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Effects of anosognosia and neuropsychiatric symptoms on the quality of life of patients with Alzheimer's disease: A 24-month follow-up study

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Key points

- During the 24-month follow-up, patients' self-appraisals of quality of life remained stable, whereas the corresponding views of caregivers became more negative.
- In patients, greater anosognosia and, to a lesser extent, fewer neuropsychiatric symptoms were associated with more positive ratings of their quality of life.
- Among caregivers, neuropsychiatric symptoms and, to a lesser extent, anosognosia in the patient were associated with more negative ratings of the patient's quality of life.
- The neuropsychiatric symptoms (NPI) associated with a more negative view of the patient's quality of life were depression, for patients' self-ratings, and apathy and agitation for caregiver ratings.

- **Key words:** Quality of life; anosognosia; Alzheimer's disease, neuropsychiatric symptoms; caregivers; patients.

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Abstract

Objectives: Neuropsychiatric symptoms and anosognosia are known to influence the perceived quality of life of patients (QoL-p) with Alzheimer's disease (AD). This study analysed their impact on patient and caregiver ratings of QoL-p and how these ratings changed in relation to the severity of dementia.

Methods: A baseline sample of 221 patients and caregivers was followed up over 24 months. Instruments: Neuropsychiatric Inventory (NPI), Anosognosia Questionnaire-Dementia (AQ-D), Quality of Life-Alzheimer's Disease (QoL-AD), and the Global Deterioration Scale (GDS). Longitudinal data were analysed using generalized linear models.

Results: In the multivariate analysis, greater anosognosia was always associated with higher ratings of QoL-p among patients, especially at 24 months ($p < 0.001$), and with more negative ratings among caregivers, especially at baseline ($p < 0.001$). A higher total NPI score was associated with a more negative rating of QoL-p among caregivers ($p < 0.001$), and it also had a smaller negative effect on patients' self-ratings ($p = 0.001$). The neuropsychiatric symptoms (NPI) associated with a more negative view of QoL-p were depression, for patients' self-ratings, and apathy and agitation for caregiver ratings. The discrepancy between patient and caregiver ratings increased in line with the severity of dementia.

Conclusion: Neuropsychiatric symptoms had a similarly negative effect on the QoL-p ratings of both patients and caregivers, whereas the effect of anosognosia differed according to the rater (positive for patients, negative for caregivers).

Key words: Alzheimer's disease, quality of life, anosognosia, neuropsychiatric symptoms, caregivers, patients.

Introduction

Alzheimer's disease (AD) is the most common subtype of dementia and its prevalence is predicted to increase in years to come (Sosa-Ortiz *et al.,* 2012). The consequences it has for both patients and caregivers make it a public health problem of considerable importance.

One of the symptoms that often accompany AD is anosognosia, defined as a lack of insight into one's own deficits (Leicht *et al.*, 2010). It is estimated that anosognosia is present in as many as 80% of patients with AD (Sevush and Leve, 1993), and it tends to worsen as the dementia becomes more severe (Kashiwa *et al*., 2005). Various factors have been linked to anosognosia, including older age, less depression, poorer functional ability (Conde-Sala *et al*., 2013) and more behavioural and psychological symptoms of dementia (BPSD) (Vogel *et al.*, 2010; Spalletta *et al*., 2012).

BPSD are also in themselves one of the main symptoms of AD, with as many as 90% of patients presenting some symptoms of this kind (Fernández *et al.*, 2010). These symptoms have serious repercussions for patients and their surroundings, and they have a direct impact on caregiver burden (Rymer *et al.*, 2002).

Some studies have shown that patients with a greater degree of anosognosia tend to hold a more positive view of their own quality of life (Hurt *et al.*, 2010). Conversely, an increased presence of BPSD has been related to more negative perceptions regarding the patient's quality of life (QoL-p) among both patients and caregivers (Ready *et al.,* 2004; Hurt *et al*., 2008). There is a need, however, to clarify the combined influence that these two factors (anosognosia and BPSD) have on patient and caregiver ratings of QoL-p.

Research has also identified discrepancies between patient and caregiver ratings of QoL-p (Karlawish *et al.*, 2001; Ready *et al.*, 2004; Zhao *et al*., 2012), with caregivers having a less positive outlook regarding QoL-p.

In clinical practice, patients with anosognosia have been observed to present more neuropsychiatric symptoms and dangerous behaviours, as well as greater difficulties with treatment adherence (Starkstein *et al*., 2007), leading to increased burden on caregivers (Turró-Garriga *et al.,* 2013). Studies have also shown that these patients may have an overly positive view of their own quality of life (Berwig *et al.,* 2009; Ready *et al.,* 2006), an aspect that should be taken into account when using quality-of-life measures to evaluate the effects of therapeutic interventions. All these findings justify the need to investigate the relationship between anosognosia, neuropsychiatric symptoms and quality of life.

The general aim of this study was to obtain patient and caregiver ratings of QoL-p and to analyse their relationship to a series of clinical and socio-demographic factors over a 24-month period. Specifically, the objectives were as follows: 1) To analyse the relationship between anosognosia, neuropsychiatric symptoms, and patient and caregiver ratings of QoL-p; and 2) to examine how these aspects change with increasing severity of dementia. The study hypotheses were that: (1) neuropsychiatric problems would be more common among patients with anosognosia, and (2) anosognosia and neuropsychiatric symptoms would have a different influence on the QoL-p ratings of patients and caregivers.

