The Longitudinal Association Between a Discrepancy Measure of Anosognosia in Patients with Dementia, Caregiver Burden and Depression

Jaime Perales[a,*], Oriol Turró-Garriga[b], Jordi Gascón-Bayarri[c], Ramón Reñé-Ramírez[c] and Josep Lluís Conde-Sala[d]

[a] *University of Kansas Medical Center, Department of Preventive Medicine and Public Health, Kansas, USA*
[b] *Research Unit, Santa Caterina Hospital, Institut d'Assistència Sanitària, Salt, Spain*
[c] *Dementia Unit, Department of Neurology, Bellvitge University Hospital, Hospitalet de Llobregat, Spain*
[d] *Faculty of Psychology, University of Barcelona, Spain*

Abstract.

Background: According to cross-sectional studies, there is an association between anosognosia in people with dementia and caregiver's burden and depression. Anosognosia in patients may be a cause of caregiver burden and depression. However, variability in caregiver anosognosia ratings may exist as caregivers with burden and depression may have a more pessimistic view of the patients' health.

Objective: To assess the variability of caregiver anosognosia ratings of patients with dementia using a widely used anosognosia scale and its longitudinal relationship with caregiver burden and depression.

Methods: A convenience cohort of 221 consecutive dementia outpatient and caregiver dyads was followed up at 12 and 24 months. The main instruments used were the Anosognosia Questionnaire-Dementia (AQ-D), Caregiver Burden Interview, and Geriatric Depression Scale. Linear mixed models were used including time as a factor in every model. Multivariate analyses controlled for caregiver's socio-demographic and possible confounding factors.

Results: Attrition at 12 and 24 months was 24.9% and 42.5% respectively. Patients at baseline were on average 77.8 years of age, 63.3% were women, and 63.3% had < 5 years of education. In the bivariate analyses, caregiver burden, depression, and gender were associated with caregiver ratings of total, cognitive, and personality AQ-D of the patient at different time points. Multivariate analyses revealed burden as the caregiver variable most consistently associated with total, cognitive, and personality caregiver AQ-D ratings of the patient.

Conclusion: Some caregiver characteristics, especially burden, are associated with caregiver ratings of AQ-D with regard to the patient.

Keywords: Anosognosia, bias, burden of illness, caregivers, dementia, depression, longitudinal studies

INTRODUCTION

Anosognosia can be defined as the "apparent unawareness, misinterpretation, or explicit denial of an illness". It is a common characteristic of Alzheimer disease and other types of dementia [1]. It may vary regarding modality (i.e., memory versus

*Correspondence to: Jaime Perales, University of Kansas Medical Center, Department of Preventive Medicine and Public Health, 4125 Rainbow Blvd. MS 1056, Kansas City, KS 66103, USA. Tel.: +1 913 945 7869; E-mail: jperales@kumc.edu.

behavior) and degree (mild, severe, or profound lack of awareness). There are different ways to measure anosognosia [2]. The investigator can directly rate the awareness of the patient (Clinical Rating). The patient's judgment on their performance can be compared to their actual performance (Objective Judgment Discrepancy). The comparison can also be made between the rating of the patient's ability by the patient's self and an informant such as their caregiver (Subjective Rating Discrepancy). All these methods of assessment present limitations [3]. For example, during a clinical interview, the patient's responses might be influenced by the desire to give the best impression. Self-rating-performance discrepancy measures fail to take into account that subjective memory complaints may be affected by current mood, personality traits, and education.

Several cross-sectional studies have found anosognosia in people with dementia to be associated with caregiver burden and, to a lesser extent, depression [4–8]. At least two different conclusions may be drawn from these results. One interpretation is that a patient's higher level of anosognosia leads to a higher burden on and depression of the caregiver. Anosognosia would increase physical wear, social isolation, dependence, and tension related to patient care [8]. However, most of these studies have assessed anosognosia using discrepancy indexes [4, 5, 7]. This method assumes caregiver ratings are more objective compared to the possibly biased assessment of the patient affected by a reduced insight [3, 9]. Another possible mechanism to explain the associations between caregiver depression, burden, and anosognosia could be that the burden and depression of the caregiver may distort their perception of the health status of their relatives with dementia leading to a more negative assessment of caregiver-rated dementia outcomes such as those used to measure discrepancy-based anosognosia [4, 5]. These two mechanisms are not mutually exclusive. A first step to understand the latter mechanism is to assess the variability of the caregiver ratings in subjective rating discrepancy scales.

In light of the above, the main objective of this manuscript is to assess the variability of the caregiver ratings of patients with dementia using a widely used anosognosia scale, and its longitudinal relationship with two caregiver factors: Burden and depression. The study hypothesis is that caregiver's burden and depression will be associated with caregiver ratings of anosognosia with regard to the patient. The variability of caregivers' ratings of the anosognosia scale in relation with caregivers' gender and education will also be analyzed. To the best of our knowledge, this is the first study to assess variability of caregiver anosognosia ratings in a longitudinal study.

METHODS

Design and sample

The CUIDA'L-AD project was an observational, longitudinal study. A convenience sample of outpatients at the Dementia Unit (Department of Neurology at Bellvitge University Hospital, Hospitalet de Llobregat, Barcelona) was assessed in 3 different waves: Wave 0, wave 1 (12 months), and wave 2 (24 months). Participants' inclusion criteria were the following: 1) being diagnosed with either AD according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders [10] 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 [11]; 2) scoring between 10 and 28 on the Mini-Mental State Examination (MMSE) [12] as the main purpose of the project was to measure quality of life; 3) having a main caregiver, defined as the relative with ongoing responsibility for helping the patient with activities of daily living (ADL); and 4) residing in Hospitalet de Llobregat. Exclusion criteria for the participants were: 1) vascular or traumatic events, alcohol or substance dependency, or abuse; and 2) severe communication problems preventing them from responding adequately to the assessment instruments.

