Published in final edited form as:

Int J Geriatr Psychiatry. 2016 July ; 31(7): 799–808. doi:10.1002/gps.4394.

Anosognosia increases caregiver burden in mild cognitive impairment

Mary Kelleher¹, Magdalena I. Tolea^{1,2}, James E. Galvin^{1,2}

¹Center for Cognitive Neurology, NYU Langone Medical Center, New York, NY, USA

²Charles E. Schmidt College of Medicine, Florida Atlantic University, Boca Raton, FL, USA

Abstract

Objective: Our aim is to determine the clinical correlates of impaired insight in patients with mild cognitive impairment (MCI) by examining its impact on cognition, functional status, neuropsychiatric symptoms, and caregiver burden.

Methods: The study involved 75 patients with MCI and their caregivers. Patients and caregivers underwent a comprehensive evaluation including the Clinical Dementia Rating, memory tests, and the Functional Assessment Questionnaire. Behavioral symptoms were assessed by the Neuropsychiatric Inventory, caregiver burden by the Zarit Burden Inventory, and insight by comparing self-report on the AD8 dementia screening tool to informant collateral. Patients were asked about their perceptions of their memory, and answers were compared with informants' responses. Patient mood was assessed with the Hospital Anxiety Depression Scale.

Results: There was a significant difference in AD8 scores among patients who retained versus lacked insight. Zarit Burden Inventory scores showed a significant rise as patient insight declined; the burden appeared greater on spouse versus non-spouse caregivers. Patients with poor insight had significantly worse ratings in Clinical Dementia Rating domains of personal care and judgment, while patients who retained insight had significantly higher depression and anxiety. Insight impairment was associated with worse caregiver mood.

Conclusions: Decreased patient awareness for cognitive problems was significantly associated with higher caregiver burden, independent of neuropsychiatric symptoms, functional abilities, and cognition. Personal care, judgment, and problem-solving skills could contribute to caregiver burden. Increased awareness seemed a source of patient depression and anxiety. The research highlights the need to focus on the needs of MCI caregivers and to incorporate psychosocial assessments of caregiver–patient dyads into office visits.

Keywords

mild cognitive impairment; neurocognitive disorders; anosognosia; caregiver burden; depression; patient insight

Correspondence to: J. E. Galvin, MD, MPH, GalvinJ@health.fau.edu.

[†]Access to data: Dr. Galvin takes full responsibility for the data, the analyses and interpretation, and the conduct of the research; has full access to all of the data; and has the right to publish any and all data, separate and apart from the guidance of any sponsor. Drs. Tolea and Galvin conducted the statistical analyses.

Introduction

Anosognosia, or lack of awareness of illness or deficit, is an important clinical symptom in neurocognitive disorders. Babinski originated the term to characterize the lack of awareness of left-sided hemiplegia (Babinski, 1914), linked to right frontal lobe damage associated with executive dysfunction, apathy, and disinhibition (Michon *et al.*, 1994; Kashiwa *et al.*, 2005). Its meaning has widened to include unawareness of sensory, perceptual, motor, affective, and/or cognitive deficits (Aalten *et al.*, 2005), varying by both the degree of impairment and the domains affected (Starkstein *et al.*, 1996).

Anosognosia is a common, well-studied symptom of dementia, especially in the later stages (Kashiwa *et al.*, 2005). Insight impairment in dementia has been associated with worsening cognition and progression of dementia, an increase in dangerous behaviors, and neuropsychiatric symptoms (Zanetti *et al.*, 1999; Starkstein *et al.*, 2007; Vogel *et al.*, 2010). Caregiver burden also increases with loss of insight, as patients become less compliant and harder to manage often leading to transitions to higher levels of care (Turro-Garriga *et al.*, 2013).

The extent of impaired insight with mild cognitive impairment (MCI), a dementia precursor, is less clear. There are fewer studies of insight in MCI, also called mild neurocognitive impairment, with most studies comparing MCI with Alzheimer's disease (AD). Some studies found more insight and an over-reporting of deficits in MCI patients, which argued against the presence of true anosognosia in MCI (Kalbe *et al.*, 2005; Hanyu *et al.*, 2007; Orfei *et al.*, 2010; Spalletta *et al.*, 2012; Lindau and Bjork, 2014). But other studies have confirmed the presence of anosognosia in patients with MCI, with a prevalence rate of up to 54% (Vogel *et al.*, 2004; Tremont and Alosco, 2011). Some studies have suggested anosognosia could be as common in MCI as in dementia (Vogel *et al.*, 2004, 2005). Certainly, in studies comparing MCI patients with healthy controls, MCI was associated with greater degrees of anosognosia than found in individuals with normal cognition (Vogel *et al.*, 2004; Berwig *et al.*, 2009; Mak *et al.*, 2015). The lack of a clear definition and method of assessing anosognosia partly could explain conflicting results. Studies have used various methods to evaluate anosognosia (Migliorelli *et al.*, 1995; Starkstein *et al.*, 2010) as well as scores based on discrepancies between patients' own reports of deficits on interview compared with collateral information and clinical assessments.

Anosognosia in MCI, when present, is significant because it could be an early symptom along the dementia continuum and may signal a conversion from MCI to dementia (Galeone *et al.*, 2011). Impaired insight into functional and olfactory deficits in MCI has been associated with progression to dementia (Devanand *et al.*, 2000; Tabert *et al.*, 2002). Anosognosia has been associated with worse cognition, including verbal and visual learning, as well as possibly behavioral symptoms (Vogel *et al.*, 2005; Tremont and Alosco, 2011; Lindau and Bjork, 2014). It also might be a precursor to the apathy commonly observed in dementia patients (Mak *et al.*, 2015).

Differences in levels of insight in MCI and insight's impact on medical care have not been as well studied in MCI as they have been in dementia. This study looked at levels of patient

insight in MCI and compared them with various key clinical correlates including cognition, functional abilities, mood and behavioral symptoms, and caregiver burden. We hypothesized that these domains would worsen with the loss of insight in MCI because that is what happens in dementia, which MCI commonly precedes.

