

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

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## 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

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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  $\chi^2$  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 <i>n</i> = 221	12 months <i>n</i> = 166	24 months <i>n</i> = 127	Differences		
				<i>Test</i>	<i>df</i>	<i>p</i>
<b>Characteristics of the patient</b>						
Age (years), mean	77.8	78.6	79.0	1.2	2	0.279
Gender (women), <i>n</i> (%)	140 (63.3)	104 (62.7)	82 (64.6)	0.1	2	0.994
Level of education (<5), <i>n</i> (%)	140 (63.3)	108 (65.1)	84 (66.1)	0.3	2	0.861
MMSE, mean	18.3	15.7 <sup>a</sup>	12.8 <sup>b,c</sup>	59.2	2	<0.001
AQ-D total, mean	15.2	17.3 <sup>a</sup>	17.1	4.3	2	<b>0.014</b>
<b>Caregiver's rating of the patient</b>						
AQ-D total, mean	49.2	56.0 <sup>a</sup>	61.4 <sup>b,c</sup>	82.4	2	<0.001
Cognitive AQ-D, mean	41.1	48.0 <sup>a</sup>	53.7 <sup>b,c</sup>	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 <sup>b,c</sup>	5.2	2	<b>0.006</b>
<b>Anosognosia discrepancy</b>						
AQ-D total discrepancy, mean	34.0	37.7 <sup>a</sup>	40.5 <sup>b,c</sup>	17.8	2	<0.001
AQ-D total discrepancy (>32), <i>n</i> (%)	120 (54.3)	106 (63.9)	84 (66.1)	6.0	2	<b>0.049</b>
<b>Characteristics of the caregiver</b>						
Age (years), mean	63.8	65.0 <sup>a</sup>	65.8 <sup>b,c</sup>	14.5	2	0.229
Gender (women), <i>n</i> (%)	151 (68.3)	107 (64.5)	81 (63.8)	1.0	2	0.611
Level of education, (<5), <i>n</i> (%)	56 (25.3)	42 (25.3)	30 (23.6)	0.1	2	0.929
Family relationship, <i>n</i> (%)				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, <i>n</i> (%)	177 (80.1)	128 (77.1)	91 (72.7)	3.2	2	0.197
ZBI total, mean (95% CI)	49.5	53.1 <sup>a</sup>	53.8 <sup>b</sup>	8.0	2	<0.001
ZBI total (>50), <i>n</i> (%)	92 (41.6)	83 (50.0)	67 (52.8)	4.8	2	0.089
GDS-d, mean	4.2	4.7 <sup>a</sup>	4.8 <sup>b,c</sup>	5.5	2	<b>0.005</b>
GDS-d (>6), <i>n</i> (%)	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: <sup>a</sup>1-2, <sup>b</sup>1-3, <sup>c</sup>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  $p = 0.231$ ). 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) <sup>a</sup>	60	58.5 (1.2) <sup>b,c</sup>	50.3	2	<0.001		
Burden	92	53.8 (1.3)	83	59.0 (1.1) <sup>a</sup>	67	63.6 (1.1) <sup>b,c</sup>	25.7	2	<0.001		
Simple effects, F (df) p				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) <sup>a</sup>	60	51.5 (1.0) <sup>b,c</sup>	72.5	2	<0.001		
Burden	92	44.1 (1.1)	83	50.0 (0.9) <sup>a</sup>	67	55.3 (0.9) <sup>b,c</sup>	48.6	2	<0.001		
Simple effects, F (df) p				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) <sup>b</sup>	5.4	2	0.005		
Simple effects, F (df) p				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) <sup>a</sup>	82	60.0 (1.1) <sup>b,c</sup>	62.8	2	<0.001		
Depression	60	54.0 (1.7)	55	58.2 (1.3) <sup>a</sup>	45	63.6 (1.4) <sup>b,c</sup>	16.6	2	<0.001		
Simple effects, F (df) p				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) <sup>a</sup>	82	52.5 (0.9) <sup>b,c</sup>	98.4	2	<0.001		
Depression	60	45.1 (1.3)	55	49.7 (1.1) <sup>a</sup>	45	55.6 (1.1) <sup>b,c</sup>	29.1	2	<0.001		
Simple effects, F (df) p				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		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: <sup>a</sup> 1-2, <sup>b</sup> 1-3, <sup>c</sup> 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) <sup>a</sup>	30	61.7 (1.9) <sup>b,c</sup>	12.4	2	<0.001		
Higher (≥5 years)	165	48.1 (1.2)	124	55.5 (1.1) <sup>a</sup>	97	61.3 (1.1) <sup>b,c</sup>	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) <sup>a</sup>	30	54.2 (1.6) <sup>b,c</sup>	25.7	2	<0.001		
Higher (≥5 years)	165	40.4 (1.0)	124	47.7 (0.9) <sup>a</sup>	97	53.5 (0.9) <sup>b,c</sup>	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) <sup>a</sup>	46	58.8 (1.6) <sup>b,c</sup>	33.9	2	<0.001		
Women	151	50.8 (1.3)	107	57.5 (1.2) <sup>a</sup>	81	62.5 (1.1) <sup>b,c</sup>	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) <sup>a</sup>	46	51.2 (1.3) <sup>b,c</sup>	46.4	2	<0.001		
Women	151	42.2 (1.0)	107	49.2 (1.0) <sup>a</sup>	81	54.8 (0.9) <sup>b,c</sup>	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: <sup>a</sup> 1-2, <sup>b</sup> 1-3, <sup>c</sup> 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)

