Longitudinal study of effects of patient characteristics on direct costs in Alzheimer disease

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Abstract—*Objectives:* To estimate long-term trajectories of direct cost of caring for patients with Alzheimer disease (AD) and examine the effects of patients' characteristics on cost longitudinally. *Methods:* The sample is drawn from the Predictors Study, a large, multicenter cohort of patients with probable AD, prospectively followed up annually for up to 7 years in three university-based AD centers in the United States. Random effects models estimated the effects of patients' clinical and sociodemographic characteristics on direct cost of care. Direct cost included cost associated with medical and nonmedical care. Clinical characteristics included cognitive status (measured by Mini-Mental State Examination), functional capacity (measured by Blessed Dementia Rating Scale [BDRS]), psychotic symptoms, behavioral problems, depressive symptoms, extrapyramidal signs, and comorbidities. The model also controlled for patients' sex, age, and living arrangements. *Results:* Total direct cost increased from approximately $9,239 per patient per year at baseline, when all patients were at the early stages of the disease, to $19,925 by year 4. After controlling for other variables, a one-point increase in the BDRS score increased total direct cost by 7.7%. One more comorbid condition increased total direct cost by 14.3%. Total direct cost was 20.8% lower for patients living at home compared with those living in an institutional setting. *Conclusions:* Total direct cost of caring for patients with Alzheimer disease increased substantially over time. Much of the cost increases were explained by patients' clinical and demographic variables. Comorbidities and functional capacity were associated with higher direct cost over time.

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Alzheimer disease (AD) is the third most costly disease to society in the United States.[1] Average annual costs of caring for patients with AD have been estimated at $80 billion to $100 billion in the United States.[2] Several important factors that influence the cost of AD have been identified in the literature, including dementia disease severity,[3-12] comorbid medical conditions,[7,13,14] behavioral problems,[12,15,16] neuropsychiatric symptoms,[17] or extrapyramidal signs.[18] However, much of the AD cost literature remains cross-sectional and cannot examine cost trajectories over time. The two studies that followed patients over time either used data from two time points over short periods of time or used a small nonrepresentative sample; they are therefore limited their ability to estimate long-term disease cost trajectories.[19,20] Consequently, we do not yet know how cost changes as disease progresses nor the relationship between cost and clinical factors over time.

Direct costs of AD related to medical and nonmedical care are substantial. In an earlier work from the Predictors Study, a large, multicenter study of patients with probable AD followed from early stages of the disease, we examined cross-sectionally the association between patient characteristics and direct costs.[21] In this study, we aim to extend our previous work and estimate empirically long-term trajectories of direct cost of AD and relate them to patients' clinical and sociodemographic characteristics.

Methods. *Sample.* The sample used in this study is drawn from the Predictors 2 cohort and consisted of 204 patients with probable AD recruited from three sites: Columbia University Medical Center, Johns Hopkins School of Medicine, and Massachusetts General Hospital. The study was approved by each local

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institutional review board. The inclusion and exclusion criteria are fully described elsewhere.[22-24] Briefly, subjects met DSM-III-R criteria for primary degenerative dementia of the Alzheimer type and National Institute of Neurological Disorders and Stroke–Alzheimer's Disease and Related Disorder Association criteria for probable AD. Enrollment required a modified Mini-Mental State Examination score of 30 or greater, equivalent to a score of approximately 16 or greater on the Folstein Mini-Mental State Examination (MMSE).[25,26] Because subjects were followed up at academic AD centers, they were well characterized with high degrees of certainty in their AD diagnosis.

Recruitment of patients in the Predictors Study began in 1998. For the current analysis sample, baseline data were collected for 13.3% of patients in 1998, 8.3% in 1999, 24.3% in 2000, 26.0% in 2001, 15.5% in 2002, 11.1% in 2003, and 1.1% in 2004. After the baseline interview, all patients were followed semiannually, with annual assessments of resource utilization. At this point in the study, patients have each had at least one assessment in resource utilization, and 82.4% have had two or more assessments. Specifically, 36 patients had one assessment only (at baseline), 62 had two assessments (baseline and one follow-up visit), 51 had three assessments (baseline and two follow-up visits), 36 had four assessments, 11 had five assessments, and 2 had six assessments. Median follow-up for the cohort was 2 years, and maximum follow-up time was 7 years. Patients who did not respond at a particular visit could respond at a subsequent visit. We excluded 6 patients with missing cost data from our analysis sample. Each of these 6 patients was assessed once at baseline and would have contributed 6 observations to the analysis sample. The final analysis sample consisted of 524 observations from 198 patients.