Methods

Study participants.

Participants were drawn from a consecutive series of 266 new patient referrals from September 2013 to December 2014. Seventy-five individuals were diagnosed with MCI using the Petersen criteria (Petersen *et al.*, 2001): of these cases, 57 were thought to be due to AD (Albert *et al.*, 2011) and 18 were attributed to other disorders (depression, Lewy body disease, etc.). Assessments were completed by a transdisciplinary team of a neurologist, geriatric nurse practitioner, social worker, and psychometrician, and all components of the assessment were part of standard of care at our center (Galvin *et al.*, 2014). During the 75- to 90-min visit, the patient and caregiver underwent a comprehensive evaluation including the Clinical Dementia Rating and its sum of boxes (CDR-SB) (Morris, 1993), mood assessment, neuropsychological testing, caregiver ratings of behavior and function, and caregiver burden and depression. The study was approved by the NYU Langone Medical Center Institutional Review Board.

Clinical assessment.

Independent semi-structured interviews were conducted with the patient and a collateral source. The Clinical Dementia Rating (CDR) (Morris, 1993) was used to determine the presence or absence of cognitive impairment and to stage its severity. The CDR rates cognitive function in six categories (memory, orientation, judgment and problem solving, and performance in community affairs, home and hobbies, and personal care); a global CDR 0 indicates no dementia; CDR 0.5 represents either MCI or very mild dementia; CDR 1, 2, or 3 corresponds to mild, moderate, or severe dementia. Diagnoses were determined using standard criteria for MCI (Petersen *et al.*, 2001; Albert *et al.*, 2011) and for dementia etiologies (i.e., AD (McKhann *et al.*, 2011), Lewy body dementia (McKeith *et al.*, 2005), etc.). Only cases of MCI were considered in this report. Extraparamidal features were assessed with the Movement Disorders Society-Unified Parkinson's Disease Rating Scale, motor subscale part III (Goetz *et al.*, 2007). The Charlson comorbidity index (Charlson *et al.*, 1987) was completed to assess the potential impact of comorbid medical conditions on the patient's cognitive status and insight.

Caregiver evaluation.

Caregivers completed evaluations to determine the presence and severity of non-cognitive symptoms observed in the patient and their impact on the caregiver. The Neuropsychiatric Inventory (NPI) (Kaufer *et al.*, 2000) assessed behavior, the Epworth sleepiness scale (Johns, 1991) assessed daytime sleepiness, and a caregiver rating of daytime alertness was collected using a 1–10 Likert scale (Boeve *et al.*, 2013). The Functional Activities Questionnaire (FAQ) (Pfeffer *et al.*, 1982) was used to rate performance of activities of daily living. The

Zarit Burden Inventory (ZBI) (Herbert *et al.*, 2000) evaluated caregiver burden and the Personal Health Questionnaire (Kroenke *et al.*, 2009) assessed caregiver depression.

Neuropsychological evaluation.

Each patient was administered a 30-min test battery at the time of the office visit to assess their cognitive status. The psychometrician was unaware of the diagnosis or CDR. A brief global assessment was performed using the mini-mental state exam (MMSE) (Folstein *et al.*, 1975). The test battery included measures of episodic memory (Hopkins Verbal Learning Task) (Brandt *et al.*, 1992), semantic memory (animal fluency) (Thurstone and Thurstone, 1949), 15-item Boston Naming Test (Goodglass and Kaplan, 1983), and working memory (Letter–Number Sequencing) (Crowe, 2000). Two-timed measures (Reitan, 1958) addressed psychomotor and executive abilities: Trailmaking A and Trailmaking B. Construction was assessed with the clock drawing task (Yamamoto *et al.*, 2004). Mood was assessed with the Hospital Anxiety Depression Scale (Snaith, 2003) providing subscale scores for depression and anxiety.

Determination of insight.

Prior to completing neuropsychological testing, the patient completed a self-report version of the AD8 (Galvin *et al.*, 2005, 2007). The AD8 is an eight-item yes/no questionnaire that captures change in cognitive and functional domains. Originally designed as an informant interview, the AD8 was validated as a patient self-report with scores greater than 2 suggesting cognitive impairment and is highly correlated with the CDR (Galvin *et al.*, 2007). In this study, the patient AD8 was used to assess whether the patient endorsed similar cognitive and functional complaints obtained from the informant during an independent interview. During the mental status evaluation by the neurologist, the patient was asked the following questions: “How is your health?”, “Why are you here today?”, “Are you having a problem with your memory or thinking?”, and “How long have you noticed these changes?” The answers were compared with the history obtained during the independent informant interview. Based on the answers to these questions and the patients self-endorsement on the AD8, a variable rating insight was created: 0 = patient demonstrates good insight into cognitive problems and their potential implications (good insight, $n = 37$); 1 = patient demonstrates limited insight into cognitive problems and grasp of implications (limited insight, $n = 28$); 2 = patient denies cognitive problems and demonstrates little to no understanding of their potential implications (poor insight, $n = 10$).

Statistical analyses.

Analyses were conducted in SAS (Cary, NC, USA). Descriptive statistics were used to present clinical characteristics of patients, informant ratings, CDR, CDR-SB, and neuropsychological testing. One-way analysis of variance with Bonferroni *post hoc* tests were used for continuous data, and Chi-squared analyses were used for categorical data. Strength of association between variables was examined with Spearman correlation coefficients. Given our ordinal level outcome (0 = poor insight; 1 = limited insight; 2 = good insight), we employed a two-step model building approach using ordinal regression with a logit link option to assess the best predictors of patient insight. Next, we ran a series of hierarchical ordinal regression models to identify the most parsimonious model predicting

good insight by adding the patient-related predictors identified in the first step one factor at a time (step 2). Last, using general linear models, we assessed the effect of patient insight on caregiver burden and mood and whether these associations vary by caregiver type (i.e., spouse versus non-spouse).