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. Three clinical psychologists conducted the 90-min interviews in external consultations. When the patients/caregivers were not able to attend, home visits or visits to the center of the Association for Relatives of People with Alzheimer's Disease in Hospitalet de Llobregat were conducted. The sample was initially recruited between January and December 2011 and followed up 12 and 24 months later. The interviews were administered to caregivers and patients separately. The administration time was approximately 30 and 60 min for patients and caregivers respectively. The study was approved by the hospital's Clinical Research Ethics Committee (ref.PR162/10).

Measures

Both patients and caregivers were asked to complete a survey providing sociodemographic data (age, gender, years of education, cohabitation with and relation to caregiver/patient) and the following clinical information:

- Anosognosia was assessed using the Anosognosia Questionnaire-Dementia (AQ-D) [1]. This scale consists of 30 questions focusing on intellectual functioning and changes in interests and personality of the patient. Each item is rated from *0 (never)* to *3 (always)*; therefore, higher scores indicate greater impairment. Two forms are completed (one by the patient and one by the caregiver). The final score is the result of the subtraction between the caregiver's rating and the patient's. For the purpose of this study, only the caregivers' rating of total, cognitive, and personality anosognosia scores were used as continuous dependent variables.
- Caregivers' burden was measured with the Caregiver Burden Interview (CBI) [13, 14]. This scale is comprised by 22 five-point Likert scale items that range from never to almost always. The total score ranges from 22 to 110 (higher scores indicate a higher burden). For bivariate analyses, scores were grouped into those with and without burden (cut-off = 50). For multivariate analyses, caregiver burden scores were entered as a continuous variable.
- Caregivers' depression was measured using the Geriatric Depression Scale (GDS)-15 item version [15, 16]. Higher scores indicate a more severe depression. For bivariate analyses, scores were grouped into those with and without depression (cut-off = 6). For multivariate analyses, caregiver burden scores were entered as a continuous variable.
- Patients' cognitive performance was measured using the MMSE, the most widely used cognitive assessment instrument for dementia. MMSE scores range from zero to 30 (higher scores indicate a better cognitive performance). Patients' MMSE scores were corrected for patients' age and level of education [17] and treated as a continuous variable.
- Behavioral and psychological symptoms of dementia were assessed with the Neuropsychiatric Inventory (NPI) [18] that assesses 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. NPI scores were treated as a continuous variable.

Statistical analysis

The descriptive analysis of categorical variables involved calculating frequencies and conducting comparisons by means of the Pearson χ^2 test. For continuous variables, linear mixed models were used to calculate the fixed effects (F, ANOVA) and simple effects of the estimated marginal means for each assessment point. A heterogeneous first order autoregressive [AR (1)] covariance structure was used as this provided the best fit to the unstructured matrix and best fulfilled the parsimony criterion. This approach enabled us to examine the general effects of the independent variables on the response variable with respect to the factors of time, patient group, and the interaction between the two (Time x Group) as well as the simple effects of differences between the groups. The contrasts involving continuous variables were corrected by means of the Bonferroni test for multiple comparisons. Multivariate analyses were also performed adjusting for patients' MMSE and NPI, and caregivers' education and gender. For hypothesis contrasts, the level of statistical significance was set at 0.05. All data processing and analyses were performed using SPSS v20.0 for Windows [19].

RESULTS

Description of sample

Out of the initial 221 patients (and corresponding caregivers), 166 and 127 patients were followed up at 12 and 24 months, respectively (see Table 1). An attrition rate analysis can be found in a previous publication [20].

The patients' mean age at baseline was 77.8 and ranged from 52.7 to 93.9; 63.3% were women and 63.3% had less than five years of education. The caregivers' mean age was 63.8 ranging from 18.8 to 90.2; 68.3% were women and 74.7% had been to school five or more years. Caregivers were mostly spouses (52.5%) or children of the patients (40.3%), and 80.1% lived with them.

Caregivers' total AQ-D ratings with regard to the patients increased gradually at 12 and 24 months

