

# Delusions and Hallucinations Are Associated With Worse Outcome in Alzheimer Disease

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**Background:** Delusions and hallucinations are common in Alzheimer disease (AD) and there are conflicting reports regarding their ability to predict cognitive decline, functional decline, and institutionalization. According to all previous literature, they are not associated with mortality.

**Objective:** To examine whether the presence of delusions or hallucinations has predictive value for important outcomes in AD.

**Design, Setting, and Participants:** A total of 456 patients with AD at early stages (mean Folstein Mini-Mental State Examination [MMSE] score of 21 of 30 at entry) were recruited and followed up semiannually for up to 14 years (mean, 4.5 years) in 5 university-based AD centers in the United States and Europe. Using the Columbia University Scale for Psychopathology in AD (administered every 6 months, for a total of 3266 visit-assessments, average of 7.2 per patient), the presence of delusions and hallucinations was extracted and examined as time-dependent predictors in Cox models. The models controlled for cohort effect, recruitment center, informant status, sex, age, education, a comorbidity index, baseline cognitive and baseline functional performance, behavioral symptoms, and use of neuroleptics and cholinesterase inhibitors.

**Main Outcome Measures:** Cognitive (Columbia MMSE score of  $\leq 20/57$  [approximate Folstein MMSE score of  $\leq 10/30$ ]), functional (Blessed Dementia Rating Scale [parts I and II] score of  $\geq 10$ ), institutionalization equivalent index, and death.

**Results:** During the full course of follow-up, 38% of patients reached the cognitive, 41% the functional, 54% the institutionalization, and 49% the mortality end point. Delusions were noted for 34% of patients at baseline and 70% at any evaluation. Their presence was associated with increased risk for cognitive (risk ratio [RR], 1.50; 95% confidence interval [CI], 1.07-2.08) and functional decline (RR, 1.41; 95% CI, 1.02-1.94). Hallucinations were present in 7% of patients at initial visit and in 33% at any visit. Their presence was associated with increased risk for cognitive decline (RR, 1.62; 95% CI, 1.06-2.47), functional decline (RR, 2.25; 95% CI, 1.54-2.27), institutionalization (RR, 1.60; 95% CI, 1.13-2.28), and death (RR, 1.49; 95% CI, 1.03-2.14).

**Conclusions:** Delusions and hallucinations are very common in AD and predict cognitive and functional decline. Presence of hallucinations is also associated with institutionalization and mortality.

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**D**ELUSIONS AND HALLUCINATIONS are generally observed in about 1 in 4 to 1 in 3 patients with Alzheimer disease (AD),<sup>1,2</sup> with reported frequencies of delusions as high as 94%<sup>2</sup> and hallucinations as high as 69.5%.<sup>3</sup> The presence of such features in AD is not only a source of caregiver distress and financial burden (because of the need for treatment with medications and often hospitalization) but also potentially associated with important disease outcomes. Many reports have examined the association between delusions, hallucinations, and various disease outcomes with conflicting re-

sults. Some studies have reported an association between delusions or hallucinations and faster rates of cognitive decline<sup>3-13</sup> or increased risk for functional decline and institutionalization.<sup>6,7,12,14,15</sup> However, many reports failed to detect significant associations for either cognition<sup>6,14,16-19</sup> or function-institutionalization.<sup>19,20</sup> All previous studies have failed to find an association between delusions or hallucinations and mortality.<sup>7,10,21-25</sup>

Many factors contribute to the variability in reported associations. Some of the inconsistency derives from variability in the definitions of delusions and hallucinations, inconsistent consideration of treat-

ments with neuroleptics, use of standardized scales vs clinical evaluation, inclusion of subjects at varying stages of disease, and variable levels of participation and duration of follow-up. Also, many studies considered neuropsychiatric features globally, and only a few reports have focused on individual subsets (delusions and hallucinations) separately. In addition, most previous studies considered delusions and hallucinations only at a single point during the course of AD, typically at the baseline visit or less frequently at any point during the disease course. Because of the progressive nature of AD and the fact that neuroleptic medications can be effective in managing delusions and hallucinations, these features are not static and invariable but may fluctuate from visit to visit.<sup>13,26-28</sup> Therefore, consideration of delusions or hallucinations as fixed parameters may lead to biased results.