Results

Sample characteristics

The mean age of the cohort was 76.4 ± 8.8 years (range 50–93) with a mean education of 15.9 ± 2.9 years (range 9–22), a mean Charlson comorbidity index of 1.9 ± 1.3 (range 0–7), a mean MMSE of 26.2 ± 3.1 (range 16–30), and 53.3% were female. The racial and ethnic make-up of the sample was 90.7% White, non-Hispanic, 4.0% African American, and 5.3% Hispanic. Caregivers were divided into 39 spouse/significant other caregivers and 36 non-spouse caregivers (22 adult children, 4 other relatives, and 10 friends). The clinician's impression was 49.3% had maintained good insight, 37.3% had limited insight, and 13.3% had poor insight. There were no significant differences between groups by gender, race/ethnicity, education level, comorbidities, physical functionality, or extrapyramidal features of patient or by type of informant. Individuals with impaired insight were older ($p = 0.007$). Groups were similar in MMSE; neuropsychological testing; and caregiver-reported FAQ, NPI, daytime sleepiness, and alertness scores. Patient-reported AD8 scores were significantly different between patients with insight and those lacking insight ($p < 0.001$). Sample characteristics and ratings are presented in Table 1.

Characteristics of mild cognitive impairment patients with anosognosia

Although the global CDR were not different (Table 1), there were differences in individual domains with patients lacking insight having a higher CDR sum of boxes ($p = 0.01$) and worse ratings in judgment and problem solving ($p = 0.01$) and personal care ($p = 0.003$). Patient with preserved insight had greater self-reported depressive features ($p = 0.01$) and anxiety ($p = 0.009$) than those who lacked insight and endorsed more cognitive and functional features on the AD8 ($p < 0.001$). Notably, lack of insight led to significantly increased perceived caregiver burden based on ZBI score ($p = 0.01$) but not caregiver depression ($p = 0.09$). Increased patient scores on the AD8 correlated with increased patient endorsement of anxiety ($R = 0.300$, $p = 0.03$) and depression ($R = 0.405$, $p = 0.003$) symptoms and was inversely proportional to caregiver endorsement of burden ($R = -0.343$, $p = 0.02$).

Predictors of patient insight

Using two-step model building approach with ordinal regression, patient-related and caregiver-related characteristics found to differ in terms of absolute mean values (Table 1) were assessed individually with adjustment for the effect of age, gender, and education (step 1). Patients with higher scores on anxiety, depression, and AD8 were more likely to have good insight (versus limited or poor insight), while higher cognitive impairment and poor caregiver mood and burden were associated with a lower likelihood of good insight (Table 2). For example, each one unit increase in the AD8 score was associated with a 67%

increase in the odds of good insight. In contrast, the odds of good insight go down 10% with each one unit increase in caregiver depression.

Next, we ran a series of hierarchical ordinal regression models to identify the most parsimonious model predicting good insight by adding the patient-related predictors identified in the first step one factor at a time (step 2). The results suggest that AD8 along with the judgment and personal care CDR items best predict level of insight with AD8 positively and CDR negatively associated with insight. A separate model in which global rather than individual cognitive domains is assessed showed a slightly stronger effect for AD8 ($OR_{AD8} = 1.75$, 95% CI: 1.294–2.371) and a weaker effect of CDR ($OR_{CDR-SB} = 0.302$, 95% CI: 0.158–0.575). In contrast, patient mood does not appear to play a role once cognition and socio-demographics are factored in (Table 3). The fully adjusted model explains over 50% of the variance in patient insight.

Last, using general linear models, we assessed the effect of patient insight on caregiver burden and mood and whether these associations vary by caregiver type (i.e., spouse versus non-spouse). Poor patient insight was associated with increased caregiver burden and depression compared with good patient insight. Although an interaction term between patient insight and caregiver type did not reach statistical significance (burden: $p = 0.549$; depression: $p = 0.685$), an analysis stratified by caregiver type supports that the impact of insight on caregiver burden and mood may be stronger for spouse than non-spouse caregivers (Table 4 and Figure 1).

Discussion

Anosognosia might be less common in MCI than in dementia, but when present, it was a significant source of increased caregiver burden and depression. About half the patient sample in this study (51%) had limited or poor insight. This was similar to rates seen in other studies and supports the existence of a substantial level of insight impairment found in MCI patients (Vogel *et al.*, 2004; Tremont and Alosco, 2011; Mak *et al.*, 2015). Interestingly in this study, impaired insight was not associated with worsening cognition, greater neuropsychiatric symptoms or functional impairment, as dementia and some MCI studies have found (Harwood *et al.*, 2000; Vogel *et al.*, 2010; Mak *et al.*, 2015). There was no significant difference in MMSE, FAQ, or NPI scores between those with intact versus impaired insight in this study. This might have been due to the relatively high average MMSE score of this patient sample that thus captured a very early stage of the disease before the development of functional or behavioral deficits. In addition, while impaired insight in MCI has been linked to worse cognition and depression, MCI patients by definition do not have the frank behavioral or functional disturbances often seen in dementia.

However, insight impairment was accompanied by a significant rise in the ZBI score in this study, highlighting the toll on MCI caregivers. The association is curious precisely because it appeared to be independent of patients' cognitive, functional and behavioral deficits, all of which contribute to caregiver burden in dementia (Seltzer *et al.*, 1997; Vogel *et al.*, 2010; Turro-Garriga *et al.*, 2013). Behavioral symptoms, such as agitation and apathy, in particular

cause the greatest caregiver burden in dementia (Matsumoto *et al.*, 2007; Germain *et al.*, 2009; Rocco *et al.*, 2010).