	Fixed effects			Parameter estimates								
				Baseline			12 months			24 months		
	<i>F</i>	<i>df</i>	<i>p</i>	B (SE)	<i>t</i>	<i>p</i>	B (SE)	<i>t</i>	<i>p</i>	B (SE)	<i>t</i>	<i>p</i>
Total AQ-D (DV)												
<i>Gender (women)</i>	2.1	3	0.091	3.72 (1.50)	2.4	<b>0.014</b>	2.33 (1.45)	1.6	0.111	2.29 (1.47)	1.5	0.123
<i>Education (lower)</i>	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
<i>Burden (ZBI)</i>	15.7	3	<b>&lt;0.001</b>	0.20 (0.05)	4.0	<b>&lt;0.001</b>	0.28 (0.04)	6.5	<b>&lt;0.001</b>	0.16 (0.04)	3.5	<b>0.001</b>
<i>Depression (GDS)</i>	2.6	3	<b>0.050</b>	-0.04 (0.21)	-0.1	0.854	-0.55 (0.21)	-2.5	<b>0.010</b>	-0.12 (0.22)	-0.5	0.576
<i>Cognition (MMSE)</i>	40.8	3	<b>&lt;0.001</b>	-1.07 (0.10)	-9.9	<b>&lt;0.001</b>	-0.83 (0.09)	-9.2	<b>&lt;0.001</b>	-0.51 (0.09)	-5.5	<b>&lt;0.001</b>
<i>Behavior (NPI)</i>	37.6	3	<b>&lt;0.001</b>	0.28 (0.03)	7.3	<b>&lt;0.001</b>	0.23 (0.03)	6.3	<b>&lt;0.001</b>	0.29 (0.04)	7.4	<b>&lt;0.001</b>
Cognitive AQ-D (DV)												
<i>Gender (women)</i>	1.8	3	0.131	2.69 (1.33)	1.9	<b>0.050</b>	1.78 (1.29)	1.3	0.171	2.56 (1.32)	1.9	0.055
<i>Education (lower)</i>	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
<i>Burden (ZBI)</i>	10.3	3	<b>&lt;0.001</b>	0.13 (0.04)	3.0	<b>0.002</b>	0.20 (0.03)	5.3	<b>&lt;0.001</b>	0.12 (0.04)	2.9	<b>0.004</b>
<i>Depression (GDS)</i>	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
<i>Cognition (MMSE)</i>	51.7	3	<b>&lt;0.001</b>	-1.03 (0.09)	-10.7	<b>&lt;0.001</b>	-0.84 (0.08)	-10.4	<b>&lt;0.001</b>	-0.61 (0.09)	-6.3	<b>&lt;0.001</b>
<i>Behavior (NPI)</i>	16.2	3	<b>&lt;0.001</b>	0.18 (0.03)	5.4	<b>&lt;0.001</b>	0.12 (0.03)	3.6	<b>&lt;0.001</b>	0.16 (0.03)	4.4	<b>&lt;0.001</b>
Personality AQ-D (DV)												
<i>Gender (women)</i>	2.7	3	<b>0.043</b>	1.16 (0.46)	2.5	<b>0.013</b>	0.54 (0.46)	1.1	0.242	-0.32 (0.57)	-0.6	0.510
<i>Education (lower)</i>	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
<i>Burden (ZBI)</i>	10.7	3	<b>&lt;0.001</b>	0.07 (0.01)	4.1	<b>&lt;0.001</b>	0.07 (0.01)	4.7	<b>&lt;0.001</b>	0.04 (0.01)	2.4	<b>0.016</b>
<i>Depression (GDS)</i>	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
<i>Cognition (MMSE)</i>	4.1	3	<b>0.007</b>	-0.04 (0.03)	-1.2	0.210	0.01 (0.03)	0.4	0.644	0.10 (0.03)	3.0	<b>0.003</b>
<i>Behavior (NPI)</i>	59.9	3	<b>&lt;0.001</b>	0.10 (0.01)	7.7	<b>&lt;0.001</b>	0.12 (0.01)	8.4	<b>&lt;0.001</b>	0.14 (0.01)	9.5	<b>&lt;0.001</b>

*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.

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