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-IV, American Psychiatric Association, 2001) 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 (NINCDS-ADRDA; McKhann *et al.*, 1984). In addition, they all scored between 10 and 28 on the Mini-Mental State Examination (MMSE; Folstein *et al.*, 1975), thereby enabling a quality-of-life scale (QoL-AD; Logsdon *et al.*, 2002) 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 who received no payment for the care they provided (i.e. informal caregivers).

Patients were excluded if they presented vascular or traumatic events, alcohol or substance dependency 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 and caregivers were gathered using a structured questionnaire designed by the researchers.

- Quality of life. The Quality of Life-Alzheimer Disease (QoL-AD) scale (Logsdon *et al.,* 2002) was used to assess the patient's quality of life (QoL-p) from the perspective of both patients and caregivers. This instrument comprises 13 items that refer to different aspects of the patient's wellbeing. Scores for each item range from 1 (poor) to 4 (excellent), yielding a total score between 13 and 52 (the higher the score the better the patient's quality of life).
- Behavioural and psychological symptoms of dementia. This aspect was evaluated by means of the Neuropsychiatric Inventory (NPI; Cummings *et al.,* 1994), which comprises 12 subscales that assess the frequency and severity of 12 neuropsychiatric symptoms (or BPSD), 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; Migliorelli *et al.,* 1995) was administered to patients and caregivers. It comprises 30 items referring to cognitive/functional deficits and changes in the patient's behaviour, 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. The authors of the AQ-D consider that anosognosia is present when this difference is ≥32.
- Cognitive assessment of the patient. This was based on the Mini Mental State Examination (MMSE; Folstein *et al.,* 1975), a brief cognitive assessment tool whose score ranges from 0 to 30 (the lower the score the greater the cognitive deterioration). The cut-off for cognitive impairment is 21/22. Patients' scores on the MMSE were corrected for age and level of education (Blesa *et al.,* 2001).
- Functional assessment of the patient. The Disability Assessment for Dementia (DAD; Gélinas *et al.,* 1999) 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).
- Stage of dementia. This was based on the criteria of the Global Deterioration Scale (GDS; Reisberg *et al.,* 1982), 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 selected eligible patients according to the inclusion criteria and then determined their stage of dementia using the GDS. The sample was initially recruited between January and December 2011, with the final assessment at 24 months being

conducted in May 2014 The baseline sample comprised 221 patients and their respective caregivers, of whom 166 were able to be re-assessed at 12 months and 127 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 aims of the study were explained to all participants in an introductory 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.

Calculation of sample size

Following previous studies (Portellano-Ortiz *et al.,* 2014) we calculated the sample size required to detect, with a power of 80% and a confidence level of 95% based on the two-tailed Student's t test for independent samples, differences in the QoL-p variable between patients and caregivers in two groups: No anosognosia (≤ 32 AQ-D) and Anosognosia (> 32 AQ-D). The program used was Ene 3.0 (GlaxoSmithKline, UK).

QoL-p patients: With mean scores of 33.4 (SD = 4.9) in the No anosognosia group and 35.7 (SD = 4.5) in the Anosognosia group it would be necessary to include 59 subjects in the first group and 81 in the second.

QoL-p caregivers: With mean scores of 29.9 (SD = 5.3) in the No anosognosia group and 23.9 (SD = 4.4) in the Anosognosia group it would be necessary to include 11 subjects in the first group and 15 in the second.

Statistical analysis

Longitudinal data were analysed by means of generalized linear models, since some dependent variables were not normally distributed (McCullagh and Nelder, 1989; Liang and

Zeger, 1986). This approach enabled us to examine the general effects of the independent variables on the response variable, 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.

Two multivariate analyses were performed, taking patient and caregiver ratings of QoL-p as the dependent variables. The first analysis used the overall scores on the AQ-D and NPI, while the second analysis was based on disaggregated scores from the NPI subscales.

Categorical variables were analysed by means of the Pearson chi-square test. Cohen's *d* was calculated as a measure of effect size in relation to between group differences in patient and caregiver ratings of QoL-p.

For hypothesis contrasts the level of statistical significance was set at .05. All data processing and analysis was performed using SPSS v19.0 for Windows (SPSS Inc., Chicago).

Results

Sample description

The baseline sample comprised 221 patients and their respective caregivers, of whom 166 completed the follow-up assessment at 12 months and 127 the assessment at 24 months. At baseline, lost cases ($n = 94$) were more impaired than were patients who completed the follow-up ($n = 127$); specifically, they had greater cognitive impairment (MMSE = 17.2 ± 5.5 vs. 19.1 ± 5.2; $z = 2.4$, $p = 0.014$), poorer functional ability (DAD = 54.7 ± 9.5 vs. 60.6 ± 10.0; $z = 4.2$, $p < 0.001$), a greater degree of anosognosia (AQ-D = 38.9 ± 18.2 vs. 30.2 ± 18.2; $t = 3.4$, $p = 0.001$), and more neuropsychiatric symptoms (NPI = 31.2 ± 21.9 vs. 20.9 ± 16.4; $z = 3.9$, $p < 0.001$).