The source of caregiver burden in MCI instead could lie in the emotional, psychological nature of the stress measured by the ZBI, like feeling angry or strained around relatives, juggling caretaking versus personal responsibilities, limiting socializing, and feeling uncertain about what to do about the patient (Herbert *et al.*, 2000). A patient with poor insight might irritate caregivers who do not understand a patient's diminishing self-awareness, puzzle people who could be new to or unprepared for the caregiver role, and alarm family who have the disturbing experience of watching a loved one lose their fundamental sense of self. These caregivers might cancel social plans or neglect their own health as they assume greater responsibility for the patient, increasing their personal burden. Patients with poor insight could refuse to go to physician appointments or comply with treatment recommendations, angering or saddening caregivers. Prior research has linked poor insight to higher caregiver burden in MCI as well as AD, where it can create social isolation and tension (Seltzer *et al.*, 1997; Turro-Garriga *et al.*, 2013; Mak *et al.*, 2015).

Another explanation for the inverse relationship between insight impairment and caregiver burden in MCI was found in patients' significantly worse scores in the individual CDR domains of judgment and problem-solving skills and personal care. These domains include solving problems, managing financial affairs, and tending to self-care. Deterioration in such abilities, essential to perform instrumental activities of daily living (IADLs), could force caregivers to assume greater time-consuming household and personal responsibilities like making financial decisions or assisting with grooming. Such deficits are consistent with the subtle functional disturbances allowed by the current definition of MCI (Petersen *et al.*, 2001) and appear to be sufficient to strain caregivers. Decreased awareness of emergent cognitive and functional deficits could limit patients' capacity to gauge and solve problems, or grasp the subtleties of grooming. The FAQ, which assesses the ability to perform more concrete, discrete IADLs living like preparing a balanced meal, or turning off the stove (Pfeffer *et al.*, 1982), might miss a slight decline in a nebulous capacity like problem solving.

Other studies already have shown the presence of caregiver burden in MCI and the need to provide support services for these people. These studies tied caregiver burden, which in some studies equaled dementia levels, to patients' behavioral, memory, and functional impairments (Ryan *et al.*, 2012; Hayashi *et al.*, 2013; Seeher *et al.*, 2013; Paradise *et al.*, 2014). The research highlights the need to target interventions aimed at the specific sources of MCI caregiver burden, such as challenging behavioral symptoms and growing functional dependence, and to study the long-term outcome of mounting burden on this cohort (Gallagher *et al.*, 2011; Seeher *et al.*, 2013). It also shows the need to incorporate psychological assessment of patient-caregiver dyads into office visits, since patient and caregiver perceptions of cognitive impairment at the earliest stages differ.

A decline in patient insight also predicted worse caregiver mood, in addition to burden. This confirms other reports of higher rates of depression among MCI caregivers (Seeher *et al.*, 2013). MCI patients who maintained the greatest insight by self-reporting cognitive

symptoms also reported significantly greater depression and anxiety although this did not burden the caregiver. Depression, which is common in MCI, could itself predict conversion to dementia (Van der Mussele *et al.*, 2014). MCI patients with worse memory deficits have been found to have fewer depressive symptoms, while those with non-amnesic MCI were more depressed (Bruce *et al.*, 2008). Likely, deficits disturb patients less as they lose insight into them; perhaps this marks a shift from anosognosia to apathy as MCI changes to dementia (Mak *et al.*, 2015).

Our study also showed patient insight might have greater impact on spouse compared with non-spouse caregivers. This might be due to cohabitation and daily contact between spouses. This was interesting given the lack of significant differences in caregiver ratings of neuropsychiatric symptoms or functional impairment, suggesting neither behavior nor IADLs contributed to the caregivers' increased perception of burden.

One limitation in this study is that there is no universal measure for rating patients' insight. The Anosognosia Questionnaire for Dementia (Migliorelli *et al.*, 1995; Starkstein *et al.*, 2010) was developed to explore the extent of cognitive and behavioral symptoms as rated by both the patient and the caregiver. The level of insight is often taken as the discrepancy between informant and patient scores. While appropriate in a research study, this 30-item questionnaire is impractical in a clinical setting. Our method was similar to the Clinical Insight Rating Scale (Ott *et al.*, 1996) that taps into reasons for the medical visit, illness duration, onset and progression of cognitive deficits, and effect of functional deficits on activities of everyday living. It also is unclear if the term anosognosia is appropriate for MCI as patients exhibit decreased awareness of their symptoms rather than a true denial (Orfei *et al.*, 2010).

Although not designed for this purpose, the patient-reported AD8 (Galvin *et al.*, 2005, 2007) provided a useful rating of the patient's perception of cognitive and functional impairment and could potentially be used in a clinical setting for a quick assessment of insight. As this is a cross-sectional study, one next step would be to demonstrate the longitudinal effects of anosognosia on caregiver outcomes and whether they change with progression of patients to AD or related neurocognitive disorders.

A strength of this study was the comprehensive evaluation it involved. In establishing the impact of anosognosia on caregivers, hypotheses were tested in a "real-world" clinic setting with patients who were referred from the community rather than in a research sample. Our clinic sample was a consecutive series of patients and had an admixture of gender; education; comorbidities; cognitive, behavioral, affective, and motor symptoms; and diagnoses. A disadvantage was that the cohort was largely White and well educated—different patient populations may experience perceptions of caregiver burden in a different fashion.

Our findings emphasize the need to better understand the concerns of caregivers and provide enhanced social support programs to reduce burden and depression. These programs have been successful for caregivers of AD patients (Gaugler *et al.*, 2010, 2011) and should be extended to include caregivers of MCI patients. Further research is needed to better

characterize the association between patient insight and caregiver burden in MCI, to reduce the illness burden on patients and caregivers.

Acknowledgements

This project was supported by grants from the National Institutes of Health (R01 AG040211) and the New York State Department of Health (DOH-2011-1004010353 and DOH-2014-1306060830).

