; Groups: 172.3 (2) **<0.001**; Time*groups: 18.0 (4) **0.001**					
B. Groups QoL-Change						
B1. Decreased-QoL	37.5 (1.0)	34.1 (1.1)[a]	33.5 (1.2)[b]	65.8	2	**<0.001**
B2. No change	34.8 (0.6)	34.7 (0.7)	35.0 (0.6)	4.8	2	0.090
B3. Increased-QoL	34.0 (0.5)[e]	35.9 (0.4)[a]	37.6 (0.5)[b,c,e,f]	283.7	2	**<0.001**
Simple effects χ^2 *(df) p*	8.1 (2) **0.017**	3.4 (2) 0.182	15.9 (2) **<0.001**			
• Model χ^2 *(df) p*	Time: 5.9 (2) 0.051; Groups: 1.7 (2) 0.427; Time* groups: 300.4 (4) **<0.001**					

Generalized estimating equations, Wald χ^2; Means, estimated marginal; SE, standard error; Significant with Bonferroni *post hoc* contrasts: [a]1-2, [b]1-3, [c]2-3, [d]A1/B1- A2/B2, [e]A1/B1-A3/B3, [f]A2/B2-A3/B3. *p*-values < 0.05 are shown in bold. QoL-AD, Quality of Life in Alzheimer's Disease scale; AQ-D, Anosognosia Questionnaire-Dementia; GDS, Geriatric Depression Scale; NPI, Neuropsychiatric Inventory; DAD, Disability Assessment in Dementia; MMSE, Mini-Mental State Examination.

Variability in baseline QoL-AD scores and clinical factors

In the QoL-Baseline model the baseline scores on the QoL-AD were as follows: Low = 29.4 ± 2.7; Medium = 35.3 ± 1.4; High = 39.6 ± 2.3 (χ^2 = 112.6, $p < 0.001$; $\eta^2 = 0.78$). In the QoL-Change model the baseline scores were: Decreased = 37.5 ± 5.5; No change = 34.8 ± 4.6; Increased = 34.0 ± 4.0 (χ^2 = 9.4, $p = 0.009$; $\eta^2 = 0.07$). Although the differences between groups were significant in both models, the between-group variability was greater in the QoL-Baseline model, with a large effect size. Conversely, the within-group variability was lower in the QoL-Baseline model, with smaller standard deviations.

At baseline the clinical factors that were significantly associated with between-group variability in the QoL-Baseline model were depression (GDS): Low = 5.2 ± 3.0, Medium = 3.3 ± 2.4, High = 1.6 ± 1.6 ($\chi^2 = 34.1$, $p < 0.001$; $\eta^2 = 0.26$); functional ability (DAD): Low = 57.5 ± 9.3, Medium = 62.5 ± 10.3, High = 61.5 ± 9.8 ($\chi^2 = 6.5$, $p = 0.038$; $\eta^2 = 0.04$); and neuropsychiatric symptoms (NPI): Low = 24.3 ± 17.4, Medium = 21.3 ± 15.7, High = 17.5 ± 15.8 ($\chi^2 = 6.3$, $p = 0.043$; $\eta^2 = 0.02$). In the QoL-Change model none of the clinical factors was associated with significant variability between the groups.

In order to examine the predictive ability of the baseline QoL-AD score on QoL scores at 24 months we conducted a linear regression analysis. The results showed that the baseline QoL score was a good predictor of QoL-AD scores at 24 months ($R^2 = 0.588$, $\beta = 0.76$, $t = 13.3$, $p < 0.001$.

Changes over time in QoL-AD scores in the two models of analysis

For the groups created in the QoL-Baseline model the GEE indicated that the general effects were significant for Time, Group, and for the Time*Group interaction. Regarding the simple effects, there were important between-group differences at all three assessment points (η^2; T1 = 0.78, T2 = 0.45; T3 = 0.41), with higher scores being observed in the High-QoL group. During follow-up, scores in the Low-QoL group increased, whereas those in the High-QoL group decreased, the effect size being weak in both cases (η^2; Low = 0.04, High = 0.02).