Sociodemographic and clinical data

The mean age of patients at baseline was 77.8 years (SD = 7.3). One hundred and forty of them (63.3%) were women, and 140 (63.3%) had received fewer than five years of formal schooling. The mean age of caregivers at baseline was 63.8 years (SD = 13.0). In this case, 151 (68.3%) of them were women, and 56 (25.3%) had fewer than five years of formal education.

Across the follow-up period, patients showed a deterioration in cognitive status (MMSE, $p < 0.001$) and functional ability (DAD, $p < 0.001$). Patients' scores on the NPI and AQ-D did not change significantly during follow-up.

Patient ratings of QoL-p did not change significantly over the follow-up period ($p = 0.443$). Caregiver ratings of QoL-p were always more negative than those of patients, and had decreased further at 24 months ($p < 0.001$) (Fig. 1a). The sociodemographic and clinical data for patients and caregivers are presented in Table 1.

TABLE 1

Anosognosia and neuropsychiatric symptoms

Model effects were analysed taking scores on the AQ-D as the dependent variable and entering total and subscale scores on the NPI as covariables. NPI scores were positively associated with anosognosia (Wald $\chi^2 = 169.9$, $p < 0.001$), although the strength of association decreased over time: Baseline (Wald $\chi^2 = 141.5$, $p < 0.001$), 12 months (Wald $\chi^2 = 84.0$, $p < 0.001$), 24 months (Wald $\chi^2 = 67.9$, $p < 0.001$).

Three NPI subscales, namely apathy (Wald $\chi^2 = 101.1$, $p < 0.001$), aberrant motor behaviour (Wald $\chi^2 = 41.3$, $p < 0.001$) and agitation (Wald $\chi^2 = 33.2$, $p < 0.001$) were directly associated with AQ-D scores at all three assessment points. Depression (Wald $\chi^2 = 20.2$, $p <$

0.001) was always negatively associated with anosognosia, although this relationship was only significant at the 12- and 24-month follow-ups.

The group of patients with anosognosia had more neuropsychiatric symptoms at all three assessment points ($p < 0.001$) (Table 2).

TABLE 2

Neuropsychiatric symptoms, anosognosia and quality of life

Comparison of patients with high and low levels of BPSD showed that the latter always gave higher ratings of QoL-p, although the difference was only significant in the assessment at 24 months. By contrast, higher levels of BPSD were always associated with significantly lower caregiver ratings of QoL-p ($p < 0.001$) (Fig. 1b). Comparison of patients with and without anosognosia revealed that the former presented more neuropsychiatric symptoms and gave higher ratings of QoL-p; conversely, caregiver ratings of QoL-p were lower for the group of patients with anosognosia (Fig. 1c). These differences increased over time (Table 2).

FIGURE 1

It can be seen in Table 3 that patients own ratings of their QoL were higher in the presence of anosognosia (regardless of the degree of neuropsychiatric symptoms). Conversely, higher caregiver ratings of QoL-p were associated with fewer neuropsychiatric symptoms (with or without anosognosia). It should also be noted that anosognosia had an opposite effect on the QoL-p ratings of patients (positive) and caregivers (negative), whereas neuropsychiatric symptoms had a similar effect on both sets of ratings, albeit to a different extent.

TABLE 3

Severity of dementia and quality of life

Both anosognosia ($p < 0.001$) and neuropsychiatric symptoms ($p < 0.001$) increased significantly in line with increasing severity of dementia, although there were no significant

differences between the three assessment points, with the exception of patients classified as GDS 6, who presented less anosognosia at 24 months.

Patient ratings of QoL-p did not differ significantly as a function of the severity of dementia in any of the three assessments. By contrast, caregiver ratings of QoL-p decreased significantly in line with increasing severity of dementia ($p < 0.001$) at all three assessment points.

The discrepancy between patient and caregiver ratings of QoL-p increased in line with the severity of the dementia (Table 4).

TABLE 4

Multivariate analysis: Effect of anosognosia and neuropsychiatric symptoms on ratings of QoL-p

Total scores: In patients, greater anosognosia was associated with higher ratings of QoL-p, most notably at 24 months ($p < 0.001$). Neuropsychiatric symptoms had less of an effect on patients' self-ratings of QoL. Greater anosognosia in the patient had a negative effect on caregiver ratings of QoL-p at all three assessment points, most notably at baseline. Neuropsychiatric symptoms had a stronger effect than did anosognosia on caregiver ratings of QoL-p at all three assessment points, although in this case the effect was strongest at 24 months.

NPI scores by subscale: Depression was the factor that had the strongest negative effect on patients' self-ratings of QoL. Conversely, apathy and agitation in the patient were the factors that most negatively influenced caregiver ratings of QoL-p at all three assessment points. The negative effect of depression on patient ratings and of apathy and agitation on caregiver ratings increased over time (Table 5).