Conflict of interest

Dr. Kelleher has nothing to disclose. Dr. Tolea has nothing to disclose. Dr. Galvin received research support from the National Institutes of Health (R01 AG040211), Michael J Fox Foundation, the New York State Department of Health (DOH-2011-1004010353 and DOH-2014-1306060830), and the Morris and Alma Schapiro Fund; and serves as an investigator in clinical trials sponsored by the National Institutes of Health, Merck, Eli Lilly, Takeda, Zinfandel, Neuronix, Lundbeck, and Medivante. Dr. Galvin holds the copyright for the AD8 in conjunction with other investigators at Washington University in St. Louis.

References

- Aalten P, van Valen E, Clare L, Kenny G, Verhey F. 2005. Awareness in dementia: a review of clinical correlates. *Aging Ment Health*9(5): 414–422. [PubMed: 16024400]
- Albert MS, DeKosky ST, Dickson D, et al. 2011. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*7: 270–279. [PubMed: 21514249]
- Babinski MJ. 1914. Contribution à l'étude des troubles mentaux dans l'hémiplégie organique cérébrale (anosognosie). *Rev Neurol*27: 845–848.
- Berwig M, Leicht H, Gertz HJ. 2009. Critical evaluation of self-rated quality of life in mild cognitive impairment and Alzheimer's disease—further evidence for the impact of anosognosia and global cognitive impairment. *J Nutr Health Aging*13(3): 226–230. [PubMed: 19262958]
- Boeve BF, Molano JR, Ferman TJ, et al. 2013. Validation of the Mayo Sleep Questionnaire to screen for REM sleep behavior disorder in a community-based sample. *J Clin Sleep Med*9: 475–480. [PubMed: 23674939]
- Brandt J, Corwin J, Krafft L. 1992. Is verbal recognition memory really different in Huntington's and Alzheimer's disease? *J Clin Exp Neuropsychol*14: 773–784.
- Bruce JM, Bhalla R, Westervelt HJ, et al. 2008. Neuropsychological correlates of self-reported depression and self-reported cognition among patients with mild cognitive impairment. *J Geriatr Psychiatry Neurol*21(1): 34–40. [PubMed: 18287168]
- Charlson ME, Pompei P, Ales KL, MacKenzie CR. 1987. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*40: 373–383. [PubMed: 3558716]
- Crowe SF. 2000. Does the letter number sequencing task measure anything more than digit span? *Assessment*7: 113–117. [PubMed: 10868248]
- Devanand DP, Michaels-Marston KS, Liu X, et al. 2000. Olfactory deficits in patients with mild cognitive impairment predict Alzheimer's disease at follow-up. *Am J Psychiatry*157(9): 1399–1405. [PubMed: 10964854]
- 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. [PubMed: 1202204]
- Galeone F, Pappalardo S, Chieffi S, Iavarone A, Carlomagno S. 2011. Anosognosia for memory deficit in amnesic mild cognitive impairment and Alzheimer's disease. *Int J Geriatr Psychiatry*26: 695–701. [PubMed: 21495076]
- Gallagher D, Mhaolain AN, Crosby L, et al. 2011. Dependence and caregiver burden in Alzheimer's disease and mild cognitive impairment. *Am J Alzheimers Dis Other Dement*26(2): 110–114. [PubMed: 21233138]

- Galvin JE, Roe CM, Powlishta KK, et al. 2005. The AD8: a brief informant interview to detect dementia. *Neurology* 65(4): 559–564. [PubMed: 16116116]
- Galvin JE, Roe CM, Coats MA, Morris JC. 2007. Patient's rating of cognitive ability: using the AD8, a brief informant interview, as a self-rating tool to detect dementia. *Arch Neurol* 64(5): 725–730. [PubMed: 17502472]
- Galvin JE, Valois L, Zweig Y. 2014. Collaborative transdisciplinary team approach for dementia care. *Neurodegener Dis Manag* 4: 455–469. [PubMed: 25531688]
- Gaugler JE, Mittelman MS, Hepburn K, Newcomer R. 2010. Clinically significant changes in burden and depression among dementia caregivers following nursing home admission. *BMC Med* 8: 85. [PubMed: 21167022]
- Gaugler JE, Roth DL, Haley WE, Mittelman MS. 2011. Modeling trajectories and transitions: results from the New York University caregiver intervention. *Nurs Res* 60(3 Suppl): S28–S37. [PubMed: 21543959]
- Germain S, Adam S, Olivier C, et al. 2009. Does cognitive impairment influence burden in caregivers of patients with Alzheimer's disease? *J Alzheimers Dis* 17: 105–114. [PubMed: 19494435]
- Goetz CG, Fahn S, Martinez-Martin P, et al. 2007. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDSUPDRS): process, format, and clinimetric testing plan. *Mov Disord* 22: 41–47. [PubMed: 17115387]
- Goodglass H, Kaplan E. 1983. *The Assessment of Aphasia and Related Disorders*. 2nd edn. Philadelphia: Lea & Febiger.
- Hanyu H, Sakurai H, Hirao K, Shimizu S, Iwamoto T. 2007. Unawareness of memory deficits depending on cerebral perfusion pattern in mild cognitive impairment. *J Am Geriatr Soc* 55(3): 470–471. [PubMed: 17341256]
- Harwood DG, Sultzer DL, Wheatley MA. 2000. Impaired insight in Alzheimer's disease: association with cognitive deficits, psychiatric symptoms, behavioral disturbances. *Neuropsychiatry Neuropsychol Behav Neurol* 13: 83–88. [PubMed: 10780626]
- Hayashi S, Terada S, Nagao S, et al. 2013. Burden of caregivers for patients with mild cognitive impairment in Japan. *Int Psychogeriatr* 25(8): 1357–1363. [PubMed: 23597161]
- Herbert R, Bravo G, Preville M. 2000. Reliability, validity, and reference values of the Zarit Burden Interview for assessing informal caregivers of community-dwelling older persons with dementia. *Can J Aging* 19: 494–507.
- Johns MW. 1991. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 14: 540–545. [PubMed: 1798888]
- Kalbe E, Salmon E, Perani D, et al. 2005. Anosognosia in very mild Alzheimer's disease but not in mild cognitive impairment. *Dement Geriatr Cogn Disord* 19(5–6): 349–356. [PubMed: 15802909]
- Kashiwa Y, Kitabayashi Y, Narumoto J, et al. 2005. Anosognosia in Alzheimer's disease: association with patient characteristics, psychiatric symptoms and cognitive deficits. *Psychiatry Clin Neurosci* 59: 697–704. [PubMed: 16401246]
- Kaufer DI, Cummings JL, Ketchel P, et al. 2000. Validation of the NPI-Q, a brief clinical form of the neuropsychiatric inventory. *J Neuropsychiatry Clin Neurosci* 12: 233–239. [PubMed: 11001602]
- Kroenke K, Spitzer RL, Williams JB, Löwe B. 2009. An ultra-brief screening scale for anxiety and depression: the PHQ-4. *Psychosomatics* 50: 613–621. [PubMed: 19996233]
- Lindau M, Bjork R. 2014. Anosognosia and anosodiaphoria in mild cognitive impairment and Alzheimer's disease. *Dement Geriatr Cogn Dis Extra* 4(3): 465–480. [PubMed: 25759713]
- Mak E, Chin R, Ng LT, Yeo D, Hameed S. 2015. Clinical associations of anosognosia in mild cognitive impairment and Alzheimer's disease. *Int J Geriatr Psychiatry*. DOI:10.1002/gps.4275.
- Matsumoto M, Ikeda M, Fukuhara R, et al. 2007. Caregiver burden associated with behavioral and psychological symptoms of dementia in elderly people in the local community. *Dement Geriatr Cogn Disord* 23: 219–224. [PubMed: 17299264]
- McKeith IG, Dickson DW, Lowe J, et al. 2005. Consortium on DLB. Diagnosis and management of dementia with Lewy bodies: third report of the DLB consortium. *Neurology* 65: 1863–1872. [PubMed: 16237129]
- McKhann GM, Knopman DS, Chertkow H, et al. 2011. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association

workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*7: 263–269. [PubMed: 21514250]

- Michon A, Deweer B, Pillon B, Agid Y, Dubois B. 1994. Relation of anosognosia to frontal lobe dysfunction in Alzheimer's disease. *J Neurol Neurosurg Psychiatr*57: 805–809.
- Migliorelli R, Tesón A, Sabe L, et al. 1995. Anosognosia in Alzheimer's disease: a study of associated factors. *J Neuropsychiatry Clin Neurosci*7(3): 338–344. [PubMed: 7580194]
- Morris JC. 1993. The Clinical Dementia Rating (CDR)—current version and scoring rules. *Neurology*43: 2412–2414.
- Orfei MD, Varsi AE, Blundo C, et al. 2010. Anosognosia in mild cognitive impairment and mild Alzheimer's disease: frequency and neuropsychological correlates. *Am J Geriatr Psychiatry*18(12): 1133–1140. [PubMed: 20808100]
- Ott BR, Lafleche G, Whelihan WM, et al. 1996. Impaired awareness of deficits in Alzheimer disease. *Alzheimer Dis Assoc Disord*10: 68–76. [PubMed: 8727167]
- Paradise M, McCade D, Hickie IB, et al. 2014. Caregiver burden in mild cognitive impairment. *Aging Ment Health*. DOI:10.1080/13607863.2014.915922.
- Petersen RC, Doody R, Kutz A, et al. 2001. Current concepts in mild cognitive impairment. *Arch Neurol*58: 1985–1992. [PubMed: 11735772]
- Pfeffer RI, Kurosaki TT, Harrah CH Jr, Chance JM, Filos S. 1982. Measurement of functional activities in older adults in the community. *J Gerontol*37: 323–329. [PubMed: 7069156]
- Reitan RM. 1958. Validity of the Trail Making Test as an indicator of organic brain damage. *Percept Mot Skills*8: 271–276.
- Rocco P, Leotta D, Liffredo C, et al. 2010. Neuropsychiatric symptoms underlying caregiver stress and insight in Alzheimer's disease. *Dement Geriatr Cogn Disord*30: 57–63. [PubMed: 20689284]
- Ryan KA, Weldon A, Persad C, et al. 2012. Neuropsychiatric symptoms and executive functioning in patients with mild cognitive impairment: relationship to caregiver burden. *Dement Geriatr Cogn Disord*34(0): 206–215. [PubMed: 23128102]
- Seeher K, Low L-F, Reppermund S, Brodaty H. 2013. Predictors and outcomes for caregivers of people with mild cognitive impairment: a systematic literature review. *Alzheimer's Dement*9: 346–355. [PubMed: 23123229]
- Seltzer B, Vasterling JJ, Yoder J, Thompson K. 1997. Awareness of deficit in Alzheimer's disease: relation to caregiver burden. *Gerontologist*37(1): 20–24. [PubMed: 9046701]
- Snaith RP. 2003. The Hospital Anxiety and Depression Scale. *Health Qual Life Outcomes*1: 29. [PubMed: 12914662]
- Spalletta G, Girardi P, Caltagirone C, Orfei MD. 2012. Anosognosia and neuropsychiatric symptoms and disorders in mild Alzheimer disease and mild cognitive impairment. *J Alzheimers Dis*29(4): 761–772. [PubMed: 22349686]
- Starkstein SE, Sabe L, Chmerinski E, Jason L, Leiguarda R. 1996. Two domains of anosognosia in Alzheimer's disease. *J Neurol Neurosurg Psychiatry*61: 485–490. [PubMed: 8937343]
- Starkstein SE, Jorge R, Mizrahi R, Adrian J, Robinson RG. 2007. Insight and danger in Alzheimer's disease. *Eur J Neurol*14: 455–460. [PubMed: 17388998]
- Starkstein SE, Brockman S, Bruce D, Petracca G. 2010. Anosognosia is a significant predictor of apathy in Alzheimer's disease. *J Neuropsychiatry Clin Neurosci*22(4): 378–383. [PubMed: 21037121]
- Tabert MH, Albert SM, Borukhova-Milov BA, et al. 2002. Functional deficits in patients with mild cognitive impairment: prediction of AD. *Neurology*58: 758–764. [PubMed: 11889240]
- Thurstone LL, Thurstone LG. 1949. Examiner Manual for the SRA Primary Mental Abilities Test. Science Research Associates: Chicago.
- Tremont G, Alosco ML. 2011. Relationship between cognition and awareness of deficit in mild cognitive impairment. *Int J Geriatr Psychiatry*26(3): 299–306. [PubMed: 20623477]
- Turro-Garriga O, Garre-Olmo J, Vilalta-Franch J, et al. 2013. Burden associated with the presence of anosognosia in Alzheimer's disease. *Int J Geriatr Psychiatry*28(3): 291–297. [PubMed: 22555993]