For the groups created in the QoL-Change model the GEE indicated that the general effects were only significant for the Time*Group interaction. Regarding the simple effects, a between-groups difference of moderate magnitude was observed at baseline ($\eta^2 = 0.07$) and at 24 months ($\eta^2 = 0.11$). During follow-up, significant differences, with a moderate effect size, were only present in the Decreased-QoL group ($\eta^2 = 0.08$) and the Increased-QoL group ($\eta^2 = 0.12$). Complete data are shown in Table 3.

Figures 1A and 1B show the change in QoL scores for the three groups in the QoL-Baseline and QoL-Change models, respectively.

The proportion of patients classified as GDS 4, 5 and 6 did not change significantly in either the QoL-Baseline model (Baseline, $\chi^2 = 0.4$, $p = 0.978$; 12 months, $\chi^2 = 1.4$, $p = 0.835$; 24 months, $\chi^2 = 7.4$, $p = 0.115$) or the QoL-Change model (Baseline, $\chi^2 = 6.6$, $p = 0.153$; 12 months, $\chi^2 = 3.3$, $p = 0.501$; 24

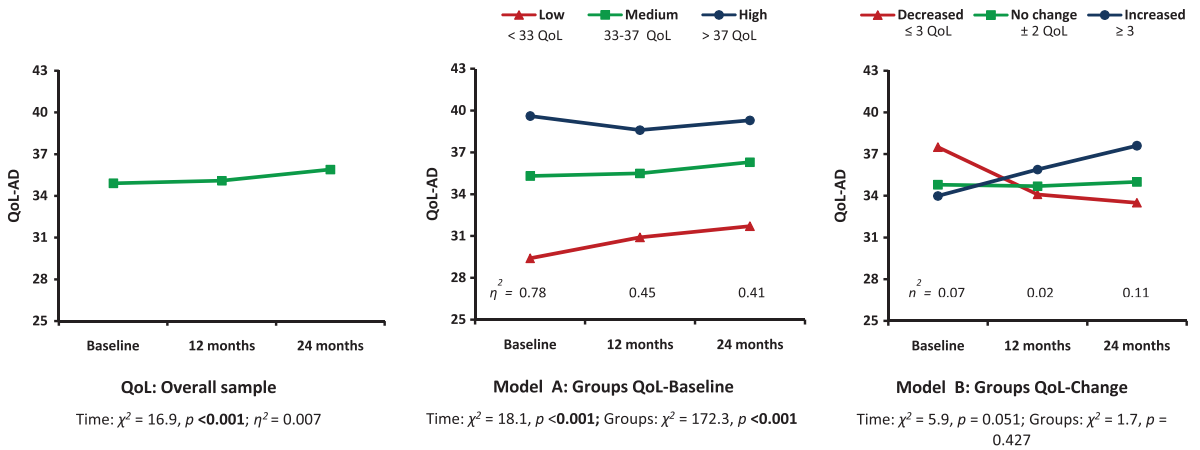

Fig. 1. Two models for analyzing QoL across follow up. Wald χ^2 = Generalized estimating equations. η^2 = Eta-squared (effect size).

months, $\chi^2 = 3.0$, $p = 0.557$). Similarly, there were no significant changes in either model (QoL-Baseline or QoL-Change) in the proportions of subjects according to age group (± 77), gender, years of schooling (± 5 years), type of family caregiver (spouse/adult child), or living with the caregiver.

Clinical variables in the QoL-Baseline model during follow-up

The data for the main variables in relation to the three subgroups formed using the QoL-Baseline model are shown in Table 4.