TABLE 5

Discussion

Quality of life of the patient, anosognosia and neuropsychiatric symptoms

The first aim of this study was to analyse the relationship between anosognosia (AQ-D), neuropsychiatric symptoms (NPI) and the quality of life of patients with AD (QoL-AD). The results showed that patients with anosognosia presented more BPSD and gave higher ratings of their own QoL. In contrast to what occurred with patients, caregiver ratings of QoL-p were more negative in the case of patients with anosognosia. This illustrates the way in which subjective and proxy ratings of quality of life may differ. While some authors have cast doubt on the reliability of QoL ratings of patients with high levels of anosognosia (Berwig *et al.*, 2009; Vogel *et al*., 2006), others have argued that the two perspectives (patients vs. caregivers) can be regarded as equally valid and as highlighting different aspects (Ready *et al.,* 2006; Logsdon *et al.*, 2002; Trigg *et al*., 2011). From a clinical perspective, therefore, different criteria should also be applied when interpreting the ratings of patients and their caregivers.

Although the strong association between anosognosia and BPSD is consistent with previous findings (Kashiwa *et al*., 2005; Starkstein *et al*., 2007), these two variables did not have the same effect on patients' ratings of their own QoL: greater anosognosia was associated with higher ratings, whereas ratings became more negative in the presence of more neuropsychiatric symptoms. This suggests that these variables have an independent and opposing effect on patients. Among caregivers, the presence of greater anosognosia (Tatsumi *et al*., 2009; Conde-Sala *et al*., 2014a) and of more neuropsychiatric symptoms (Karttunen *et al*., 2011; Tay *et al*., 2014) always had the same negative effect on their ratings of QoL-p.

Quality of life and severity of dementia

The second aim of this study was to analyse how anosognosia, neuropsychiatric symptoms, and patient and caregiver ratings of QoL-p change with increasing severity of dementia. In line with previous studies, both anosognosia (Kashiwa *et al.,* 2005; Starkstein *et al.,* 2006) and the number of BPSD (Zuidema *et al*., 2009; Robles-Castiñeiras *et al.,* 2012) increased as the dementia became more severe (higher GDS stage). This increase could be due to neurological deterioration, and specifically to frontal lobe alterations, which would be exacerbated with increasing disease severity (Vogel *et al.*, 2005; Spalletta *et al.,* 2012).

Regarding QoL-p, the perception of caregivers was significantly more negative as the dementia became more severe, although patients' own ratings did not alter significantly (Trigg *et al.*, 2014). This more negative view among caregivers would be related to the severity of the dementia and the distress they experience when having to deal with a greater number of BPSD (Karlawish *et al.,* 2001; Cheng *et al.*, 2013) and increased functional impairment in the patient (Conde-Sala *et al.,* 2014b).

The lower ratings of QoL-p obtained from patients without anosognosia (in the early stages of dementia) could be related to psychological factors, as these individuals are likely to be more depressed by the awareness of their own deficits (Sevush and Leve, 1993; Conde-Sala *et al.,* 2014a). A recent 12-month follow-up study (Portellano-Ortiz *et al.,* 2014) that assessed depression directly using the Geriatric Depression Scale likewise found that it was associated with less anosognosia, although the observed association was not as strong as when depression was evaluated by caregivers using the NPI.

Conversely, the greater anosognosia and higher ratings of QoL-p observed in more advanced stages of dementia could be related to the biological factors that are implicit to increased neurological impairment (Sedaghat *et al.,* 2010; Spalletta *et al.,* 2012).

Limitations and future directions

Although it is a common problem in follow-up studies the loss of cases between the two assessment points could have influenced some of the results. For instance, if the lost cases had had higher baseline scores for anosognosia and neuropsychiatric symptoms, the trend would be similar to that observed in the followed-up cases, although QoL-AD scores would have been even more different between the subgroups.

A further limitation of the study is that certain caregiver factors which may influence the evaluation of anosognosia and quality of life, namely gender, burden and depression, were not analysed in sufficient detail.

Future studies should focus on the analysis of anosognosia in the early stages of dementia and of the factors associated with it, since the majority of patients with more severe dementia will be affected by anosognosia.

Conclusions

Anosognosia and neuropsychiatric symptoms both increased in line with the severity of dementia, although they had differential effects on patient and caregiver ratings of QoL-p. Patients gave more positive ratings of their own QoL in the presence of greater anosognosia and fewer neuropsychiatric symptoms. Among caregivers, greater anosognosia and more neuropsychiatric symptoms were always associated with more negative ratings of QoL-p.

Caregivers' views of QoL-p became significantly more negative in line with the severity of dementia (GDS stage), whereas no such change was observed among patients. Caregiver ratings of QoL-p were always more negative than those of patients.

Clinical implications

BPSD are common among patients with AD and they have a significant impact on caregivers. Consequently, there is a need for interventions that can help caregivers develop coping strategies for dealing with these symptoms (García-Alberca *et al.,* 2013).

When assessing the quality of life of patients with dementia it is important to take into account those factors which may influence patients' own ratings depending on the stage of their illness, with depression and anosognosia being especially relevant in this regard. It would seem advisable, therefore, for greater attention to be paid to the assessment of anosognosia, using specific brief instruments (Turró-Garriga *et al.*, 2014).

Conflict of interest: None.