- Author Manuscript
- Author Manuscript
- Author Manuscript
- Author Manuscript
- Van der Mussele S, Fransen E, Struyfs H, et al. 2014. Depression in mild cognitive impairment is associated with progression to Alzheimer's disease: a longitudinal study. *J Alzheimers Dis* 42: 239–250.
- Vogel A, Stokholm J, Gade A, et al. 2004. Awareness of deficits in mild cognitive impairment and Alzheimer's disease: do MCI patients have impaired insight? *Dement Geriatr Cogn Disord* 17(3): 181–187. [PubMed: 14739542]
- Vogel A, Hasselbalch S, Gade A, Ziebell M, Waldemar G. 2005. Cognitive and functional neuroimaging correlates for anosognosia in mild cognitive impairment and Alzheimer's disease. *Int J Geriatr Psychiatry* 20: 238–246. [PubMed: 15717342]
- Vogel A, Waldorff FB, Waldemar G. 2010. Impaired awareness of deficits and neuropsychiatric symptoms in early Alzheimer's disease: The Danish Alzheimer's Intervention Study (DAISY). *J Neuropsychiatry Clin Neurosci* 22(1): 93–99. [PubMed: 20160215]
- Yamamoto S, Mogi N, Umegaki H, et al. 2004. The clock drawing test as a valid screening method for mild cognitive impairment. *Dem Geriatr Cog Disord* 18: 172–179.
- Zanetti O, Vallotti B, Frisoni G, et al. 1999. Insight in dementia: when does it occur? Evidence for a non-linear relationship between insight and cognitive status. *J Gerontol B Psychol Sci Soc Sci* 54B(2): P100–P106.

Key points

- Anosognosia was common among patients with mild cognitive impairment (MCI).
- Anosognosia was associated with increased caregiver burden and depression.
- Judgment and problem-solving skills deteriorated with impaired insight among patients.
- The burden on caregivers appeared greater on spouses than non-spouse caregivers.

Figure 1.

Plot of ANCOVA analyses of caregiver (A) burden and (B) depression. Clinician ratings of loss of patient insight were associated with increased caregiver burden and depression. Although an interaction term between patient insight and caregiver type did not reach statistical significance (burden: $p = 0.549$; depression: $p = 0.685$), an analysis stratified by caregiver type supports that the impact of insight on caregiver burden and mood may be stronger for spouse (blue line) than non-spouse caregivers (red line). ZBI, Zarit Burden Inventory; PHQ-4, Personal Health Questionnaire.

Table 1

Patient characteristics

Variables	Good N = 37	Limited N = 28	Poor N = 10	p-value
Patient characteristics				
Age, years	73.8 (9.2)	80.4 (7.0)	74.8 (7.9)	0.007
Education, years	16.3 (3.1)	15.7 (2.7)	15.1 (2.4)	0.47
Gender, % Female	59.5	50.0	40.0	0.49
Race, % White, non-Hispanic	94.6	85.7	90.0	0.42
Charlson comorbidity index	1.9 (1.2)	1.8 (1.2)	2.6 (1.9)	0.43
FAQ	3.2 (4.1)	3.2 (4.3)	6.4 (4.7)	0.09
UPDRS III	1.7 (3.7)	3.8 (9.0)	3.0 (3.7)	0.56
Mini-PPT	12.2 (2.4)	11.2 (2.9)	10.5 (3.2)	0.14
NPI	5.1 (4.9)	4.9 (4.8)	6.7 (3.8)	0.59
Epworth sleepiness scale	6.4 (3.5)	7.3 (4.9)	8.0 (6.4)	0.55
Alertness	7.9 (1.8)	7.7 (1.8)	6.6 (1.8)	0.13
HADS-depression	6.6 (3.9)	4.5 (3.1)	3.6 (1.8)	0.01
HADS-anxiety	7.4 (3.8)	5.0 (3.2)	4.6 (2.6)	0.009
Dementia ratings				
CDR sum boxes	1.6 (0.9)	2.0 (0.8)	2.5 (1.1)	0.01
Memory	0.5 (0.1)	0.5 (0.01)	0.5 (0.2)	0.69
Orientation	0.2 (0.2)	0.3 (0.3)	0.3 (0.2)	0.09
Judgment/problem-solving	0.4 (0.3)	0.5 (0.2)	0.6 (0.2)	0.01
Community affairs	0.2 (0.2)	0.2 (0.2)	0.3 (0.2)	0.26
Home and hobbies	0.3 (0.3)	0.3 (0.3)	0.4 (0.2)	0.41
Personal care	0.0 (0.2)	0.1 (0.3)	0.4 (0.5)	0.003
Patient AD8	3.6 (1.6)	2.1 (2.0)	1.1 (1.3)	<0.001
MMSE	26.5 (2.6)	25.8 (3.7)	26.5 (3.2)	0.66
Animal naming	16.8 (4.7)	14.3 (5.8)	18.7 (7.2)	0.06
Boston naming	11.9 (2.9)	11.3 (2.6)	11.9 (2.4)	0.68
HVLT-total	16.2 (3.6)	14.9 (3.8)	18.4 (5.7)	0.07
HVLT-delay	3.2 (2.0)	2.1 (2.6)	3.5 (3.5)	0.15