The effect of depression (GDS) was strongest in the Low-QoL group. There were important between-group differences at each assessment point (η^2; T1 = 0.26, T2 = 0.24, T3 = 0.26), but in none of the groups was a significant change observed in this variable across follow-up. When depression was analyzed with the NPI (Depression subscale) the results obtained were consistent with those from the GDS: The Low-QoL group scored higher and the High-QoL group lower, although the effect sizes were smaller than those for the GDS (η^2; T1 = 0.13, T2 = 0.09, T3 = 0.10).

With respect to anosognosia the lowest scores corresponded to the Low-QoL group and the highest scores to the High-QoL group, the opposite of the effect observed for depression. Between-group differences increased across the three assessment points (η^2; T1 = 0.04, T2 = 0.06, T3 = 0.07). During follow-up, anosognosia increased in all three groups, most notably in the High-QoL group, although the effect sizes were weak (η^2; Low = 0.01, Medium = 0.02, High = 0.04).

The greatest number of neuropsychiatric symptoms was presented by patients in the Low-QoL group. Between-group differences were only significant at 24 months, with a weak effect size ($\eta^2 = 0.049$). During follow-up, all the groups showed an increase in NPI scores, although the effect sizes were weak (η^2; Low = 0.05, Medium = 0.02, High = 0.04).

With respect to functional impairment the between-group differences were small, and only at baseline did the Low-QoL group score significantly lower ($\eta^2 = 0.04$). By contrast, all three groups showed a notable deterioration across the follow-up period (η^2; Low = 0.12, Medium = 0.16, High = 0.21), with the change being greatest in the High-QoL group.

The results for cognitive status were similar to those for functional ability: The between-group differences were not significant at any of the assessment points, but there was a moderate-to-large deterioration in cognitive function in all three groups across follow-up (η^2; Low = 0.09, Medium = 0.08, High = 0.15), with the greatest change corresponding to the High-QoL group.

Clinical variables in the QoL-Change model during follow-up

The data for the main variables in relation to the three subgroups formed using the QoL-Change model are shown in Supplementary Table 1.

Depression scores (GDS) were always lower in the Increased-QoL group, although the between-group differences were only significant, with a moderate effect size, at 24 months ($\eta^2 = 0.07$). Only in the Increased-QoL group was a decrease in scores, with a

Table 4
Groups according to the QoL-Baseline model. Scores for clinical variables