Measures. Data on several clinical characteristics that can be assessed easily and reliably by a clinician were recorded at each visit. At baseline and annually thereafter, data on patients' utilization of seven domains of medical and nonmedical care also were collected. We converted physical quantities for each domain of care into monetary values based on cost estimates from several public sources.[27-30] We summed costs across all domains to obtain a total direct cost as a measure of intensity of resource utilization. We briefly describe below the clinical characteristics, health services utilization, and cost outcomes used in this study. Details of our costing methods were reported in an earlier study.[21]

Clinical characteristics. Disease progression was characterized by transition from milder stages of dementia to more severe stages, measured by MMSE.[25] Higher MMSE scores indicate better cognitive status. Blessed Dementia Rating Scale (BDRS) Parts I (Instrumental Activities of Daily living, IADLs) and II (Basic Activities of Daily living, BADLs) was used to assess patients' functional capacity.[31] This is a 17-point scale, with higher scores indicating worse functional status. Columbia University Scale for Psychopathology in Alzheimer's Disease, a semistructured interview administered by a physician or a trained research technician, was used to measure the presence or absence of psychotic symptoms, behavior problems, and depressive symptoms.[32] Following previous work,[33,34] we constructed a dichotomous variable to indicate the presence of psychotic symptoms if the patient had any delusions, hallucinations, or illusions. We constructed a dichotomous variable to indicate the presence of behavioral problems if the patient had any of the following five symptoms: wandering away from home or caregiver, verbal outbursts, physical threats or violence, agitation or restlessness, or sundowning (more confusion at night or during the evening, compared with during the day). We also constructed a dichotomous variable to indicate the presence of depressive symptoms if the patient had any depressed mood (i.e., sad, depressed, blue, down in the dumps) and either had difficulty sleeping or had a change in appetite. A modified Unified Parkinson's Disease Rating Scale was used to measure the presence or absence of extrapyramidal signs (EPS).[35,36] Following our previous work,[24,37] we constructed a dichotomous indicator for the presence of EPS if any of the following 11 items was rated 2 or higher (with 0 being normal and 4 indicating maximum impairment): speech, facial expression, tremor at rest, neck rigidity, right arm rigidity, left arm rigidity, right leg rigidity, left leg rigidity, posture, gait, or bradykinesia. Patients' medical histories were used to construct a modified version of the Charlson index of comorbidity.[34,37,38] Comorbidities included items for myocardial infarction, congestive heart failure, peripheral vascular disease, hypertension, chronic obstructive pulmonary disease, arthritis, gastrointestinal diseases, liver disease, diabetes, chronic renal disease, and systemic malignancy from the baseline visit. No patients with strokes, metastatic tumors, or AIDS were included in the sample. Finally, disease duration was estimated by a neurologist based on interviews with the patient and informant at the baseline visit.

Sociodemographic characteristics. At the baseline visit, demographic characteristics (e.g., age, ethnicity, sex, education) were recorded. Because patients' living arrangement may change over time and patterns of health service utilization and costs may differ substantially between patients in different living arrangements,[39] information on patients' living arrangements was collected at each follow-up visit.