Table 1
Participants' socio-demographic and clinical characteristics

	Baseline	12 months	24 months	Differences		
	$n = 221$	$n = 166$	$n = 127$	*Test*	*df*	*p*
Characteristics of the patient						
Age (years), mean	77.8	78.6	79.0	1.2	2	0.279
Gender (women), *n* (%)	140 (63.3)	104 (62.7)	82 (64.6)	0.1	2	0.994
Level of education (<5), *n* (%)	140 (63.3)	108 (65.1)	84 (66.1)	0.3	2	0.861
MMSE, mean	18.3	15.7[a]	12.8[b,c]	59.2	2	**<0.001**
AQ-D total, mean	15.2	17.3[a]	17.1	4.3	2	**0.014**
Caregiver's rating of the patient						
AQ-D total, mean	49.2	56.0[a]	61.4[b,c]	82.4	2	**<0.001**
Cognitive AQ-D, mean	41.1	48.0[a]	53.7[b,c]	130.8	2	**<0.001**
Personality AQ-D, mean	8.1	8.0	7.7	0.4	2	0.654
NPI, mean	25.3	25.5	29.9[b,c]	5.2	2	**0.006**
Anosognosia discrepancy						
AQ-D total discrepancy, mean	34.0	37.7[a]	40.5[b,c]	17.8	2	**<0.001**
AQ-D total discrepancy (>32), *n* (%)	120 (54.3)	106 (63.9)	84 (66.1)	6.0	2	**0.049**
Characteristics of the caregiver						
Age (years), mean	63.8	65.0[a]	65.8[b,c]	14.5	2	0.229
Gender (women), *n* (%)	151 (68.3)	107 (64.5)	81 (63.8)	1.0	2	0.611
Level of education, (<5), *n* (%)	56 (25.3)	42 (25.3)	30 (23.6)	0.1	2	0.929
Family relationship, *n* (%)				6.0	4	0.198
Spouse	116 (52.5)	95 (57.2)	70 (55.1)			
Children	89 (40.3)	67 (40.4)	53 (41.7)			
Other	16 (7.2)	4 (2.4)	4 (3.1)			
Living with the patient, *n* (%)	177 (80.1)	128 (77.1)	91 (72.7)	3.2	2	0.197
ZBI total, mean (95% CI)	49.5	53.1[a]	53.8[b]	8.0	2	**<0.001**
ZBI total (>50), *n* (%)	92 (41.6)	83 (50.0)	67 (52.8)	4.8	2	0.089
GDS-d, mean	4.2	4.7[a]	4.8[b,c]	5.5	2	**0.005**
GDS-d (>6), *n* (%)	60 (27.1)	54 (32.7)	45 (35.4)	2.9	2	0.231

F ANOVA, fixed effects; 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; AQ-D, Anosognosia Questionnaire-Dementia; ZBI, Zarit Burden Interview; GDS-d, Geriatric Depression Scale; NPI, Neuropsychiatric Inventory.

and so did caregivers' cognitive AQ-D ratings ($p < 0.001$). Caregivers' personality AQ-D ratings, however, remained stable across the three points in time ($p = 0.654$). The patients' total AQ-D ratings were much lower than those rated by their caregivers increasing from baseline to month 12 but remaining stable from month 12 to 24 ($p = 0.014$). The total AQ-D discrepancy score increased with time, this increase being statistically significant ($p < 0.001$).

The cognition of the patients as measured by the MMSE decreased gradually at 12 and 24 months ($p < 0.001$). Caregivers' ratings of patients' behavior (NPI) did not change from baseline to month 12 but increased significantly in month 24 ($p = 0.006$). Caregivers' burden score was higher as the time went by (<0.001) and so was the percentage of caregivers with burden although, in this case, not significant ($p = 0.089$). This was the case for caregivers' depression too ($p = 0.004$ and $p = 231$). Caregivers' depression was consistently associated with caregivers' burden at baseline, 12, and 24 months ($p < 0.001$).

Association of caregivers' burden and depression with caregivers' AQ-D ratings with regard to the patients

The raw differences in the different caregiver AQ-D ratings in relation to caregiver burden and depression groups can be found in Table 2. Comparison of caregivers with and without burden showed systematically lower total AQ-D scores in the latter at baseline, 12, and 24 months ($p < 0.001$ in all three cases). Caregiver AQ-D scores also increased with time within each caregiver burden group ($p < 0.001$ in both), the burden being significantly higher at 24 months than the other two points in time and likewise at 12 months than baseline. The caregiver ratings of cognitive AQ-D followed exactly the same pattern. Caregiver ratings of personality AQ-D were higher and statistically significant at all points in time for caregivers with burden compared to those without it. However, while the personality AQ-D ratings remained stable in the no-burden group, these scores decreased by almost one point per year (time

x group interaction $p = 0.024$) in burdened caregivers.

Caregivers with depression rated the total, cognitive, and personality AQ-D higher at all points in time than did those with no depression. These differences reached statistical significance in every case except for personality AQ-D at 24 month follow up ($p = 0.163$). A time effect can also be seen in the total and cognitive caregiver ratings significantly increasing with time in both caregiver depression groups ($p < 0.001$). Regarding the personality caregiver AQ-D rating, caregivers with depression had statistically non-significant lower rates as the time went by while scores in the no-depression group remained stable.

Association of caregivers' education and gender with caregivers' AQ-D ratings with regard to the patients

None of the caregiver education group differences were statistically significant in any of the caregiver AQ-D ratings (Table 3). Caregiver ratings of total and cognitive AQ-D increased at a similar rate within each caregiver education group ($p < 0.001$ for time effects). Caregiver ratings of personality AQ-D of the patient remained stable in time among caregivers with five years or more of education ($p = 0.943$) and decreased among caregivers with less than five years of education, although marginally significantly ($p = 0.054$).

Female caregivers tended to give higher AQ-D total, cognitive, and personality ratings with gender differences being statistically significant at baseline and 12 months in the total and personality ratings and at all times in cognitive ratings. Caregiver total and cognitive AQ-D ratings increased gradually at 12 and 24 months in both gender groups ($p < 0.001$) whereas caregiver personality AQ-D ratings remained stable in time ($p = 0.123$).

Multivariate analysis

Table 4 shows the adjusted models predicting the total, cognitive and personality caregiver AQ-D ratings with regard to the patients with caregiver's burden, depression, gender, and education and patient's cognition and behavior as covariates. In the first model, total caregiver AQ-D ratings were associated with caregiver gender, burden, and depression and with patient cognition and behavior. The higher the caregiver burden, behavioral symptoms, and lower cognition, the higher the total caregiver rated AQ-D with regard to the patient at all three

points in time ($p < 0.001$). Lower scores in caregiver depression were associated with higher scores in total caregiver AQ-D ratings only at 12 months ($p = 0.001$). Female caregivers rated total AQ-D higher at baseline ($p = 0.014$). The above findings apply to caregiver ratings of cognitive AQ-D except for the punctual association with caregiver depression. Caregiver burden and patient's behavior were the only two variables that are consistently associated with caregiver ratings of personality AQ-D. Higher scores in caregiver burden and patient behavioral symptoms were associated with higher personality caregiver ratings at all times. Female caregivers rated personality AQ-D higher at baseline ($p = 0.013$). Cognition of the patient was only associated with caregiver ratings of personality AQ-D of the patient at 24 months, being a higher patient cognition associated with higher caregiver ratings of personality AQ-D ($p = 0.003$).