Variables	Good N = 37	Limited N = 28	Poor N = 10	p-value
HVLT-cued	9.5 (1.7)	9.0 (1.9)	9.0 (2.4)	0.52
Trailmaking A, sec	37.9 (17.8)	42.8 (19.2)	44.5 (24.1)	0.47
Trailmaking B, sec	103.8 (39.1)	113.5 (40.6)	111.4 (40.3)	0.65
Caregiver characteristics				
Relationship, % spouse	60.0	46.4	60.0	0.72
Burden	9.1 (7.5)	12.6 (8.4)	17.8 (7.4)	0.01
Depression	1.0 (2.2)	1.5 (2.4)	3.2 (2.8)	0.09

Means (standard deviations).

Significance at $p < 0.05$ is indicated in bold.

FAQ, Functional Activities Questionnaire; UPDRS, Unified Parkinson's Disease Rating Scale; Mini-PPT, mini physical performance test; NPI, Neuropsychiatric Inventory; HADS, Hospital Anxiety and Depression Scale; CDR, Clinical Dementia Rating; MMSE, mini-mental state exam, HVLT, Hopkins Verbal Learning Test.

Table 2

Ordinal regression predictors of patient insight

	Model 1: socio-demo	Model 1 + PT anxiety	Model 1 + PT depression	Model 1 + PT AD8	Model 1 + CDR-SB	Model 1 + CDR judgment	Model 1 + CDR personal care	Model 1 + CG depression	Model 1 + CG burden
Patient characteristics									
Age	0.940	0.959	0.943	0.956	0.936	0.944	0.942	0.931	0.915
Male versus Female	0.451	0.529	0.484	0.556	0.449	0.408	0.643	0.399	0.655
Education	1.107	1.109	1.200	1.070	1.104	1.169	1.079	1.172	1.193
Anxiety		1.182							
Depression			1.307						
AD8				1.669					
Clinical dementia rating									
Sum of boxes					0.410				
Judgment						0.026			
Personal care							0.142		
Caregiver characteristics									
Depression								0.900	
Burden									0.713

Values represent regression coefficients.

Significance at $p < 0.05$ is indicated in bold.

CDR, Clinical Dementia Rating; CDR-SB, Clinical Dementia Rating and its sum of boxes; PT, patient; CG, caregiver.

Table 3

Patient-related and caregiver-related predictors of insight (OR of good insight)

Characteristic	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Patient socio-demographics						
Age	0.940 (0.890; 0.993)	956 (0.900; 1.015)	0.966 (0.908; 1.028)	0.977 (0.917; 1.041)	0.984 (0.922; 1.050)	0.978 (0.915; 1.046)
Male versus Female	0.451 (0.178; 1.138)	0.556 (0.211; 1.463)	0.502 (0.182; 1.380)	0.767 (0.258; 2.278)	0.791 (0.262; 2.386)	0.794 (0.264; 2.395)
Education	1.107 (0.946; 1.296)	1.070 (0.900; 1.272)	1.150 (0.959; 1.379)	1.115 (0.923; 1.346)	1.121 (0.926; 1.356)	1.152 (0.933; 1.422)
Cognition		1.669 (1.249; 2.231)	1.618 (1.216; 2.154)	1.636 (1.221; 2.191)	1.571 (1.160; 2.128)	1.511 (1.087; 2.101)
CDR judgment			0.031 (0.003; 0.322)	0.037 (0.003; 0.395)	0.029 (0.002; 0.364)	0.033 (0.003; 0.426)
CDR personal care				0.099 (0.015; 0.669)	0.109 (0.016; 0.746)	0.104 (0.015; 0.713)
Patient mood					1.147 (0.956; 1.375)	1.088 (0.854; 1.385)
Anxiety						1.098 (0.816; 1.477)
Depression						
R^2 (Nagelkerke)	0.124	0.304	0.418	0.480	0.503	0.506

Higher values indicate a higher likelihood of good insight (versus poor or limited insight) per unit change in predictor.

Confidence Intervals in bold represent significant contributors to model.

CDR, Clinical Dementia Rating; OR, odds ratio.

Table 4
Relationships between patient insight, caregiver outcomes, and caregiver relationship to patient

	Caregiver burden						Caregiver depression					
	Caregiver relation to patient			Model with interaction			Caregiver relation to patient			Model with interaction		
	All	Spouse	Non-spouse	Est. (p)	Est. (p)	Est. (p)	All	Spouse	Non-spouse	Est. (p)	Est. (p)	Est. (p)
Intercept	9.11 (<0.001)	9.42 (<0.001)	8.38 (0.014)	10.47 (0.028)	1.05 (0.057)	1.33 (0.067)	0.20 (0.789)	2.47 (0.142)				
Individual effects												
Poor insight	8.69 (0.004)	8.41 (0.022)	9.38 (0.099)	7.45 (0.409)	2.17 (0.029)	2.67 (0.050)	1.47 (0.243)	3.87 (0.192)				
Limited insight	3.47 (0.123)	1.34 (0.620)	6.35 (0.138)	-3.66 (0.596)	0.48 (0.549)	0.44 (0.699)	1.05 (0.282)	-1.16 (0.948)				
Good insight	0	0	0	0	0	0	0	0				
Non-spouse versus spouse												
Interaction terms												
Poor insight * CG												
Limited insight * CG												
Good insight * CG												
P for insight * caregiver												
N	61	38	23	61	46	30	16	46				

CG, caregiver.