Outcomes. Patients and informants reported utilization of seven domains of medical and nonmedical care. Medical care included hospitalization, outpatient treatment and procedures, assistive devices, and medications. Nonmedical care included home health aides, respite care, and adult day care. We annualized utilization rates when domains were reported for 3 months (outpatient medical test, treatments, and procedures; nonmedical care) and 6 months (medications). To convert physical quantities of resource use into monetary values, we multiplied for each domain the quantity used for that domain and the corresponding unit cost, and then summed across all domains to obtain a total direct cost as a measure of intensity of total resource utilization. Unit costs for each domain were obtained from several databases and described in detail in an earlier report.[21,27-30] All cost values were adjusted to constant 2004 dollars using the medical care component of the Consumer Price Index.[40]

Analysis. Because total direct cost was highly skewed to the right (skewness = 2.26), we examined log cost as the dependent variable. Three patients at five different visits reported zero cost, generating missing values on log costs. Instead of arbitrarily adding a constant (e.g., $1) to the cost measure before log-transformation, we excluded these five observations. Because the number of observations with zero cost was so small, excluding them did not change the cost distribution in the sample. The Shapiro–Wilk W test did not reject the hypothesis that log cost was normally distributed ($p > 0.08$).

In our multivariate analysis, we aimed to estimate two components of change in total direct cost trajectories as disease progresses over time: within-person change and between-person change. We used random effects models (also known as hierarchical linear models, multilevel models, or random coefficient models) to estimate these changes over time.[41,42] The unit of observation was person-year.

We hypothesized an overall upward trajectory of direct costs for the sample as a whole. Time in this study was measured in years after baseline (Time 0). We began by estimating a simple model that included an intercept and time (year) as fixed effects, and a random intercept term. In this model, the (fixed) intercept estimates the average baseline cost. The coefficient on time (year) estimates the average linear trend in direct costs over time. The random intercept estimates deviations from average cost trajectories for each patient. We then included a term for time (year) squared in the estimation model. The coefficient on the time-squared term was statistically insignificant and was dropped in subsequent models. In the next step, we included a random slope in our estimation model to allow subjects to differ in their overall rate of cost increase. Likelihood ratio tests suggested that cost trajectories differed significantly across patients. Finally, we included clinical and sociodemographic variables as fixed effects to control for any systematic differences in our sample on these variables. The clinical variables included MMSE score, BDRS score, number of comorbidities, and presence or absence of behavioral problems, EPS, depressive and psychotic symptoms. Each of the clinical variables was measured at each visit and was therefore time variant.

Sociodemographic variables included age at baseline, sex, and living arrangement at each visit. Patients' living arrangement at each visit was measured in the following four categories: at home, in retirement homes, in assisted living facilities, or in nursing homes. These four categories initially were entered separately in the estimation model to examine the effects of different care environments on costs. However, earlier estimation results suggested that costs were not significantly different between patients who lived in retirement homes, in assisted living facilities, or in nurs-

ing homes, possibly because of the relatively small proportions of patients in these groups in our sample. Therefore, these three categories were combined in the final estimation model. Because the patients in the sample were overwhelmingly white (96%), we did not include race as an explanatory variable. In addition, we controlled for site differences by including site dummy variables. In this model, the fixed effects parameters are interpreted as the average effect of each explanatory variable. The random effects are interpreted as deviations from the average for each patient.

Our final model took the form

$$y_{it} = \beta_1 + \beta_2 year_{it} + \beta_3 w_{it} + \zeta_{1t} + \zeta_{2t} year_{it} + \varepsilon_{it},$$

where y_{it} is the log cost of patient i at year t, $year_{it}$ is the corresponding year, w_{it} refers to the clinical and sociodemographic variables, ζ_{1t} is the random intercept that allows baseline cost of each patient to differ from average cost, ζ_{2t} is the random slope that allows the rate of change for each patient to differ from average rate of change over time, ε_{it} is the random error, and the βs are the estimated fixed effects parameters.

Because our dependent variable was log-transformed, the coefficient estimates are semielasticities. The interpretation of the coefficient estimates requires some care. For continuous explanatory variables, a coefficient of $\hat{\beta}$ estimates the proportional change in direct cost for a unit change in the explanatory variable, holding all other variables constant. That is, for a unit increase in the explanatory variable, direct cost increases by 100 $\hat{\beta}$ percent. For dichotomous explanatory variables, the corresponding proportional change on cost of the explanatory variable from the reference group is estimated by

$$(e^{\frac{\hat{\beta} - V(\hat{\beta})}{2}} - 1),$$

holding all other variables constant.[43] We interpreted these proportional changes as the marginal effect of each explanatory variable on direct cost. We used a Wald test to test the hypothesis that all variables in the model were jointly significant. All analyses were performed using Stata 9.0.[44]