	1. Baseline	2. 12 months	3. 24 months	Simple effects		
	Mean (SE)	Mean (SE)	Mean (SE)	χ^2	*df*	*p*
Depression (GDS)						
Low-QoL	5.2 (0.4)	5.2 (0.5)	4.9 (0.4)	3.5	2	0.171
Medium	3.3 (0.3)[d]	3.5 (0.3)[d]	3.3 (0.3)[d]	0.4	2	0.810
High-QoL	1.6 (0.2)[e,f]	1.7 (0.2)[e,f]	1.3 (0.2)[e,f]	5.3	2	0.069
Simple effects χ^2 *(df) p*	49.2 (2) **<0.001**	46.6 (2) **<0.001**	47.0 (2) **<0.001**			
• Model χ^2 *(df) p*	Time: 4.0 (2) 0.132; Groups: 58.6 (2) **<0.001**; Time*groups: 0.9 (4) 0.913					
Depression (NPI)						
Low-QoL	3.2 (0.5)	3.7 (0.5)	3.9 (0.6)	1.1	2	0.569
Medium	3.1 (0.4)	2.6 (0.5)	1.6 (0.3)[c,d]	11.3	2	**0.003**
High-QoL	1.0 (0.2)[e,f]	1.2 (0.3)[e]	1.4 (0.5)[e]	1.0	2	0.587
Simple effects χ^2 *(df) p*	26.0 (2) **<0.001**	13.9 (2) **0.001**	12.0 (2) **0.002**			
• Model χ^2 *(df) p*	Time: 0.2 (2) 0.863; Groups: 22.6 (2) **<0.001**; Time*groups: 12.0 (4) **0.017**					
Anosognosia (AQ-D)						
Low-QoL	26.5 (2.8)	30.5 (3.1)[a]	32.6 (2.9)[b]	14.4	2	**0.001**
Medium	28.4 (2.7)	31.5 (3.0)	36.2 (2.7)[b,c]	13.4	2	**0.001**
High-QoL	35.5 (2.5)	40.9 (2.3)[a,e,f]	44.4 (2.3)[b,c,e]	19.2	2	**<0.001**
Simple effects χ^2 *(df) p*	6.3 (2) **0.042**	9.4 (2) **0.009**	10.9 (2) **0.004**			
• Model χ^2 *(df) p*	Time: 45.1 (2) **<0.001**; Groups: 10.1 (2) **0.006**; Time*groups: 3.0 (4) 0.555					
Behavior (NPI)						
Low-QoL	24.3 (2.7)	28.0 (2.7)	34.4 (2.8)[b]	8.8	2	**0.012**
Medium	21.3 (2.3)	20.4 (2.2)	26.1 (2.9)[c]	7.3	2	**0.025**
High-QoL	17.5 (2.3)	22.2 (2.3)	25.8 (2.2)[b]	15.8	2	**<0.001**
Simple effects χ^2 *(df) p*	3.6 (2) 0.158	4.7 (2) 0.092	6.4 (2) **0.039**			
• Model χ^2 *(df) p*	Time: 25.2 (2) **<0.001**; Groups: 6.7 (2) **0.035**; Time*groups: 3.9 (4) 0.415					
Function (DAD)						
Low-QoL	57.5 (1.4)	52.6 (1.5)[a]	48.8 (1.4)[b,c]	66.6	2	**<0.001**
Medium	62.5 (1.5)	56.9 (1.6)[a]	51.2 (1.4)[b,c]	67.2	2	**<0.001**
High-QoL	61.5 (1.4)	56.7 (1.2)[a]	49.9 (1.3)[b,c]	82.4	2	**<0.001**
Simple effects χ^2 *(df) p*	6.3 (2) **0.042**	4.9 (2) 0.082	1.3 (2) 0.506			
• Model χ^2 *(df) p*	Time: 209.6 (2) **<0.001**; Groups: 4.3 (2) 0.112; Time*groups: 8.9 (4) 0.063					
Cognition (MMSE)						
Low-QoL	17.7 (0.8)	15.4 (1.0)[a]	12.5 (1.1)[b,c]	39.9	2	**<0.001**
Medium	19.4 (0.7)	16.9 (0.8)[a]	15.0 (0.9)[b,c]	38.3	2	**<0.001**
High-QoL	20.1 (0.7)	18.0 (0.7)[a]	14.3 (1.0)[b,c]	34.0	2	**<0.001**
Simple effects χ^2 *(df) p*	4.5 (2) 0.101	4.1 (2) 0.123	2.7 (2) 0.255			
• Model χ^2 *(df) p*	Time: 108.5 (2) **<0.001**; Groups: 3.8 (2) 0.148; Time*groups: 6.1 (4) 0.189					

Generalized estimating equations, Wald χ^2; Means, estimated marginal; SE, standard error; Significant with Bonferroni *post hoc* contrasts: [a]1-2, [b]1-3, [c]2-3, [d]Low-Medium, [e]Low-High, [f]Medium-High. *p*-values < 0.05 are shown in bold. QoL-AD, Quality of Life in Alzheimer's Disease scale; AQ-D, Anosognosia Questionnaire-Dementia; GDS, Geriatric Depression Scale; NPI, Neuropsychiatric Inventory; DAD, Disability Assessment in Dementia; MMSE, Mini-Mental State Examination.

weak effect size ($\eta^2 = 0.01$), observed during follow-up. When depression was analyzed with the NPI (Depression subscale) the results were consistent with those obtained from the GDS: The Increased-QoL group had the lowest scores. However, the differences between groups were not significant at any of the assessment points, and the effect sizes were small (η^2; T1 = 0.01, T2 = 0.03, T3 = 0.01).