DISCUSSION

To our knowledge, this is the first longitudinal study to assess the variability of the caregiver ratings of anosognosia with regard to dementia patients exploring their relationship with caregiver factors, namely burden and depression. The results showed that caregiver AQ-D ratings of the patient were associated consistently with caregiver burden and not so much so with caregiver depression. These results are consistent with our previous research [4] and suggests that not only patient characteristics such as lack of insight accounts for variability in anosognosia discrepancy measures, but caregiver characteristics might also account for this variability.

The association of caregiver factors with caregiver anosognosia ratings with regard to the patient

As previously hypothesized, caregiver burden was associated with all types of caregiver AQ-D ratings with regard to the patient with AD. In fact, caregiver burden was the most consistent caregiver characteristic associated with caregiver ratings of AQ-D. Mainly, the higher the caregiver burden, the worse the caregiver total, cognitive, and personality AQ-D ratings were. These associations persisted even after controlling for a performance cognitive test (MMSE) and a caregiver rating of the patient's behavioral symptoms (NPI) both of which are highly associated with cognitive (correlation with MMSE = –0.509, –0.561, and –0.452 at baseline, 12 and 24 months) and personality

Table 2
Raw differences in caregiver AQ-D total, cognitive and personality ratings in relation to caregiver's burden and depression groups

	Baseline $n=221$		12 months $n=166$		24 months $n=127$		Simple effects		
	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)	F	df	p
Total AQ-D & ZBI groups									
No burden	129	45.9 (1.2)	83	52.5 (1.1)[a]	60	58.5 (1.2)[b,c]	50.3	2	**<0.001**
Burden	92	53.8 (1.3)	83	59.0 (1.1)[a]	67	63.6 (1.1)[b,c]	25.7	2	**<0.001**
Simple effects, F (df) p	30.9 (1) **<0.001**		34.0 (1) **<0.001**		14.5 (1) **<0.001**				
Fixed effects, F (df) p	Time=71.8 (2) **<0.001**; Groups=53.2 (1); **<0.001**; Time*Groups=1.1 (2) 0.320								
Cognitive AQ-D & ZBI groups									
No burden	129	39.0 (1.0)	83	45.8 (0.9)[a]	60	51.5 (1.0)[b,c]	72.5	2	**<0.001**
Burden	92	44.1 (1.1)	83	50.0 (0.9)[a]	67	55.3 (0.9)[b,c]	48.6	2	**<0.001**
Simple effects, F (df) p	19.0 (1) **<0.001**		20.3 (1) **<0.001**		11.1 (1) **0.001**				
Fixed effects, F (df) p	Time=117.0 (2) **<0.001**; Groups=34.3 (1); **<0.001**; Time*Groups=0.4 (2) 0.674								
Personality AQ-D & ZBI groups									
No burden	129	6.6 (0.3)	83	6.6 (0.4)	60	6.8 (0.4)	0.2	2	0.849
Burden	92	10.1 (0.4)	83	9.2 (0.3)	67	8.4 (0.4)[b]	5.4	2	**0.005**
Simple effects, F (df) p	55.5 (1) **<0.001**		34.9 (1) **<0.001**		8.1 (1) **0.005**				
Fixed effects, F (df) p	Time=2.2 (2) 0.113; Groups=62.5 (1); **<0.001**; Time*Groups=3.8 (2) **0.024**								
Total AQ-D & GDS-d groups									
No depression	161	47.4 (1.2)	111	54.8 (1.1)[a]	82	60.0 (1.1)[b,c]	62.8	2	**<0.001**
Depression	60	54.0 (1.7)	55	58.2 (1.3)[a]	45	63.6 (1.4)[b,c]	16.6	2	**<0.001**
Simple effects, F (df) p	14.5 (1) **<0.001**		6.4 (1) **0.012**		5.6 (1) **0.019**				
Fixed effects, F (df) p	Time=56.9 (2) **<0.001**; Groups=15.7 (1); **<0.001**; Time*Groups=1.7 (2) 0.185								
Cognitive AQ-D & GDS-d groups									
No depression	161	39.6 (1.0)	111	47.0 (0.9)[a]	82	52.5 (0.9)[b,c]	98.4	2	**<0.001**
Depression	60	45.1 (1.3)	55	49.7 (1.1)[a]	45	55.6 (1.1)[b,c]	29.1	2	**<0.001**
Simple effects, F (df) p	15.7 (1) **<0.001**		6.0 (1) **0.015**		6.1 (1) **0.015**				
Fixed effects, F (df) p	Time=94.6 (2) **<0.001**; Groups=16.3 (1); **<0.001**; Time*Groups=1.9 (2) 0.147								
Personality AQ-D & GDS-d groups									
No depression	161	7.6 (0.3)	111	7.6 (0.3)	82	7.4 (0.4)	0.1	2	0.913
Depression	60	9.3 (0.5)	55	8.7 (0.4)	45	8.3 (0.5)	1.2	2	0.302
Simple effects, F (df) p	8.3 (1) **0.004**		5.4 (1) **0.021**		2.0 (1) 0.163				
Fixed effects, F (df) p	Time=1.1 (2) 0.324; Groups=9.7 (1); **0.002**; Time*Groups=0.6 (2) 0.553								

F, ANOVA, linear mixed model; Means, estimated marginal; SE, standard error; Significant with Bonferroni *post hoc* contrasts: [a]1-2, [b]1-3, [c]2-3. AQ-D, Anosognosia Questionnaire-Dementia; ZBI, Zarit Burden Interview; GDS-d, Geriatric Depression Scale.