To investigate these issues, we analyzed data from a large, multicenter cohort of patients with probable AD followed from the early stages of the disease for up to 14 years. Standardized assessments of delusions and hallucinations were administered semiannually. We assessed the association between the presence of these features and 4 outcomes: cognitive end point, functional end point, institutionalization, and death. Taking advantage of the multiple assessments of delusions and hallucinations throughout the course of the disease, we were able to consider their predictive ability in a time-dependent fashion. We also considered the potential effect on the outcome of interest of medications administered for delusions and hallucinations.

## METHODS

### PARTICIPANTS

Subjects from 2 Predictors Study cohorts<sup>29,30</sup> were included in these analyses. For the predictors 1 cohort, patients were recruited and studied at 3 sites in the United States: Columbia University, New York, NY; Johns Hopkins University, Baltimore, Md; and Harvard University, Boston, Mass. For the predictors 2 cohort, in addition to the 2 United States centers, 2 sites in Europe were added: Hospital de la Salpetriere, Paris, France, and University of Thessaly, Larissa, Greece. The study was approved by the appropriate local institutional review boards.

The inclusion and exclusion criteria, as well as the evaluation procedures of the Predictors Study, have been fully described elsewhere.<sup>29,30</sup> Briefly, patients met *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition* criteria for primary degenerative dementia of the Alzheimer type and National Institute of Neurological Disorders and Stroke-Alzheimer Disease and Related Disorders Association criteria for probable AD. Enrollment required a Columbia Mini-Mental State Examination (MMSE) score of 30 or more (maximum Columbia MMSE score of 57) which is equivalent to a score of approximately 16 or more on the Folstein MMSE.<sup>31,32</sup> Exclusion criteria were diagnosis of Parkinson disease or parkinsonism at any time prior to the onset of intellectual decline; clinical or historical evidence of stroke; history of alcohol abuse or dependence; any electroconvulsive treatment within 2 years of recruitment or 10 or more electroconvulsive sessions at any time; and history or current clinical evidence of schizophrenia or schizoaffective disorder that started before the onset of intellectual decline.

## EVALUATION

At the initial visit, demographic characteristics (such as age, ethnicity, sex, and education) were recorded and disease severity features were assessed. A physician or a trained research technician administered the Columbia University Scale for Psychopathology in Alzheimer's Disease (CUSPAD)<sup>33</sup> to the informant at the initial examination and at 6-month intervals thereafter. Interrater reliabilities between the principal CUSPAD developer and a research technician (trained by the principal scale developer) have been reported as follows:  $k=0.77$  for delusions and  $k=1.00$  for hallucinations when concurrently rating a single interview, and  $k=0.61$  for delusions and  $k=0.63$  for hallucinations when conducting separate interviews.<sup>33</sup>

Most CUSPAD items are scored dichotomously (ie, present or absent). For delusions, the categories were general delusions (strange ideas or unusual beliefs); paranoid (people are stealing things, or unfaithful wife/husband, or unfounded suspicions); abandonment (accusing caregiver of plotting to leave him/her); somatic (the patient has cancer or other physical illness); misidentification (people are in the house when nobody is there, or that someone else is in the mirror, or that spouse/caregiver is an imposter or that the patient's house is not his/her home, or that the characters on television are real); and a miscellaneous category. A patient was considered to have delusions if he/she had at least 1 of the previously described types of delusions. Initially, delusions were considered present irrespective of frequency of occurrence (transient [ $<3$ /week] or persistent [ $\geq 3$ /week]). In subsequent analyses, we considered a 3-level severity of delusions (absent, transient, or persistent). Four categories of hallucinations were recorded: auditory, visual, tactile, and olfactory. Patients were considered to have hallucinations if they had hallucinations in any of the previously mentioned 4 sensory modalities. Hallucinations were initially included dichotomously (present-absent). In subsequent analyses, we considered a 3-level severity of hallucinations (absent, vague, or clear). We note here that although it is not clear whether these symptoms represent truly disturbed ideation vs rooting from amnesic or perceptual changes in patients with AD, we use the terms delusions and hallucinations operationally in this manuscript.