Results. *Sociodemographic and clinical characteristics.* Longitudinal patterns of demographic and clinical characteristics of the sample are shown in table 1. The first row in table 1 presents the number of patients who contributed to our analysis sample at each visit. Differences in the number of observations over the years of follow-up reflect the continuous accrual of subjects even at present and patient deaths (8%). During the period in which each subject was followed up, missed visits were rare: 15.6% missing one visit, 2.5% missed two visits, and 1% missed three visits. Because only eight patients remained in years 5 and 6 (contributing to 12 observations), descriptive statistics of the sample were presented for the first 4 years of the study. The average patient in the sample was 76.3 years old. Slightly more than half were women (55.9%). The patients in the sample were largely non-Hispanic white (95.8%), well educated (with an average of 14.3 years of schooling), and either married (59.9%) or widowed (31.1%). At baseline, 85.9% of the patients lived at home, 8.1% lived in a nursing home, and 6% lived in a retirement home or an assisted living facility. There were no differences in subjects' sociodemographic characteristics across sites.

Because of the study inclusion criteria, all patients were initially at the early stages of AD. At baseline, most patients (95%) were mildly demented, with a Clinical Dementia Rating of 1;[45] the mean MMSE score was 22.0 (SD = 3.7), and the mean BDRS score was 3.6 (SD = 2.2). As expected, patients' cognition and function worsened over time. Over time, MMSE and BDRS scores both worsened monotonically. By the end of the study period or the last assessment for patients who died, 71.2% of the cohort remained mildly demented, 19.2% were moderately demented, and 9.7% were severely demented. Neurologists' estimate of duration of illness at baseline was 4.1 years (SD = 2.2 years). At baseline, half of the patients did not have any comorbid conditions, 32% had one, 10% had two, 6% had three, and 2% had four comorbid conditions. On average, patients had less than one comorbid condition (mean = 0.8). The most common comorbid conditions at baseline included hypertension (36.1%), diabetes (9.7%), and myocardial infarction (6.7%).

Utilization and annual per-patient costs over time. Table 2 presents data on utilization rates, intensity of use, and annual direct costs for medical and nonmedical care over time. All patients used some type of medical care each year, mainly because of high rates of medication use (>96% each year). There were no discernible trends over

Table 1 *Descriptive statistics of the sample demographic and clinical characteristics*

	Baseline	Year 1	Year 2	Year 3	Year 4	All sample
Sample size*	198	132	93	59	30	524
Sociodemographic variables						
Age at baseline,	76.4	76.7	76.8	75.5	74.6	76.3
mean (SD), y	(8.1)	(8.2)	(8.5)	(7.4)	(8.2)	(8.1)
Female, %	59.1	55.3	58.1	47.5	50.0	55.9
Race, %						
White	94.9	97.0	94.6	96.6	96.7	95.8
Black	4.5	2.3	4.3	3.4	3.3	3.6
Other	0.5	0.8	1.1	0.0	0.0	0.6
Years of schooling,	14.3	14.6	14.3	14.5	13.6	14.3
mean (SD)	(3.2)	(3.1)	(3.2)	(3.2)	(3.7)	(3.2)
Marital status, %						
Married	60.1	59.8	57.0	61.0	66.7	59.9
Widowed	30.8	31.1	31.2	33.9	26.7	31.1
Other	9.1	8.3	8.6	1.7	6.7	7.8
Living arrangement, %						
At home	85.9	77.3	75.3	69.5	83.3	79.6
Nursing home	8.1	11.4	12.9	16.9	3.3	10.5
Retirement home	2.5	4.5	1.1	1.7	0.0	2.5
Assisted living facility	3.5	6.1	7.5	11.9	13.3	6.7
Site, %						
Columbia	44.9	34.1	44.1	42.4	50.0	42.6
Johns Hopkins	23.2	24.2	19.4	20.3	36.7	23.5
Massachusetts General	31.8	41.7	36.6	37.3	13.3	34.0
Clinical characteristics						
MMSE, mean (SD)	22.0	19.6	19.1	17.7	15.7	20.1
	(3.7)	(6.0)	(6.2)	(7.4)	(7.8)	(5.7)
BDRS total, mean (SD)	3.6	5.2	5.6	6.8	8.1	5.0
	(2.2)	(3.2)	(3.4)	(3.9)	(3.5)	(3.3)
Behavioral problems, %	42.4	49.2	60.2	57.6	60.0	50.6
EPS, %	14.1	20.5	18.3	23.7	16.7	17.7
Depressive symptoms, %	20.2	24.2	17.2	11.9	23.3	19.7
Psychotic symptoms, %	31.3	32.6	36.6	40.7	40.0	34.5
Modified comorbidity index	0.8	0.8	0.8	0.8	0.8	0.8
	(0.9)	(1.0)	(1.0)	(0.9)	(0.9)	(0.9)