Table 3
Raw differences in caregiver AQ-D total, cognitive and personality ratings in relation to caregiver's education and gender

	Baseline n = 221		12 months n = 166		24 months n = 127		Simple effects		
	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)	F	df	p
Total AQ-D & education									
Lower (<5 years)	56	52.2 (2.0)	42	57.5 (1.9)[a]	30	61.7 (1.9)[b,c]	12.4	2	**<0.001**
Higher (≥5 years)	165	48.1 (1.2)	124	55.5 (1.1)[a]	97	61.3 (1.1)[b,c]	72.4	2	**<0.001**
Simple effects, F (df) p		2.9 (1) 0.085		0.8 (1) 0.345		0.0 (1) 0.871			
Fixed effects, F (df) p		Time=53.3 (2) **<0.001**; Groups=0.8 (1) 0.345; Time*Groups=0.0 (2) 0.871							
Cognitive AQ-D & education									
Lower (<5 years)	56	43.0 (1.6)	42	48.8 (1.6)[a]	30	54.2 (1.6)[b,c]	25.7	2	**<0.001**
Higher (≥5 years)	165	40.4 (1.0)	124	47.7 (0.9)[a]	97	53.5 (0.9)[b,c]	106.5	2	**<0.001**
Simple effects, F (df) p		1.8 (1) 0.177		0.3 (1) 0.539		0.1 (1) 0.688			
Fixed effects, F (df) p		Time=90.9 (2) **<0.001**; Groups=0.8 (1) 0.365; Time*Groups=0.6 (2) 0.510							
Personality AQ-D & education									
Lower (<5 years)	56	8.9 (0.6)	42	8.4 (0.5)	30	7.2 (0.6)	2.9	2	0.054
Higher (≥5 years)	165	7.7 (0.3)	124	7.8 (0.3)	97	7.8 (0.3)	0.0	2	0.943
Simple effects, F (df) p		2.9 (1) 0.088		0.8 (1) 0.363		0.8 (1) 0.359			
Fixed effects, F (df) p		Time=1.9 (2) 0.150; Groups=0.4 (1) 0.511; Time*Groups=2.5 (2) 0.077							
Total AQ-D & gender									
Men	70	45.4 (1.8)	59	52.7 (1.6)[a]	46	58.8 (1.6)[b,c]	33.9	2	**<0.001**
Women	151	50.8 (1.3)	107	57.5 (1.2)[a]	81	62.5 (1.1)[b,c]	48.9	2	**<0.001**
Simple effects, F (df) p		6.0 (1) **0.015**		5.9 (1) **0.015**		3.6 (1) 0.058			
Fixed effects, F (df) p		Time=77.8 (2) **<0.001**; Groups=6.6 (1) **0.010**; Time*Groups=0.4(2) 0.665							
Cognitive AQ-D & gender groups									
Men	70	38.5 (1.5)	59	45.5 (1.3)[a]	46	51.2 (1.3)[b,c]	46.4	2	**<0.001**
Women	151	42.2 (1.0)	107	49.2 (1.0)[a]	81	54.8 (0.9)[b,c]	84.4	2	**<0.001**
Simple effects, F (df) p		4.3 (1) **0.039**		4.7 (1) **0.030**		4.7 (1) **0.031**			
Fixed effects, F (df) p		Time=119.2 (1) **<0.001**; Groups=5.8 (1) **0.016**; Time*Groups=0.0 (1) 0.993							
Personality AQ-D & gender groups									
Men	70	6.7 (0.5)	59	7.0 (0.4)	46	7.5 (0.5)	0.8	2	0.416
Women	151	8.6 (0.3)	107	8.4 (0.3)	81	7.7 (0.4)	2.1	2	0.123
Simple effects, F (df) p		9.5 (1) **0.002**		5.4 (1) **0.021**		0.1 (1) 0.702			
Fixed effects, F (df) p		Time=0.0 (2) 0.968; Groups=5.6 (1) **0.018**; Time*Groups=2.5 (2) 0.076							

F, ANOVA, linear mixed model; Means, estimated marginal; SE, standard error; Significant with Bonferroni *post hoc* contrasts: [a]1-2, [b]1-3, [c]2-3. AQ-D, Anosognosia Questionnaire-Dementia; ZBI, Zarit Burden Interview; GDS-d, Geriatric Depression Scale.