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Table 1. Sociodemographic and clinical data of patients and caregivers

	Baseline	12 months	24 months	Differences		
	1 (*n* = 221)	2 (*n* = 166)	3 (*n* = 127)	Test	df	*p*
Patient factors						
Women, *n* (%)	140 (63.3)	104 (62.7)	82 (64.6)	0.1	2	0.944 [1]
School (<5 years), *n* (%)	140 (63.3)	108 (65.1)	84 (66.1)	0.2	2	0.861 [1]
Age, mean (SE)	77.8 (0.4)	78.6 (0.5)	79.0 (0.6)	2.5	2	0.276 [2]
MMSE, mean (SE)	18.3 (0.3)	16.3 (0.4) [a]	15.8 (0.6) [b]	17.0	2	< **0.001** [2]
DAD, mean (SE)	58.1 (0.6)	54.0 (0.7) [a]	50.0 (0.8) [b, c]	55.7	2	< **0.001** [2]
NPI, mean (SE)	25.3 (1.2)	24.4 (1.4)	28.6 (1.6)	4.3	2	0.116 [2]
AQ-D, mean (SE)	33.9 (1.2)	34.3 (1.5)	36.2 (2.0)	1.1	2	0.603 [2]
Caregiver factors						
Women, *n (%)*	151 (68.3)	107 (64.5)	81 (63.8)	0.9	2	0.611 [1]
School <5 years), *n (%)*	56 (25.3)	42 (25.3)	30 (23.6)	0.1	2	0.929 [1]
Age, mean (SE)	63.8 (0.8)	65.7 (0.9)	65.7 (1.1)	2.9	2	0.226 [2]
Quality of life (QoL-AD)						
Patients, mean (SE)	35.1 (0.3)	35.4 (0.4)	35.9 (0.5)	1.6	2	0.443 [2]
Caregivers, mean (SE)	27.3 (0.3)	26.2 (0.4) [a]	25.0 (0.4) [b]	15.5	2	< **0.001** [2]
Simple effects. χ^2 *(df) p*	246.5 (1) < **0.001**	235.8 (1) < **0.001**	218.9 (1) < **0.001**			
• Model. χ^2 *(df) p*	Time = 2.7 (2) 0.254; Groups = 678.1 (1) < **0.001**; Time*Groups = 12.7 (2) **0.002**					

[1] Pearson χ^2 test.; [2] Generalized linear model Wald χ^2; Means, estimated marginal; SE, standard error; Significant with Bonferroni post hoc contrasts: [a]1-2, [b]1-3, [c]2-3.
MMSE, Mini Mental State Examination; DAD, Disability Assessment for Dementia; NPI, Neuropsychiatric Inventory; AQ-D, Anosognosia Questionnaire-Dementia; QoL-AD, Quality of Life-Alzheimer's Disease; QoL-p, Quality of life of patient.

Table 2. Differences in QoL between the groups defined in relation to AQ-D and NPI

	1. Baseline		2. 12 months		3. 24 months		Simple effects		
	n	Mean (SE)	*n*	Mean (SE)	*n*	Mean (SE)	χ^2	df	*p*
NPI & AQ-D groups									
No anosognosia	101	14.4 (1.6)	55	16.2 (2.1)	31	17.2 (2.9)	0.9	2	0.627
Anosognosia	120	34.5 (1.4)	111	28.4 (1.5) [a]	96	32.3 (1.6)	8.1	2	**0.017**
Simple effects. χ^2 *(df) p*	83.7 (1) < **0.001**		20.5 (1) < **0.001**		20.1 (1) < **0.001**				
• Model. χ^2 *(df) p*	Time = 1.8 (2) 0.392; Groups = 96.2 (1) < **0.001**; Time* Groups = 5.4 (2) 0.065								
QoL & BPSD groups									
QoL-p Patient									
Low BPSD	121	35.1 (0.4)	90	36.0 (0.5)	58	36.9 (0.7)	5.2	2	0.071
High BPSD	100	35.1 (0.4)	76	34.7 (0.6)	69	34.7 (0.7)	0.3	2	0.856
Simple effects χ^2 *(df) p*	0.0(1) 0.963		2.4 (1) 0.118		4.6 (1) **0.032**				
• Model. χ^2 *(df) p*	Time = 1.3 (2) 0.505; Groups = 5.8 (1) **0.016**; Time* Groups = 3.7 (2) 0.156								
QoL-p Caregiver									
Low BPSD	121	29.9 (0.4)	90	28.3 (0.5)	58	28.0 (0.6) [b]	8.7	2	**0.003**
High BPSD	100	24.1 (0.4)	76	23.7 (0.5)	69	22.6 (0.5)	4.1	2	0.123
Simple effects χ^2 *(df) p*	77.9 (1) < **0.001**		38.1 (1) < **0.001**		38.5 (1) < **0.001**				
• Model. χ^2 *(df) p*	Time = 11.1 (2) **0.004**; Groups = 143.1 (1) < **0.001**; Time* Groups = 1.1 (2) 0.532								
QoL & AQ-D groups									
QoL-p Patient									
No anosognosia	101	34.1 (0.4)	55	33.3 (0.6)	31	33.7 (0.8)	1.1	2	0.570
Anosognosia	120	35.9 (0.4)	111	36.9 (0.5)	96	37.2 (0.6)	4.2	2	0.122
Simple effects χ^2 *(df) p*	7.7 (1) **0.006**		19.5 (1) < **0.001**		11.4 (1) < **0.001**				
• Model. χ^2 *(df) p*	Time = 0.5 (2) 0.748; Groups = 36.5 (1) < **0.001**; Time* Groups = 4.2 (2) 0.121								
QoL-p Caregiver									
No anosognosia	101	30.4 (0.4)	55	29.1 (0.6)	31	29.8 (0.8)	2.3	2	0.315
Anosognosia	120	24.7 (0.4)	111	24.8 (0.4)	96	23.5 (0.5)	4.3	2	0.114
Simple effects χ^2 *(df) p*	73.4 (1) < **0.001**		29.4 (1) < **0.001**		39.1 (1) < **0.001**				
• Model. χ^2 *(df) p*	Time = 2.6 (2) 0.271; Groups = 126.9 (1) < **0.001**; Time* Groups = 2.6 (2) 0.272								