Finally, using CUSPAD items, we constructed a dichotomous variable reflecting whether the patient experienced any behavioral abnormalities (either confusion, wandering, verbal outbursts, physical threats, or agitation) at every evaluation.

At every 6-month visit, medications that the patients were taking were recorded. All cholinesterase inhibitors were grouped in a single category and considered as a dichotomous variable in the analyses. The same was done for all neuroleptics. We additionally calculated duration of use of neuroleptics for each patient.

A modified version of the Charlson Comorbidity Index<sup>34</sup> (herein referred to as the comorbidity index) included items for myocardial infarct, congestive heart failure, peripheral vascular disease, hypertension, chronic obstructive pulmonary disease, arthritis, gastrointestinal disease, mild liver disease, diabetes, chronic renal disease, and systemic malignancy from initial visit. All items received weights of 1, with the exception of chronic renal disease and systemic malignancy, which were weighted 2. No patients with clinical strokes, metastatic tumors, or AIDS were included in the sample. At baseline visit, 68% of patients had a comorbidity index of 0, 19% an index of 1, 8% an index of 2, 4% an index of 3, and 1% an index of 4. Therefore, dichotomized scores (0 [68%] vs  $\geq 1$  [32%]) were used. Exploratory use of the index in a trichotomized (0 vs 1 vs  $\geq 2$ ) or a continuous form did not change the results.

## OUTCOMES

### Cognitive Outcome

Neurologic and mental status examinations were conducted at study entry and at 6-month intervals thereafter. The cognitive function measure used for the analysis was the Columbia MMSE (in English for the United States sites and in French and Greek translated versions for the sites in Europe).<sup>31,32,35</sup> This is a 57-point version of the original Folstein MMSE<sup>31</sup> that includes the addition of digit span forward and backward,<sup>36</sup> 2 additional calculation items, recall of the current and 4 previous presidents of the country, confrontation naming of 10 items from the Boston Naming Test,<sup>37</sup> 1 additional sentence to repeat, and a different copy task including 2 figures. We used a Columbia MMSE score of 20 out of 57 or less (equivalent to approximately a Folstein MMSE score  $\leq 10/30$ ) as the cognitive outcome end point. This cutoff was chosen because similar scores have been used as outcomes by many other studies.<sup>6,12,38</sup> Exploratory analyses of neighboring end points (ie, Columbia MMSE  $\leq 15$  [Folstein MMSE  $\leq 8$ ]) did not change the results.

### Functional Outcome

Functional capacity was assessed using the Blessed Dementia Rating Scale (BDRS) parts I and II.<sup>39</sup> The range is between 0 and 17, with higher scores indicating worse functional status. We chose a BDRS score of 10 out of 17 or higher as the functional end point. The rationale for the functional cutoff was similar to the one described earlier for the cognitive cutoff. Again, exploratory analyses of neighboring BDRS end points gave similar results.

### Institutionalization

The equivalent institutional care<sup>40</sup> that the patient was receiving was rated at each 6-month follow-up interval. This rating is the second section of a dependency scale<sup>40</sup> that rates the patient's need for care. It summarizes the interviewer's impression, based on data from the entire study protocol and of the care the patient receives and requires, regardless of the patient's location. Rating categories are limited home care (independent living, with some help in shopping, cooking, or housekeeping, but not with all tasks); adult home (a supervised setting with regular assistance in shopping, cooking, and housekeeping, and constant companionship, security, legal, or financial help); and health-related facility (around-the-clock supervision of personal care, safety, or medical care). We used the equivalent institutional care rating of health-related facility as an end point for prediction. Interrater reliability for the equivalent institutional care is good, with an intraclass correlation coefficient of 0.73.<sup>40</sup> In supplementary analyses, we also used actual (rather than equivalent) placement in either nursing home, retirement home, or assisted living facility as an outcome.