Table 4
Multivariate analysis. AQ-D ratings as dependent variable, caregiver covariates (gender, education, burden, and depression) and patient covariates (cognition and behavior)

				Parameter estimates									
	Fixed effects			Baseline			12 months			24 months			
	F	df	p	B (SE)	t	p	B (SE)	t	p	B (SE)	t	p	
Total AQ-D (DV)													
Gender (women)	2.1	3	0.091	3.72 (1.50)	2.4	**0.014**	2.33 (1.45)	1.6	0.111	2.29 (1.47)	1.5	0.123	
Education (lower)	0.4	3	0.710	–1.52 (1.55)	–0.9	0.326	–1.22 (1.54)	–0.7	0.428	–1.63 (1.61)	–1.0	0.312	
Burden (ZBI)	15.7	3	**<0.001**	0.20 (0.05)	4.0	**<0.001**	0.28 (0.04)	6.5	**<0.001**	0.16 (0.04)	3.5	**0.001**	
Depression (GDS)	2.6	3	**0.050**	–0.04 (0.21)	–0.1	0.854	–0.55 (0.21)	–2.5	**0.010**	–0.12 (0.22)	–0.5	0.576	
Cognition (MMSE)	40.8	3	**<0.001**	–1.07 (0.10)	–9.9	**<0.001**	–0.83 (0.09)	–9.2	**<0.001**	–0.51 (0.09)	–5.5	**<0.001**	
Behavior (NPI)	37.6	3	**<0.001**	0.28 (0.03)	7.3	**<0.001**	0.23 (0.03)	6.3	**<0.001**	0.29 (0.04)	7.4	**<0.001**	
Cognitive AQ-D (DV)													
Gender (women)	1.8	3	0.131	2.69 (1.33)	1.9	**0.050**	1.78 (1.29)	1.3	0.171	2.56 (1.32)	1.9	0.055	
Education (lower)	0.4	3	0.696	–1.29 (1.37)	–0.9	0.348	–0.68 (1.37)	–0.5	0.617	–1.28 (1.45)	–0.8	0.376	
Burden (ZBI)	10.3	3	**<0.001**	0.13 (0.04)	3.0	**0.002**	0.20 (0.03)	5.3	**<0.001**	0.12 (0.04)	2.9	**0.004**	
Depression (GDS)	1.4	3	0.221	–0.07 (0.19)	–0.3	0.698	–0.37 (0.19)	–1.9	0.053	–0.04 (0.20)	–0.1	0.845	
Cognition (MMSE)	51.7	3	**<0.001**	–1.03 (0.09)	–10.7	**<0.001**	–0.84 (0.08)	–10.4	**<0.001**	–0.61 (0.09)	–6.3	**<0.001**	
Behavior (NPI)	16.2	3	**<0.001**	0.18 (0.03)	5.4	**<0.001**	0.12 (0.03)	3.6	**<0.001**	0.16 (0.03)	4.4	**<0.001**	
Personality AQ-D (DV)													
Gender (women)	2.7	3	**0.043**	1.16 (0.46)	2.5	**0.013**	0.54 (0.46)	1.1	0.242	–0.32 (0.57)	–0.6	0.510	
Education (lower)	0.4	3	0.710	–0.32 (0.47)	–0.6	0.494	–0.54 (0.48)	–1.1	0.257	–0.42 (0.53)	–0.7	0.427	
Burden (ZBI)	10.7	3	**<0.001**	0.07 (0.01)	4.1	**<0.001**	0.07 (0.01)	4.7	**<0.001**	0.04 (0.01)	2.4	**0.016**	
Depression (GDS)	1.3	3	0.256	0.01 (0.07)	0.1	0.860	–0.14 (0.07)	–1.8	0.061	–0.04 (0.08)	–0.4	0.620	
Cognition (MMSE)	4.1	3	**0.007**	–0.04 (0.03)	–1.2	0.210	0.01 (0.03)	0.4	0.644	0.10 (0.03)	3.0	**0.003**	
Behavior (NPI)	59.9	3	**<0.001**	0.10 (0.01)	7.7	**<0.001**	0.12 (0.01)	8.4	**<0.001**	0.14 (0.01)	9.5	**<0.001**	

F, ANOVA, linear mixed model; B, beta; SE, standard error. DV, Dependent Variable; AQ-D, Anosognosia Questionnaire-Dementia; ZBI, Zarit Burden Interview; GDS-d, Geriatric Depression Scale; MMSE, Mini Mental Scale Examination; NPI, Neuropsychiatric Inventory.

(correlation with NPI = 0.697, 0.687, and 0.707 at baseline, 12 and 24 months) AQ-D scores. These results provide evidence supporting a mechanism in which burden related to taking care of people with dementia may lead to more negative caregiver ratings of the patients health [4, 9]. This variability is not specific of anosognosia and has been found in several other caregiver ratings including functional capacities [4, 21, 22], neuropsychiatric symptoms [4, 21, 23], and quality of life [4, 24, 25].

Caregiver AQ-D ratings were not consistently associated with caregiver depression. When controlling for other covariates, the association with caregiver depression was only statistically significant at month 12 with regard to the caregiver's rating of total AQ-D. Similar trends were found for caregiver ratings of cognitive and personality AQ-D at 12 months, but these were marginally significant. In addition, the few associations found were in the opposite direction as was expected. These results do not support the idea that caregiver depression contributes to the variability in caregiver ratings of patients with dementia and contrast with previous findings [23, 24, 26].

Sociodemographic characteristics of the caregiver were not consistently associated with caregiver ratings of anosognosia. Caregiver education was not associated with any type of caregiver anosognosia rating at any point in time in the multivariate analysis. Female caregivers' total, cognitive, and personality AQ-D ratings were higher than men's at baseline but that association disappeared later, especially in the case of personality AQ-D. Women might be more affected by the personality and cognitive changes of the person with dementia given their expected gender roles as caregivers and homemakers [27, 28]. Another explanation could be that women express their emotions more through these ratings in earlier stages, but, given their emotional skills, they are able to adapt themselves to the situation better than men.