With respect to anosognosia the highest scores corresponded to the Increased-QoL group and the lowest scores to the Decreased-QoL group, although the between-group differences only showed a moderate effect at 24 months ($\eta^2 = 0.06$). During follow-up, anosognosia increased in all the groups, although the effect sizes were weak (η^2; Decreased = 0.00, No change = 0.02, Increased = 0.04).

The greatest number of neuropsychiatric symptoms was presented by patients in the Increased-QoL group, although between-group differences were not significant. Across follow-up a significant change, with a weak effect size, was only observed in the No change ($\eta^2 = 0.04$) and the Increased-QoL ($\eta^2 = 0.03$) groups.

With respect to functional impairment the between-group differences were not significant at any of the assessment points, but each of the three groups showed a notable deterioration across follow-up (η^2; Decreased = 0.19, No Change = 0.15,

Table 5
Clinical variables. Multinomial logistic regression analysis at baseline assessment

Method: Enter together	B	(SE)	Wald	*p*	OR	95% CI
A. Groups QoL-Baseline						
Low QoL (<33 QoL)						
Depression (GDS)	0.18	(0.09)	3.89	**0.048**	1.20	1.00–1.45
Anosognosia (AQ-D)	–0.04	(0.02)	3.71	0.054	0.95	0.91–1.00
Function (DAD)	–0.08	(0.03)	4.57	**0.032**	0.92	0.85–0.99
Behavior (NPI)	0.01	(0.01)	0.92	0.335	1.01	0.98–1.05
Cognition (MMSE)	–0.04	(0.05)	0.63	0.426	0.95	0.86–1.06
High QoL (>37 QoL)						
Depression (GDS)	–0.38	(0.13)	8.29	**0.004**	0.68	0.52–0.88
Anosognosia (AQ-D)	0.06	(0.02)	6.28	**0.012**	1.07	1.01–1.13
Function (DAD)	0.02	(0.04)	0.40	0.524	1.02	0.94–1.11
Behavior (NPI)	–0.04	(0.02)	5.74	**0.017**	0.95	0.91–0.99
Cognition (MMSE)	0.08	(0.05)	2.65	0.103	1.08	0.98–1.20
Reference group: Medium QoL (33–37 QoL)						
B. Groups QoL-Change						
Decreased (≤ 3 QoL)						
Depression (GDS)	–0.09	(0.10)	0.89	0.344	0.90	0.74–1.10
Anosognosia (AQ-D)	–0.01	(0.02)	0.27	0.597	0.98	0.94–1.03
Function (DAD)	0.04	(0.04)	0.96	0.327	1.04	0.96–1.13
Behavior (NPI)	0.03	(0.02)	1.98	0.159	1.03	0.98–1.07
Cognition (MMSE)	0.03	(0.05)	0.37	0.540	1.03	0.92–1.15
Increased (≥ 3 QoL)						
Depression (GDS)	–0.18	(0.08)	4.69	**0.030**	0.83	0.70–0.98
Anosognosia (AQ-D)	–0.00	(0.01)	0.24	0.624	0.99	0.95–1.02
Function (DAD)	0.00	(0.03)	0.02	0.866	1.00	0.94–1.06
Behavior (NPI)	0.02	(0.01)	1.40	0.236	1.02	0.98–1.05
Cognition (MMSE)	–0.02	(0.04)	0.28	0.595	0.97	0.89–1.06
Reference group: No change QoL (±2 QoL)						

B, unstandardized coefficient; SE, standard error; OR, odds ratio; CI, confidence interval QoL-AD, Quality of Life in Alzheimer's Disease scale; AQ-D, Anosognosia Questionnaire-Dementia; GDS, Geriatric Depression Scale; NPI, Neuropsychiatric Inventory; DAD, Disability Assessment in Dementia; MMSE, Mini-Mental State Examination.