### Death

We typically learned of patients' deaths from family members or when attempting to complete follow-up visits. For patients who could not be contacted for Predictors Study follow-up or were otherwise lost to follow-up, death information was obtained as available through the National Death Index.

## STATISTICAL ANALYSES

Baseline characteristics of patients who did and those who did not reach the 4 outcomes of interest during the study period were compared using *t* test for continuous variables and  $\chi^2$  test for categorical variables.

We calculated separate Cox proportional hazards models<sup>41,42</sup> with the following dichotomous outcomes: cognitive end-

point, functional endpoint, institutionalization, and death. Duration (in 6-month blocks) between the initial visit and either development of the outcome or last evaluation without the outcome served as the timing variable in each of the models described earlier. The main predictors in the Cox models were either hallucinations or delusions, in the form of dichotomous time-dependent covariates. When the 3-level severity form of delusions or hallucinations were used, it was in the form of a dummy variable with absence of the symptom as the reference category. The Cox proportional hazards model with time-dependent covariates takes into account changes in the status of the predictor variable at each study visit (eg, a patient may not have delusions at the first visit but may manifest delusions at the second and third visit). In subsequent Cox models, we simultaneously adjusted for the following variables: cohort (first or second predictors cohort; dichotomous); recruitment center (dummy variable with New York center as the reference); informant status (dummy variable with spouse as the reference); age at intake in the study; sex; education in years; Columbia MMSE score at initial evaluation; BDRS score at initial evaluation; and the comorbidity index (dichotomous). Because the ethnic distribution of the patients enrolled in the Predictors Study was heavily weighted toward Caucasians (94%) with very few African Americans (5%) or other (1%), no ethnicity variable was included in the models. Neuroleptic medication, cholinesterase inhibitor use, and presence of behavioral abnormalities at each visit were also included as time-dependent covariates in the adjusted models. Supplementary analyses that used duration of use of neuroleptics as a fixed covariate produced similar results.

## RESULTS

Overall, 456 subjects with AD, approximately half from each predictors cohort, were included in the study (**Table 1**). Center recruitment was as follows: New York, 173 (38%); Baltimore, 118 (26%); Boston, 112 (24%); Paris, 37 (8%); Larissa, 16 (4%). The majority of patients (88%) were recruited from the 3 centers in the United States. As dictated by the inclusion criteria, patients were at the early stages of AD at the time of initial recruitment: Columbia MMSE was 40 (Folstein MMSE of approximately 21). The subjects were, on average, well educated and in general good health (as indicated by the fact that approximately two thirds had a comorbidity index of 0).

Patients were followed from 0.11 to 14 years, during which there were 3266 visit-assessments of delusions and hallucinations (on average 7.1, up to 25 per patient). The informant was usually the spouse or, less likely, the patients' children. During the period that each subject was followed, missed visits were rare; fewer than 18% missed more than 1 semiannual visit and fewer than 9% missed more than 2. Follow-up information was complete for 94.5% of the cohort, while only 5.5% of the cohort ( $n=27$  subjects) had missing follow-up information for the period of the last year before the most updated data entry.

At the baseline evaluation, delusions were present for 34% (most were transient), while 70% developed delusions at some point during follow-up (most persistent). Overall, 32 patients (7%) had hallucinations at baseline: 12 (2.4%) auditory, 11 (2%) visual, 9 (2%) olfactory, 2 (0.4%) tactile, and 3 (0.7%) other. Among 130 patients (33%) who had hallucinations at any time during the follow-up, 85 (18.7%) had auditory, 108 (23.8%) visual, 20 (4.4%)