Generalized linear model, Wald χ^2, for time, groups and interaction; Simple effects, Wald χ^2 for differences between groups; Means, estimated marginal; SE, standard error; Significant with Bonferroni post hoc contrasts: [a]1-2, [b]1-3, [c]2-3.

NPI, Neuropsychiatric Inventory; AQ-D, Anosognosia Questionnaire-Dementia; QoL-AD, Quality of Life-Alzheimer's Disease; QoL-p, Quality of life of patient; BPSD, Behavioural and Psychological Symptoms of Dementia.

Groups: No anosognosia (< 32 AQ-D), Anosognosia (≥ 32 AQ-D); Low BPSD (< 25 NPI), High BPSD (≥ 25 NPI). In the NPI groups the mean score was used as the reference.

Table 3. Differences in QoL-p between groups, combining scores from the AQ-D and NPI

	Baseline		12 months		24 months		Simple effects		
	n	Mean (SE)	*n*	Mean (SE)	*n*	Mean (SE)	χ^2	df	*p*
QoL-p Patient									
1. Anosog / Low NPI	41	36.2 (0.7)	49	36.8 (0.6)	31	37.4 (0.8)	0.5	2	0.763
2. Anosog / High NPI	79	35.7 (0.5)	57	35.7 (0.6)	53	36.2 (0.6)	1.1	2	0.561
3. No-anosog / Low NPI	80	34.5 (0.5)	41	34.3 (0.7)	27	34.4 (0.8)	1.9	2	0.379
4. No-anosog / High NPI	21	32.8 (0.9) [c]	19	31.1 (1.0) [c, e]	16	31.0 (1.1) [c, e]	0.0	2	0.979
Simple effects. χ^2 *(df) p*	10.5 (3) **0.014**		23.8 (3) < **0.001**		24.0 (3) < **0.001**				
• Model. χ^2 *(df) p*	Time = 0.3 (2) 0.828; Groups = 56.5 (3) < **0.001**; Time* Groups = 3.2 (6) 0.775								
QoL-p Caregiver									
1. Low NPI / No-anosog	80	31.3 (0.5)	41	30.4 (0.7)	27	29.7 (0.8)	2.7	2	0.248
2. Low NPI / Anosog	41	27.3 (0.7) [a]	49	26.6 (0.6) [a]	31	26.4 (0.8) [a]	0.6	2	0.721
3. High NPI / No-anosog	21	26.9 (1.0) [b]	19	24.8 (1.0) [b]	16	24.8 (1.1) [b]	2.4	2	0.292
4. High NPI / Anosog	79	23.4 (0.5) [c, e, f]	57	23.3 (0.6) [c, e]	53	21.9 (0.6) [c, e]	4.0	2	0.132
Simple effects. χ^2 *(df) p*	117.9 (3) < **0.001**		59.3 (3) < **0.001**		56.1 (3) < **0.001**				
• Model. χ^2 *(df) p*	Time = 7.0 (2) **0.029**; Groups = 205.2 (3) < **0.001**; Time* Groups = 2.1 (6) 0.910								

Generalized linear model, Wald χ^2, for time, groups and interaction; Simple effects, Wald χ^2 for differences between groups; Means, estimated marginal; SE, standard error; Significant with Bonferroni post hoc contrasts: [a] 1-2, [b] 1-3, [c] 1-4, [d] 2-3, [e] 2-4, [f] 3-4

NPI, Neuropsychiatric Inventory; AQ-D, Anosognosia Questionnaire-Dementia; QoL-AD, Quality of Life-Alzheimer's Disease; QoL-p, Quality of life of patient.

Groups: No anosognosia (< 32 AQ-D), Anosognosia (≥ 32 AQ-D); Low NPI (< 25), High NPI (≥ 25). In the NPI groups the mean score was used as the reference.