* At baseline, data were collected from 198 patients. At year 1 and each year thereafter through year 4, data were collected from 132, 93, 59, and 30 patients from the original 198 patients for a total number of 524 observations.

MMSE = Mini-Mental State Examination (range 0 to 30); BDRS = Blessed Dementia Rating Scale (range 0 to 17); EPS = extrapyramidal signs.

Table 2 *Descriptive statistics of utilization and costs over time*

	Baseline	Year 1	Year 2	Year 3	Year 4	All sample
Sample size	198	132	93	59	30	524
Utilization rate, %						
Medical care						
Medication	96.5	98.5	100.0	98.3	100.0	98.1
Outpatient treatment	72.7	66.7	75.3	71.2	70.0	71.4
Assistive device	42.9	31.8	37.6	40.7	50.0	38.9
Hospitalization	21.2	20.5	15.1	25.4	20.0	20.4
Nonmedical care	15.7	28.0	24.7	27.1	40.0	23.7
Intensity of use, mean (SD)						
Medication	6.4	7.5	7.4	7.7	8.1	7.1
	(3.5)	(3.6)	(3.1)	(3.7)	(3.8)	(3.5)
Outpatient treatment	2.0	1.9	1.9	2.0	1.9	2.0
	(2.1)	(2.1)	(2.2)	(2.3)	(2.4)	(2.1)
Assistive device	0.8	0.6	0.6	0.8	1.3	0.7
	(1.3)	(1.2)	(1.2)	(1.3)	(2.3)	(1.3)
Hospitalization	0.3	0.2	0.2	0.4	0.4	0.3
	(0.6)	(0.5)	(0.5)	(0.7)	(0.9)	(0.6)
Per-patient cost, mean (SD)						
Medication	2,872	3,349	3,874	4,186	4,301	3,403
	(1,857)	(2,014)	(2,866)	(2,604)	(2,639)	(2,294)
Outpatient treatment	1,786	1,397	1,458	1,374	1,589	1,559
	(3,318)	(3,351)	(2,703)	(2,183)	(2,796)	(3,046)
Assistive device	144	175	189	184	300	172
	(337)	(493)	(648)	(437)	(448)	(460)
Hospitalization	3,089	2,209	3,182	7,155	4,387	3,627
	(8,081)	(6,049)	(11,639)	(20,482)	(16,407)	(12,053)
Total medical care	7,105	7,890	8,699	12,899	10,577	8,753
	(7,686)	(9,060)	(12,838)	(20,301)	(17,311)	(12,875)
Total nonmedical care	1,349	5,000	4,672	2,429	9,348	3,835
	(7,527)	(16,339)	(18,365)	(5,709)	(17,057)	(14,121)
Total direct cost	9,239	12,105	13,371	15,328	19,925	12,587
	(12,125)	(19,514)	(23,055)	(20,968)	(29,104)	(20,849)

time in the utilization rates of medications, outpatient treatments or procedures, assistive devices, and hospitalizations. Utilization rate of nonmedical care increased substantially from 15.7% at baseline to 40% at year 4. Average number of medications taken increased from 6.4 at baseline to 8.1 in year 4 (a 26.5% increase). Average intensity of use did not change substantially for outpatient treatments or procedures, assistive devices, and hospitalizations.