**Table 1. Demographic and Clinical Characteristics of Patients**

Cohort 1/cohort 2, No. (%)	234 (51)/222 (49)
Mean (SD) duration of follow-up (range), y	4.5 (3.2) (0.11-14.0)
Mean (SD) age at study entry (range), y	74 (8.8) (49-99)
Mean (SD) education, y	13 (3.8) (1-20)
Men/women, No. (%)	187 (41)/269 (59)
Mean (SD) Columbia MMSE at study entry (range)	40 (6.1) (30-57)
Mean (SD) Folstein MMSE at study entry (range)	21 (3.0) (16-30)
Mean (SD) BDRS at study entry (range)	3.5 (2.0) (0-13)
Comorbidity index 0/comorbidity index $\geq 1$ , No. (%)	310 (68)/146 (32)
Informant spouse/child/other, No. (%)	231 (53)/141 (32)/67 (15)
Behavioral abnormalities baseline/all evaluations, No. (%)	211 (47)/374 (82)
Delusions, No. (%)	
Transient baseline/all evaluations	91 (20)/90 (20)
Persistent baseline/all evaluations	65 (14)/227 (50)
Any baseline/all evaluations	156 (34)/317 (70)
Hallucinations, No. (%)	
Vague baseline/all evaluations	12 (3)/52 (12)
Clear baseline/all evaluations	20 (4)/103 (23)
Any baseline/all evaluations	32 (7)/150 (33)
Neuroleptics use, all evaluations, No. (%)	140 (28)
Cholinesterase inhibitor use, all evaluations, No. (%)	182 (41)
Cognitive end point during follow-up, No. (%)	171 (38)
Functional end point during follow-up, No. (%)	186 (41)
Equivalent institutionalization during follow-up, No. (%)	234 (54)
Actual institutionalization, No. (%)	168 (38)
Dead during follow-up, No. (%)	224 (49)

Abbreviations: BDRS, Blessed Dementia Rating Scale; MMSE, Mini-Mental State Examination.

**Table 2. Cox Models Predicting Occurrence of the 4 Outcomes by Delusions and Hallucinations as Time-Dependent Covariates\***

Predictors	Cognitive		Functional		Institutionalization		Death	
	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)
<b>Unadjusted Models</b>								
Delusions, transient	1.72†	(1.16-2.54)	1.71†	(1.17-2.49)	1.38	(0.98-1.93)	0.75	(0.50-1.12)
Delusions, persistent	2.06†	(1.46-2.92)	2.04†	(1.46-2.85)	1.87†	(1.39-2.51)	0.94	(0.68-1.29)
Delusions, any	1.91†	(1.41-2.60)	1.90†	(1.41-2.54)	1.63†	(1.26-2.12)	0.86	(0.65-1.13)
Hallucinations, vague	1.53	(0.80-2.93)	2.65†	(1.57-4.47)	1.77†	(1.06-2.96)	1.61	(0.97-2.69)
Hallucinations, clear	2.48†	(1.58-3.92)	2.49†	(1.62-3.84)	2.06†	(1.38-3.07)	1.46	(0.95-2.27)
Hallucinations, any	2.08†	(1.41-3.07)	2.55†	(1.80-3.62)	1.94†	(1.40-2.70)	1.52†	(1.08-2.15)
<b>Adjusted Models‡</b>								
Delusions, transient	1.42	(0.94-2.14)	1.48	(1.00-2.19)	1.03	(0.72-1.47)	0.85	(0.56-1.30)
Delusions, persistent	1.55†	(1.07-2.26)	1.36	(0.94-1.95)	1.07	(0.77-1.49)	0.81	(0.57-1.15)
Delusions, any	1.50†	(1.07-2.08)	1.41†	(1.02-1.94)	1.05	(0.79-1.40)	0.83	(0.61-1.12)
Hallucinations, vague	1.33	(0.66-2.69)	2.62†	(1.52-4.51)	1.42	(0.83-2.41)	1.66	(0.97-2.86)
Hallucinations, clear	1.77†	(1.09-2.88)	2.04†	(1.28-3.24)	1.74†	(1.14-2.65)	1.39	(0.88-2.18)
Hallucinations, any	1.62†	(1.06-2.47)	2.25†	(1.54-3.27)	1.60†	(1.13-2.28)	1.49†	(1.03-2.14)

Abbreviations: CI, confidence interval; RR, risk ratio.

\*Reference is absence of delusions or hallucinations.