Discrepancy in the different anosognosia domains

AQ-D domains were differently associated with caregiver characteristics. In particular, caregiver depression, burden, education, and gender groups rated the cognitive AQ-D higher with time whereas this was not the case for personality AQ-D. Personality AQ-D ratings conducted by caregivers all remained stable in time except for those of burdened caregivers. This means that all ratings of cognition

worsen with time, which is consistent with the natural history of dementia [10]. Caregivers with burden, however, rate the patients' personality better as the time goes by. Behavioral and psychological symptoms of dementia have been found to be associated with caregiver burden [29] which may account for the differences at baseline. However, the symptoms included in the AQ-D are more common in early dementia stages [30] and diminish in later stages, which would explain the decrease in ratings of personality AQ-D of burdened caregivers.

Limitations

Despite the fact that longitudinal studies can provide a fuller picture compared to cross-sectional studies, attrition rate was 42.5% at 24 months. Given the differential in severity at baseline, this could have affected both estimates and associations by decreasing the numbers of those with a more severe dementia. It is also important to note that given the observational nature of the study, causality cannot be inferred. Indeed the patient's cognition and behavioral symptoms can lead to caregiver burden; however, the associations remained relatively strong after controlling for a performance cognition measure and a caregiver rating of the patient's behavioral symptoms. There is potential for selection bias for two reasons. First, an Alzheimer's disease diagnosis might not be completely accurate given the need for an autopsy for complete certainty. Second, this study used a clinical convenience sample not including people with undiagnosed dementia or those who for any reason did not go to the clinic. Finally, even though controlling for a performance measure of cognition has helped in telling apart the difference between caregiver rating variability and actual cognition, no performance or observational measure of behavior was assessed in this study, instead, a caregiver-rated scale was used, the NPI.

Future directions and research implications

Studies assessing anosognosia using subjective rating discrepancy scales should take several factors into account. Future anosognosia studies should control for caregiver burden and to a lesser extent, caregiver depression and gender, or at least conduct sensitivity analyses to report the possible caregiver bias. One study found that substituted caregiver judgment decreases variability in ratings associated with caregiver burden and depression [24, 31].

In this study, caregivers were asked to rate the patients' quality of life from their "own" perspectives and 'as if' they were the person with dementia. Caregivers' "own" ratings were associated with caregiver burden and depression, whereas these associations disappeared when rating "as if". Future anosognosia discrepancy studies should analyze the difference between subtracting patients' ratings from caregivers' "own" ratings and subtracting patients' ratings from caregivers' ratings "as if" they were the patient. Clinical measurements of anosognosia or patient-performance discrepancy are not free of variability either [3]. Studies would benefit, though, from assessing anosognosia in more than one way for all participants. When doing so, isomorphism in the measures used is recommended [32]. As found in the present and also previous studies, anosognosia for different dimensions can be assessed, and those different aspects can, in fact, be associated with different variables [3, 7, 33]. Studies including caregiver-patient ratings in a wide range of disease areas are needed to better understand variability in caregiver anosognosia rating of patients with dementia. Future studies should also look at which specific areas of caregiver burden are longitudinally associated with caregiver rating variability. One previous cross-sectional study using a clinical anosognosia rating approach found that not all domains are associated to anosognosia [8].

CONCLUSIONS

Our findings suggest that some caregiver characteristics are associated with variability in caregiver AQ-D ratings with regard to the patient. Caregiver burden, and to a lesser extent caregiver gender may lead to a more negative judgment of the patient with dementia on behalf of the caregiver. If caregiver characteristics lead to a more negative judgment, they have the potential to bias the scores in subjective rating discrepancy anosognosia scales. Future studies will determine whether a bias exists or not. In the meantime, caution is advisable when drawing conclusions from subjective rating discrepancy anosognosia scales.

ACKNOWLEDGMENTS

REFERENCES

[1] Migliorelli R, Tesón A, Sabe L, Petracca G, Petracchi M, Leiguarda R, Starkstein SE (1995) Anosognosia in Alzheimer's disease: A study of associated factors. *J Neuropsychiatry Clin Neurosci* **7**, 338-344.

[2] Hannesdottir K, Morris RG (2007) Primary and secondary anosognosia for memory impairment in patients with Alzheimer's disease. *Cortex* **43**, 1020-1030.

[3] Clare L (2004) Awareness in early-stage Alzheimer's disease: A review of methods and evidence. *Br J Clin Psychol* **43**, 177-196.

[4] Conde-Sala JL, Reñé-Ramírez R, Turró-Garriga O, Gascón-Bayarri J, Juncadella-Puig M, Moreno-Cordón L, Viñas-Diez V, Vilalta-Franch J, Garre-Olmo J (2013) Factors associated with the variability in caregiver assessments of the capacities of patients with Alzheimer disease. *J Geriatr Psychiatry Neurol* **26**, 86-94.

[5] DeBettignies BH, Mahurin RK, Pirozzolo FJ (1990) Insight for impairment in independent living skills in Alzheimer's disease and multi-infarct dementia. *J Clin Exp Neuropsychol* **12**, 355-363.

[6] Rymer S, Salloway S, Norton L, Malloy P, Correia S, Monast D (2002) Impaired awareness, behavior disturbance, and caregiver burden in Alzheimer disease. *Alzheimer Dis Assoc Disord* **16**, 248-253.

[7] Seltzer B, Vasterling JJ, Yoder J, Thompson KA (1997) Awareness of deficit in Alzheimer's disease: Relation to caregiver burden. *Gerontologist* **37**, 20-24.

[8] Turró–Garriga O, Garre-Olmo J, Vilalta-Franch J, Conde-Sala JL, Gracia Blanco M, López-Pousa S (2013) Burden associated with the presence of anosognosia in Alzheimer's disease. *Int J Geriatr Psychiatry* **28**, 291-297.