Table 4. Severity of dementia: anosognosia, behaviour and quality of life

	Baseline		12 months		24 months		Simple effects		
	n	Mean (SE)	*n*	Mean (SE)	*n*	Mean (SE)	χ^2	df	*p*
AQ-D (Anosognosia)									
GDS 4	97	22.5 (1.5)	38	20.8 (2.4)	12	16.4 (4.3)	1.8	2	0.390
GDS 5	78	38.4 (1.5) [a]	67	35.1 (1.8) [a]	40	38.3 (2.4) [a]	1.9	2	0.375
GDS 6	46	50.3 (2.2) [b, c]	61	48.4 (2.6) [b, c]	75	41.1 (2.6) [c, e]	7.5	2	**0.023**
Simple effects. χ^2 *(df) p*	116 (2) < **0.001**		58.2 (2) < **0.001**		24.8 (2) < **0.001**				
• Model. χ^2 *(df) p*	Time = 6.0 (2) **0.048**; GDS = 139.1 (2) < **0.001**; Time*GDS = 5.9 (4) 0.206								
NPI (Behaviour)									
GDS 4	97	16.9 (1.6)	38	15.0 (2.6)	12	11.6 (4.7)	1.2	2	0.529
GDS 5	78	28.2 (1.8) [a]	67	23.5 (2.0) [a]	40	24.4 (2.6)	3.1	2	0.209
GDS 6	46	38.0 (2.4) [b, c]	61	31.2 (2.1) [b, c]	75	33.6 (1.9) [b, c]	4.5	2	0.103
Simple effects. χ^2 *(df) p*	54.2 (2) < **0.001**		22.6 (2) < **0.001**		21.8 (2) < **0.001**				
• Model. χ^2 *(df) p*	Time = 7.8 (2) **0.020**; GDS = 77.7 (2) < **0.001**; Time*GDS = 1.4 (4) 0.835								
QoL-p Patient									
GDS 4	97	35.6 (0.4)	38	35.4 (0.7)	12	35.1 (1.3)	0.1	2	0.933
GDS 5	78	35.1 (0.5)	67	35.4 (0.5)	40	36.7 (0.7)	3.2	2	0.194
GDS 6	46	34.0 (0.7)	61	35.5 (0.8)	75	35.2 (0.8)	2.3	2	0.315
Simple effects. χ^2 *(df) p*	3.4 (2) 0.178		0.0 (2) 0.991		2.1 (2) 0.337				
• Model. χ^2 *(df) p*	Time = 1.9 (2) 0.380; GDS = 1.9 (2) 0.371; Time*GDS = 3.0 (4) 0.550								
QoL-p Caregiver									
GDS 4	97	30.3 (0.4)	38	31.0 (0.7)	12	32.4 (1.3)	2.3	2	0.305
GDS 5	78	26.1 (0.5) [a]	67	26.5 (0.5) [a]	40	27.4 (0.7) [a]	2.0	2	0.361
GDS 6	46	23.0 (0.5) [b, c]	61	23.0 (0.5) [b, c]	75	22.6 (0.5) [b, c]	0.2	2	0.863
Simple effects. χ^2 *(df) p*	84.0 (2) < **0.001**		69.7 (2) < **0.001**		60.3 (2) < **0.001**				
• Model. χ^2 *(df) p*	Time = 2.4 (2) 0.299; GDS = 176.3 (2) < **0.001**; Time*GDS = 3.2 (4) 0.523								
Discrepancy QoL-p Patients-Caregivers									
GDS 4	97	5.3 (0.5)	38	4.4 (0.9)	12	2.7 (1.6)	2.4	2	0.289
GDS 5	78	8.9 (0.6) [a]	67	8.8 (0.7) [a]	40	9.1 (0.9) [a]	0.0	2	0.972
GDS 6	46	10.9 (0.8) [b]	61	11.9 (0.9) [b, c]	75	10.6 (0.9) [b]	1.0	2	0.592
Simple effects. χ^2 *(df) p*	36.6 (2) < **0.001**		32.3 (2) < **0.001**		17.2 (2) < **0.001**				
• Model. χ^2 *(df) p*	Time = 1.4 (2) 0.492; GDS = 69.7 (2) < **0.001**; Time*GDS = 2.8 (4) 0.583								

Generalized linear model, Wald χ^2, for time, groups and interaction; Simple effects, Wald χ^2 for differences between groups; Means, estimated marginal; SE, standard error; Significant with Bonferroni post hoc contrasts: [a] GDS 4-5, [b] GDS 4-6 , [c] GDS 5-6; [e] Baseline-24 months