Increased = 0.17). The results for cognitive status were similar to those for functional ability: No significant between-group differences were observed, but there was a moderate-to-large deterioration in cognitive function in all three groups across follow-up (η^2; Decreased = 0.22, No change = 0.06, Increased = 0.12).

Multinomial regression analysis of the groups of patients at baseline assessment

In the multinomial regression we took the intermediate group in each model (i.e. Medium in the QoL-Baseline model and No change in the QoL-Change model) as the reference group (Table 5).

In the QoL-Baseline model the predictors for the Low-QoL group were greater depression and poorer functional ability. In the High-QoL group the predictors were less depression, more anosognosia, and fewer neuropsychiatric symptoms.

In the QoL-Change model there were no significant predictors for the Decreased-QoL group, and only less depression was a predictor in the Increased-QoL group.

DISCUSSION

Factors associated with QoL in the sample as a whole

Depression, neuropsychiatric symptoms, anosognosia, and functional ability were all shown to be relevant when analyzing the overall sample, although the most important factors were anosognosia and depression.

The association between greater depression and lower scores on self-perceived QoL has been widely reported in longitudinal and cross-sectional studies of community samples [5, 6, 8, 11, 18, 34–38] and of patients attending day centers [39] or living in residential care [2, 4, 40]. Furthermore, the results obtained have been similar despite the variety of instruments used to assess depression: Cornell Scale for Depression in Dementia (CSDD) [2, 4], Center for

Epidemiologic Studies-Depression Scale (CES-D) [6], Hospital Anxiety and Depression Scale (HADS) [8], NPI-Depression [5, 11, 37], Geriatric Depression Scale (GDS) [18, 36, 38, 39], Hamilton Depression Scale (HRSD) [35], and the Beck Depression Inventory (BDI) [34].

Although depression is the neuropsychiatric symptom most widely reported to be associated with poorer QoL, this association with impaired QoL has also been found for the total NPI score [5, 11, 17], as well as for other specific neuropsychiatric symptoms, including apathy [39], anxiety [2, 4], agitation [40], and psychotic symptoms assessed by the NPI (Delusions, Hallucinations) [5].

The association between greater anosognosia and a more positive view of QoL among patients with dementia has been well documented in both cross-sectional [41–45] and longitudinal studies [10, 11, 18].

Finally, some studies have also reported an association between better functional ability and higher self-ratings of QoL [3, 6].

Anosognosia, depression, and quality of life

The relationship between anosognosia and depression, however, requires a more detailed analysis. The first authors to report an inverse relationship between anosognosia and depression were Sevush and Leve [46]. Subsequent research confirmed this inverse association, suggesting that depression is more likely to be present when patients have a greater awareness of their deficits (less anosognosia), and therefore that it is a reaction to the process of deterioration [25, 47–49].

The combination of these two factors and their relationship to perceived QoL has also been investigated, with similar findings being obtained: Greater anosognosia was associated with less depression and a more positive view of QoL, and vice-versa, that is, poorer self-perceived QoL was linked to more depression and less anosognosia [11, 18, 50, 51].

Comparison of the QoL-Baseline and QoL-Change models

Focusing on the baseline scores in the two models the QoL-Baseline model showed greater between-group variability (better differentiation between groups) and less within-group variability (greater homogeneity of subjects in each group) than did the QoL-Change model. It should also be noted that certain clinical factors (depression, functional ability, and neuropsychiatric symptoms) were shown to be significantly associated with this between-group variability in the QoL-Baseline model. These results support our initial hypothesis and the findings of previous studies in community samples [6, 7, 9] regarding the superiority of the QoL-Baseline model for the analysis of data, as well as the good predictive ability of the baseline QoL score.

In addition, the analysis of the QoL-Baseline model showed that the influence of the clinical variables differed according to the groups. Depression was greater in the Low-QoL group and lower in the High-QoL group. The opposite pattern was observed for anosognosia, that is, scores were lower in the Low-QoL group and higher in the High-QoL group. These distributions were the same at all three assessment points. The Low-QoL group also presented more neuropsychiatric symptoms and poorer functional ability. The analysis of the QoL-Change model showed less variability between the groups formed according to this model. The only notable finding was that the Increased-QoL group presented less depression and greater anosognosia, although this was only the case at 24 months.