†Significant risk ratios (95% CI not including 1).

‡Adjusted models simultaneously controlled for cohort, recruitment center, age, sex, education, baseline Columbia Mini-Mental State Examination, baseline Blessed Dementia Rating Scale, comorbidity index, informant status, behavioral symptoms, and use of cholinesterase inhibitors and neuroleptics (as time-dependent covariates).

olfactory, 15 (3.3%) tactile, and 12 (2.6%) other. Therefore, 1 out of 4 to 1 out of 3 of the noted hallucinations were of visual type. Most hallucinations were clear.

Subjects who were taking neuroleptics (28%) were taking them for 6.9 years (range, 1-14; SD, 4.73). Neuroleptic medication use was associated with higher risk for reaching the functional end point (risk ratio [RR], 1.68; 95% confidence interval [CI], 1.12-2.50) and for insti-

tutionalization (RR, 1.75; 95% CI, 1.17-2.62). There was no association with the cognitive outcome (RR, 0.90; 95% CI, 0.55-1.48) or with mortality (RR, 1.26; 95% CI, 0.89-1.77).

Presence of both delusions and hallucinations were associated with increased risk of reaching both the cognitive and the functional outcomes in both unadjusted and adjusted models (**Table 2**).

More than half of the patients (54%) reached the equivalent institutional care end point. Although both delusions and hallucinations were associated with risk for reaching this end point at the unadjusted models, delusions were not a significant predictor in the adjusted models (Table 2). On the contrary, presence of hallucinations was associated with a 1.6-time higher risk of reaching the institutionalization end point in the adjusted models. Overall, 38% of patients were actually placed in either a nursing home, retirement home, or assisted living facility. Use of actual placement as the outcome produced similar results.

Almost half the patients died during the follow-up period. Median survival from recruitment into the study was 6.6 years (95% CI, 6.0-7.2). Delusions were not a significant predictor of mortality in any of the models (Table 2). There was a significant association between hallucinations and mortality risk in both the adjusted and unadjusted models; presence of hallucinations was associated with an approximately 1.5-time higher risk of death.

For most of the outcomes and in both adjusted and unadjusted models, the associations were stronger for persistent delusions. There was no clear pattern for hallucinations, with associations being stronger for clear hallucinations for some outcomes and vague hallucinations for others.

Autopsy data were available for 96 patients; 93% had AD-type pathological changes (87% received the pathological diagnosis of AD and 6% had senile changes of the Alzheimer type). Dementia with Lewy bodies was diagnosed in 22% (coexisting with AD-type changes in all but 1 patient). Excluding subjects with pathological dementia with Lewy bodies diagnoses from the analyses did not change the associations between neuropsychiatric symptoms and outcomes. Comparing patients with and without pathological diagnosis of dementia with Lewy bodies, there was no difference in proportions reaching the cognitive outcome ( $P=.91$ ), functional outcome ( $P=.11$ ), institutionalization ( $P=.64$ ), or mortality ( $P=.98$ ). Additionally, there was no difference in proportions of baseline delusions ( $P=.73$ ), delusions at any visit ( $P=.12$ ), baseline hallucinations ( $P=.38$ ), baseline visual hallucinations ( $P=.48$ ), hallucinations at any visit ( $P=.31$ ), or visual hallucinations at any visit ( $P=.31$ ). To further explore associations between Lewy body pathology and clinical indices, we combined extrapyramidal signs with hallucinations. Using presence of severe extrapyramidal signs (Unified Parkinson's Disease Rating Scale score  $>1$  at any motor domain) at any visit and presence of hallucinations at any visit, we constructed a 3-level categorical variable: absence of both, presence of 1 out of 2, and presence of both. There was no association between this variable and neuropathological diagnosis of dementia with Lewy bodies ( $P=.21$ ). Using a combination of extrapyramidal signs and visual hallucinations at any visit produced similar results ( $P=.18$ ).