In terms of average per-patient cost, cost of outpatient treatments or procedures, assistive devices, and hospitalizations fluctuated year to year, but medication cost increased steadily from $2,872 to $4,301 (a 50% increase). Total medical care costs and nonmedical care costs both increased substantially, from $7,105 to $10,577 (a 49% increase) and from $1,349 to $9,348 (a 7-fold increase). Taken together, in this group of patients, total direct cost per patient doubled from $9,239 at baseline to $19,925 at year 4.

Adjusted medical costs over time. Table 3 presents results of random effects regression models of log cost on patients' clinical and sociodemographic characteristics. We began by specifying a simple model with only a random intercept (results not shown). Results of the random intercept model suggested that total direct cost increased by 16% each year, but cost differed substantially across patients. A second model that included both a random intercept and a random slope suggested that total direct cost increased by 13% each year, and there were substantial differences in both baseline cost and rate of increase in cost between patients. Our final model included both random intercept and random slope terms and estimated the effects on direct cost of patients' clinical and sociodemographic characteristics. Results of this model (table 3) suggested that patients' clinical and sociodemographic variables explained much of the time effect that was observed. Specifically, higher BDRS scores and higher number of comorbid conditions were associated with higher direct costs; women and patients living at home were associated with lower direct costs. The coefficient estimate on year in table 3 became insignificant, and that of total direct cost increased only by 1.2% each year after controlling for subjects' clinical and sociodemographic variables.

Table 3 also presents marginal effects of each variable on direct cost. For continuous explanatory variables, we defined the marginal effect of an explanatory variable as the proportional change in cost for a unit change in the explanatory variable, holding all other variables constant. For dichotomous explanatory variables, we defined the marginal effect of an explanatory variable as the proportional change in cost as the explanatory variable changes from the reference group, holding all other variables con-

Table 3 *Random effects models of total direct costs*

	Dependent variable, log (cost)		
Fixed effects parameters	Coef	SE	Marginal effect
Year	0.012	0.038	1.171
MMSE score	−0.001	0.009	−0.082
BDRS score	0.077	0.020	7.705‡
Number of comorbidities	0.143	0.051	14.301‡
Behavior problems (1 = present, 0 = absent)	0.056	0.090	5.347
Extrapyramidal signs (1 = present, 0 = absent)	0.010	0.115	0.386
Depressive symptoms (1 = present, 0 = absent)	0.126	0.101	12.874
Psychotic symptoms (1 = present, 0 = absent)	0.102	0.096	10.198
Younger than 65 y (1 = yes, 0 = no)	−0.115	0.168	−12.080
Women (1 = yes, 0 = no)	−0.238	0.100	−21.545†
Lives at home (1 = yes, 0 = no)	−0.225	0.130	−20.846*
Site (reference = Massachusetts General)			
Columbia	0.303	0.118	34.435†
Johns Hopkins	0.227	0.138	24.233*

* $p < 0.10$.
† $p < 0.05$.
‡ $p < 0.01$.

Coef = coefficient; MMSE = Mini-Mental State Examination; BDRS = Blessed Dementia Rating Scale.

stant. Results showed that after controlling for other variables, a one-point increase in the BDRS score increased total direct cost by 7.7%, and one more comorbid condition increased total direct cost by 14.3%. Log cost was 0.238 lower for women than for men, corresponding to a 21.5% lowered total direct cost for women as compared with men. Log cost was 0.225 lower for patients living at home than those living in an institutional setting, corresponding to a 20.8% lowered direct cost for patients living at home. Other clinical variables (MMSE scores, presence of behavioral problems, EPS, depressive symptoms, and psychotic symptoms) were not significantly associated with total direct cost. Finally, results also showed substantial site differences in costs, with the Boston site having lower cost than Baltimore and New York City sites.

Discussion. In this study, we estimated empirically long-term trajectories of direct health care cost for a sample of patients initially at early stages of AD and related them to patients' clinical and sociodemographic characteristics. As discussed below, we will investigate indirect costs in a separate report. We estimated that total direct cost of caring for patients with AD was $9,239 per patient per year at baseline, when all patients were in the early stages of the disease. We also estimated that total direct cost increased substantially at each subsequent follow-up. By year 4, total direct cost more than doubled to $19,925 per patient per year. The magnitude of these cost estimates are consistent with existing studies.[21,46]

With longitudinal data, we showed that much of the cost increases were explained by patients' clinical and demographic variables. Without controlling for other covariates, total direct cost increased by approximately 13% each year. After controlling for patients' clinical and sociodemographic variables, however, the time (year) effect became insignificant and was only associated with a 1.2% increase in direct cost each year.