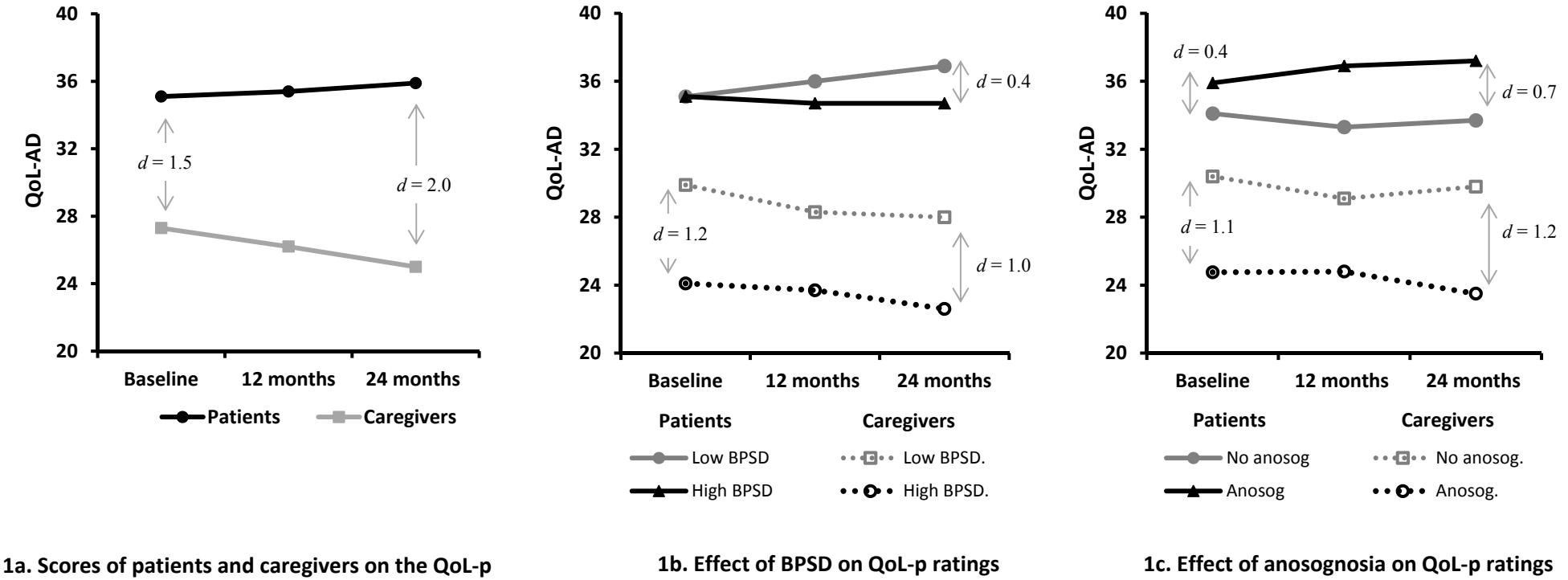
NPI, Neuropsychiatric Inventory; AQ-D, Anosognosia Questionnaire-Dementia; QoL-AD, Quality of Life-Alzheimer's Disease; QoL-p, Quality of life of patient; GDS, Global Deterioration Scale.

Table 5. Multivariate analysis. QoL-AD, Time & Factors

	Model effects		Parameter estimates								
			Baseline			12 months			24 months		
	χ^2	*p*	B (SE)	χ^2	*p*	B (SE)	χ^2	*p*	B (SE)	χ^2	*p*
Global score											
QoL-p Patients											
Anosognosia (AQ-D)	149.7	**< 0.001**	0.13 (0.01)	59.4	**< 0.001**	0.15 (0.01)	65.3	**< 0.001**	0.19 (0.02)	68.1	**< 0.001**
Behaviour (NPI)	62.4	**< 0.001**	-0.08 (0.01)	23.2	**< 0.001**	-0.11 (0.02)	17.6	**< 0.011**	-0.16 (0.03)	23.8	**< 0.001**
QoL-p Caregivers											
Anosognosia (AQ-D)	43.6	**< 0.001**	-0.10 (0.01)	34.7	**< 0.001**	-0.07 (0.01)	15.1	**< 0.001**	-0.04 (0.02)	3.5	0.060
Behaviour (NPI)	94.1	**< 0.001**	-0.10 (0.01)	30.5	**< 0.001**	-0.16 (0.02)	33.8	**< 0.001**	-0.19 (0.03)	33.4	**< 0.001**
NPI disaggregated											
QoL-p Patients											
Depression	56.6	**< 0.001**	-0.40 (0.08)	22.1	**< 0.001**	-0.53 (0.09)	30.8	**< 0.001**	-0.57 (0.14)	16.0	**< 0.001**
Sleep disorders	11.2	**0.010**	-0.33 (0.10)	10.6	**0.001**	-0.15 (0.18)	0.6	0.422	0.04 (0.21)	0.0	0.825
QoL-p Caregivers											
Apathy	246.5	**< 0.001**	-0.54 (0.06)	66.7	**< 0.001**	-0.80 (0.07)	124.5	**< 0.001**	-0.82 (0.07)	138.6	**< 0.001**
Agitation	31.2	**< 0.001**	-0.25 (0.09)	6.8	**0.009**	-0.35 (0.10)	12.6	**< 0.001**	-0.37 (0.10)	11.7	**0.001**
Depression	11.5	**0.009**	-0.23 (0.08)	7.3	**0.007**	-0.16 (0.09)	2.9	0.087	-0.12 (0.10)	1.5	0.215
Sleep disorders	11.2	**0.010**	-0.28 (0.09)	9.0	**0.003**	-0.18 (0.14)	1.4	0.225	-0.11 (0.13)	0.8	0.362
Eating abnormalities	9.4	**0.024**	-0.24 (0.09)	7.1	**0.008**	-0.10 (0.15)	0.4	0.492	-0.19 (0.13)	1.9	0.161
Delusions	8.7	**0.033**	-0.24 (0.09)	6.3	**0.012**	-0.04 (0.11)	0.1	0.676	-0.16 (0.11)	2.2	0.133

Generalized linear model, Wald $\chi 2$; B, Beta coefficient; SE, standard error

NPI, Neuropsychiatric Inventory; AQ-D, Anosognosia Questionnaire-Dementia; QoL-AD, Quality of Life-Alzheimer's Disease; QoL-p, Quality of life of patient.



1a. Scores of patients and caregivers on the QoL-p

1b. Effect of BPSD on QoL-p ratings

1c. Effect of anosognosia on QoL-p ratings

Figure 1. Quality of life of patients, in patients and caregivers. Effects of neuropsychiatric symptoms and anosognosia