#### COMMENT

In this study, both delusions and hallucinations were associated with higher risk for cognitive and functional de-

cline in patients with AD. For both of these outcomes, the risk ratio associated with hallucinations was stronger than that for delusions. Persistent nature of delusions conferred a somehow higher risk, while clarity or vagueness of hallucinations did not seem to provide additional prognostic information. Presence of hallucinations was also associated with higher risk of institutionalization and death. All these associations were significant even after adjusting for multiple potential confounders.

We confirmed the associations of the assessed neuropsychiatric symptoms with functional decline and institutionalization that have been noted in previous studies, including those that used part of the predictors 1 cohort.<sup>22,43</sup> However, these new results additionally show a previously unobserved association between hallucinations and both cognitive decline and mortality. There are several explanations for this additional finding. The present analyses are much more powerful since we included more than twice as many patients with AD with data from an additional 6 to 8 years of follow-up. Data from 2 centers in Europe were also included improving the generalizability of the findings. We examined delusions and hallucinations separately. We also controlled for additional covariates such as medications and comorbid diseases. Most importantly, we used a time-dependent approach in the analyses.

Survival in our study was very close to a recent report including patients with AD with similar disease severity at enrollment.<sup>25</sup> However, to our knowledge, this is the first study reporting that hallucinations carry a significant risk for death in AD. Hallucinations may reflect higher burden or more biologically detrimental localization of neuropathology. They may also be associated with more risk-taking behavior or lower attention to medical problems that could eventually lead to mortality.

There was a disparity between presence of delusions (70%) and treatment with neuroleptics (28%). This may relate to clinical decision processes that take into account not only presence but also the severity and persistence of the symptoms; whether the behavior seems disruptive for the patient and the family; possible medication intolerance and side effects; presence of supportive and involved caregiver environment; and possible use of other classes of medication to control behavior. The noted association between hallucinations and increased risk for death was not confounded by medication effects. Antipsychotic medications may affect the natural course of AD since they have been associated with poor outcomes<sup>6</sup> and more recently with increased risk for stroke.<sup>44</sup> In our analyses, use of antipsychotic medications was associated with increased risk for functional outcome and institutionalization but not cognitive outcome or mortality. The noted association with risk for functional abnormalities and institutionalization could be related to motor abnormalities or increased sedation that often occur in subjects taking these medications.

Studies on the relation between psychiatric symptoms and presence of Lewy bodies have produced mixed results with some studies reporting significant associations<sup>45-47</sup> and some (including a previous study from the present population)<sup>48</sup> reporting no associations.<sup>48-50</sup> Even with this larger sample, we detected no associations be-

tween either delusions or hallucinations and presence of Lewy bodies. The physiological changes underlying the emergence of neuropsychiatric symptoms in AD is far from clear. Delusions or hallucinations in AD have been associated with increased neocortical<sup>51,52</sup> and prosubiculum<sup>52</sup> neurofibrillary tangles and senile plaque<sup>52</sup> densities and lower neuronal counts in the CA1 area of the hippocampus.<sup>53</sup> Associations between these neuropsychiatric symptoms in AD and lower cell counts in the dorsal raphe nucleus,<sup>53</sup> reduced levels of serotonin and 5-hydroxyindoleacetic acid,<sup>52</sup> and polymorphic variations in 5-HT2A and 5-HT2C<sup>54</sup> have suggested a possible role of the serotonergic system.<sup>55</sup> Delusions and hallucinations have been associated with either no changes in the locus coeruleus neuronal counts<sup>53</sup> or preservation of norepinephrine in the substantia nigra<sup>52</sup> leaving the link with the adrenergic system still unclear.<sup>56</sup> Finally, associations between psychotic behavior and dopaminergic receptor DRD1, DRD2, and DRD3 polymorphisms have also been reported.<sup>57</sup>

The noted frequencies of both delusions and hallucinations were within previously reported ranges.<sup>1-3</sup> It is important to note the discrepancy between the frequency of delusions and hallucinations between the first and all subsequent evaluations. For example, only about half of patients who had delusions at some point during the follow-up had them at first visit. Among patients who had hallucinations, only less than a quarter had them at baseline evaluation. These results likely relate to both an increasing prevalence of these symptoms during the course of disease and to the well-described phenomenon of fluctuations of these symptoms from visit to visit.<sup>13,26-28</sup> Therefore, the usual approach of considering the presence of these symptoms only at baseline could be one of the major explanations for discrepant predictive ability results in the literature.