It should be noted that when scores on the NPI Depression subscale were used as a measure of depression in the groups of both models, the results were consistent with those obtained with the GDS, although their statistical relevance was reduced. This finding is in line with previous research [39]. Depression is clearly the most important clinical factor associated with poorer self-perceived QoL in both models (Low-QoL group and Decreased-QoL group), although the statistical effect is more notable in the QoL-Baseline model.

The results of this study confirm that the self-rating of QoL at baseline (Low, High) is more relevant than the change in QoL ratings over time (Decreased, Increased). Although a number of previous studies [2, 4, 9, 14] have used a model based on deterioration-stability-improvement in QoL scores across follow-up, the model based on the baseline QoL score seems to offer certain advantages. From a psychometric point of view the QoL-Baseline model was a better predictor of perceived QoL at 24 months, and it also enabled us to observe the effect of the different variables in each group. This model would likewise be useful from a clinical point of view. Given that QoL scores have been shown to remain relatively stable over time in both community samples [3, 5–11] and residential populations [2, 4, 14], the baseline

score could be used to predict how a patient is likely to evolve, thus enabling suitable interventions to be targeted at the factors known to influence QoL, especially depression and anosognosia/cognitive status.

Clinical implications

The results of this study suggest that a longitudinal analysis of self-perceived QoL among patients with AD should use a model in which groups are created according to baseline scores, since this model is better than one based on a change in scores when it comes to identifying trajectories and predictors of QoL. This recommendation follows from the fact that the key feature of QoL scores is not change over time but, rather, the stability of the different score ranges.

In terms of intervention, the assessment of a patient's baseline status, covering depression, cognitive and functional ability, and neuropsychiatric symptoms, should serve as a platform on which to implement strategies that can help ameliorate the negative effects of the condition, especially among patients with poor perceived QoL. There is an extensive literature on non-pharmacological interventions in patients with dementia, although they appear to have only a moderate effect on the different variables involved. A recent review of six randomized controlled studies found beneficial effects with respect to depression and anxiety symptoms [52]. Music therapy has also been shown to have some benefits with regard to reducing neuropsychiatric symptoms [53, 54], improving symptoms of anxiety and depression [55, 56], enhancing cognitive performance and quality of life [55, 57], and even for improving or stabilizing certain aspects of self-awareness [58]. Other studies have found that cognitive stimulation therapy can improve cognition [59, 60] and quality of life [59, 61], reducing apathy and symptoms of depression. Reminiscence programs appear to improve symptoms of depression and interpersonal relationships [62, 63]. Physical exercise reduced neuropsychiatric symptoms in patients with mild dementia [64]. A program of therapeutic education for patients and caregivers improve the quality of life [65]. Finally, multicomponent programs have been shown to improve apathy, anxiety, depression, and quality of life [66].

Limitations and future research

The main limitation of this study is that depression and anosognosia were not assessed clinically, the data being based solely on self- and informant report measures.

Our results are unlikely to have been seriously affected by the loss of some cases to follow-up, since QoL scores do not appear to be influenced by the severity of dementia.

Future research should nonetheless aim to replicate the present analysis with patients in residential care facilities, since, although the severity of dementia was not shown here to have an effect on perceived QoL, it is possible that community and institutionalized samples would yield different results. Indeed, whereas all research in community samples reports stability of QoL scores over follow-up [3, 5–13, 18], these scores have been reported to decrease over time in some residential samples [15–17], probably due to increased severity of dementia in these patients. It would also be interesting to examine possible changes in QoL related to pharmacological and non-pharmacological interventions, and also to analyze in greater depth the variability associated with family and contextual factors.

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SUPPLEMENTARY MATERIAL

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