[9] Perales J (2014) On the measurement of anosognosia in Alzheimer's disease. *Rev Neurol* **59**, 576.

[10] American Psychiatric Association (2000) *Diagnostic and statistical manual-text revision (DSM-IV-TRim, 2000)*, American Psychiatric Association, Washington, DC.

[11] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* **34**, 939-939.

[12] Folstein MF, Folstein SE, McHugh PR (1975) Mini-mental state: A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12**, 189-198.

[13] Zarit SH, Todd PA, Zarit JM (1986) Subjective burden of husbands and wives as caregivers: A longitudinal study. *Gerontologist* **26**, 260-266.

[14] Marín M (1996) Adaptación para nuestro medio de la escala de sobrecarga del cuidador de Zarit. *Rev Multidiscip Gerontol* **6**, 338-345.

[15] Aguado C, Martínez J, Onís M, Dueñas R, Albert C, Espejo J (2000) Adaptación y validación al castellano de la versión abreviada de la Geriatric Depresión Scale (GDS) de Yesavage. *Aten Prim* **26**, 328.

[16] Yesavage JA, Sheikh JI (1986) 9/Geriatric Depression Scale (GDS) recent evidence and development of a shorter violence. *Clin Gerontol* **5**, 165-173.

[17] Blesa R, Pujol M, Aguilar M, Santacruz P, Bertran-Serra I, Hernández G, Sol JM, Peña-Casanova J NORMACO-DEM Group (2001) Clinical validity of the 'mini-mental state'for Spanish speaking communities. *Neuropsychologia* **39**, 1150-1157.

[18] Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J (1994) The Neuropsychiatric Inventory comprehensive assessment of psychopathology in dementia. *Neurology* **44**, 2308-2308.

[19] IBM Corp. Released 2013. IBM SPSS Statistics for Windows. Version 22.0 (2013) IBM Corp, Armonk, NY.

[20] Conde-Sala JL, Turró-Garriga O, Piñán-Hernández S, Portellano-Ortiz C, Viñas-Diez V, Gascón-Bayarri J, Reñé-Ramírez R (2015) Effects of anosognosia and neuropsychiatric symptoms on the quality of life of patients with Alzheimer's disease: A 24-month follow-up study. *Int J Geriatr Psychiatry* **31**, 109-119.

[21] Mangone CA, Sanguinetti R, Baumann P, Gonzalez R, Pereyra S, Bozzola F, Gorelick P, Sica R (1993) Influence of feelings of burden on the caregiver's perception of the patient's functional status. *Dementia* **4**, 287-293.

[22] Zanetti O, Geroldi C, Frisoni GB, Bianchetti A, Trabucchi M (1999) Contrasting results between caregiver's report and direct assessment of activities of daily living in patients affected by mild and very mild dementia: The contribution of the caregiver's personal characteristics. *J Am Geriatr Soc* **47**, 196-202.

[23] Sink KM, Covinsky KE, Barnes DE, Newcomer RJ, Yaffe K (2006) Caregiver characteristics are associated with neuropsychiatric symptoms of dementia. *J Am Geriatr Soc* **54**, 796-803.

[24] Banerjee S, Samsi K, Petrie CD, Alvir J, Treglia M, Schwam EM, del Valle M (2009) What do we know about quality of life in dementia? A review of the emerging evidence on the predictive and explanatory value of disease specific measures of health related quality of life in people with dementia. *Int J Geriatr Psychiatry* **24**, 15-24.

[25] Conde-Sala JL, Reñé-Ramírez R, Turró-Garriga O, Gascón-Bayarri J, Campdelacreu-Fumadó J, Juncadella-Puig M, Rico-Pons I, Garre-Olmo J (2014) Severity of dementia, anosognosia, and depression in relation to the quality of life of patients with Alzheimer disease: Discrepancies between patients and caregivers. *Am J Geriatr Psychiatry* **22**, 138-147.

[26] Argüelles S, Loewenstein DA, Eisdorfer C, Argüelles T (2001) Caregivers' judgments of the functional abilities of the Alzheimer's disease patient: Impact of caregivers' depression and perceived burden. *J Geriatr Psychiatry Neurol* **14**, 91-98.

[27] Gove WR, Tudor JF (1973) Adult sex roles and mental illness. *AJS* **78**, 812-835.

[28] Kessler RC, McRae JA Jr (1981) Trends in the relationship between sex and psychological distress: 1957-1976. *Am Sociol Rev* **46**, 443-452.

[29] Berger G, Bernhardt T, Weimer E, Peters J, Kratzsch T, Frolich L (2005) Longitudinal study on the relationship between symptomatology of dementia and levels of subjective burden and depression among family caregivers in memory clinic patients. *J Geriatr Psychiatry Neurol* **18**, 119-128.

[30] World Health Organization (2012) *Dementia: a public health priority*, World Health Organization.

[31] Karlawish JH, Casarett D, Klocinski J, Clark CM (2001) The relationship between caregivers' global ratings of Alzheimer's disease patients' quality of life, disease severity, and the caregiving experience. *J Am Geriatr Soc* **49**, 1066-1070.

[32] Clare L, Wilson BA, Carter G, Roth I, Hodges JR (2002) Assessing awareness in early-stage Alzheimer's disease: Development and piloting of the Memory Awareness Rating Scale. *Neuropsychol Rehabil* **12**, 341-362.

[33] Vasterling JJ, Seltzer B, Foss MW, Vanderbrook V (1995) Unawareness of deficit in Alzheimer's disease: Domain-specific differences and disease correlates. *Cogn Behav Neurol* **8**, 26-32.