Our results confirm those of many previous studies that noted increased risk for cognitive decline<sup>3-12</sup> and functional decline/institutionalization<sup>6,7,14,15</sup> for hallucinations and partially for delusions. One major milestone in the progression of dementia is admission to a skilled nursing facility. In our sample, 66 patients (15%) were still at home despite having reached the equivalent institutional care outcome. Decision for institutionalization in real life is influenced by factors other than the severity of dementia. Such nonmedical factors include existence of living family members, willingness and ability of the family to provide care, geographic location of family, financial and insurance status, cultural beliefs, and other factors. Thus, actual institutional placement is not always a good proxy for a patient's true level of dependence or need for care. We used the equivalent institutional care, which provides a more uniform and objective assessment of the factors mentioned earlier. The associations between either actual or equivalent institutionalization and neuropsychiatric symptoms were similar.

This study has limitations. Patients with AD were selected from tertiary care university hospitals and specialized diagnostic and treatment centers and thus represent a nonrandom sample of those affected by AD in the population. In addition, the proportion of African Americans and Hispanics in our sample was very small.

Therefore our results might not be generalized to population-based AD and all ethnicities. Although we used survival analyses, which take advantage of variable follow-up times, a longer average duration of follow-up may have provided a more complete conclusion. This could have been achieved with enrollment of patients at even earlier stages of their disease or even before symptom onset; however, it is not clear that this would change the results since delusions and hallucinations are usually absent early on. Because prominent language difficulties may interact with the Columbia MMSE scores, results pertaining to the cognitive outcome may not fully apply to such subpopulation of patients with AD. Medication use was coded in a dichotomous fashion. Although we used a time-dependent approach for the medication covariate, we cannot completely take into account the potential effect of various types of neuroleptics, differential doses, alterations in prescriptions occurring in intervals shorter than 6 months, or even response of symptoms to these medications.

In general, confidence in our findings is strengthened by several factors. To our knowledge, this is the largest study of its kind examining the issue of hallucinations in AD, supplying enough power for detection and more precise calculation of effects of interest and ability to control for potential confounders. A major contribution of the present analyses lies in the careful diagnosis and clinical follow-up that patients received. Clinical diagnosis took place in university hospitals with specific expertise in dementia and was based on uniform application of widely accepted criteria via consensus diagnostic conference procedures. The clinical diagnosis of AD has been confirmed in a high proportion (93%) of those who have come to postmortem evaluation.<sup>30</sup> The patients were observed prospectively, which eliminates the potential biases inherent in deriving information from retrospective chart reviews. Evaluations were performed semiannually, which provides multiple assessments of delusions and hallucinations and therefore permits more accurate coefficient calculations. They were also considered in a time-dependent fashion. Our cohort had a very high rate of follow-up participation with very few missing data. Clinical signs of interest were ascertained and coded in a standardized fashion at each visit. Most previous reports studied more impaired patients with AD, capturing the part of the disease course corresponding to more advanced stages. Baseline Columbia MMSE score for this cohort was 40 (Folstein MMSE approximately 21); therefore, patients with AD were included from early stages so that the cohort describes the full range of progression over time. Finally, we took medication administration into account in a time-dependent manner, which provides higher confidence that the occurrence of outcomes of interest in the present study is strictly related to the presence of delusions and hallucinations rather than treatment for them.

Prognosis is a standard part of medical evaluation and knowledge of prognostic indicators is important to practitioners, patients, and families. These data provide a basis for expanding our understanding of predictors in the course of AD. We confirm results of previous reports that both delusions and hallucinations predict faster cogni-

tive and functional decline in AD. We add to the previous literature by reporting an association between hallucinations and mortality. The underlying pathophysiological substrate of the associations between such neuropsychiatric features and clinical outcomes remains to be explored.

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