The longitudinal analysis in this study confirms results from an earlier cross-sectional study using the same sample.[21] There we found that small differences in function were associated with large differences in medical care costs; this study further showed that the relationship between disease cost and function was consistent over time. As a secondary analysis, we tested our models using BDRS factors instead of the total score to examine which specific domains were most sensitive to cost increases. As a group, the BDRS factors were significantly associated with higher costs. Both IADLs and BADLs factors were associated with higher direct costs. Our longitudinal analysis also confirms the relationship between comorbidities and higher costs. A limitation of using the number of comorbidities is that it treats each condition equally when some conditions may be more costly than others. We tested which comorbid conditions were associated with higher cost by including each condition in our estimation model instead of using the modified comorbidity index. Results show that myocardial infarction, chronic obstructive pulmonary disease, and chronic liver disease were significantly associated with higher direct cost. These results are consistent with the findings in the Odense study; this study reported that between baseline and 3-year follow-up interviews in a sample of patients initially living in the community, patients' total health care costs were significantly associated with disease progression (measured by transition to moderate or severe dementia), development of and declines in functional abilities, and transition in living arrangement (moving from community to residential homes).[20]

The effects of psychotic and behavior problems and extrapyramidal signs on the cost of caring for patients with AD are not yet well understood. Similar to our baseline study, but contrary to several cross-sectional studies that examined the effects of behavior problems[12,15,16] and EPS[18] on AD costs, we did not find the presence of psychotic symptoms, behavior problems, or EPS to be significantly associated with increased direct cost of care. We believe the nonsignificant results may be due to the roughness of the measures used in this study. For example, subcategories of extrapyramidal and psychotic symptoms were grouped together, and we only used dichotomous gradations of severity. Additionally, behavioral and psychiatric symptoms in AD fluctuate

over time, and particular symptoms can occur any time during the course of AD.[34] Persistence of these symptoms also differs from symptom to symptom.[47] Although our multivariate model with time-dependent covariates takes into account the status of patients' symptoms (presence or absence) at each visit, we will examine in detail the effects on costs of finer gradations of subtype and severity of each symptom in future studies.

Consistent with other studies,[3,7] we found that costs are substantially lower for patients living at home than for those living in an institutional setting. Possibly because the proportion of patients who lived in retirement homes and assisted living facilities were small, we were unable to separate out the effects on cost of different institutional living arrangements. The lower direct cost at home as compared with that in institutional settings suggests that interventions aimed at delaying or preventing institutionalization could reduce direct cost of care. However, potential cost savings in direct cost of care with delayed institutionalization need to be balanced with the potential increase in cost to caregivers providing unpaid care. In our future work, we will explore the relationship between the cost of caregiving and institutionalization.

In this study, we also found that women had 21% lowered total direct cost compared with men. This result is consistent with earlier studies that found differences in health care utilization between men and women. For example, one study found that in a sample of patients who eventually developed AD, use of Medicare reimbursed primary care was lower in women than in men.[48] Another study of a nationally representative sample of noninstitutionalized disabled elderly reported lower use of both paid home care and informal care in women than in men, even within married households.[49] Although the results of this study and these earlier studies are consistent and suggest gender disparities in health care utilization, this result requires further investigation.

We found substantial cost differences across sites. This result is consistent with regional differences in health services utilization and costs documented in the literature[50] and, more specifically, a recent study on service utilization and costs among patients with AD.[51] Because different sites were included in these studies, results are not directly comparable across studies. Further investigations are needed to examine whether variations in utilization and costs reflect differences in regional preferences, availability or access of services, ethnic and cultural differences, or socioeconomic factors.

At this point in the study, 16 of the 198 patients in the analysis sample have died, contributing to 42 observations in the longitudinal sample. Many studies show substantially higher medical care utilization and cost during the last year of life.[52,53] To examine the effects of including patients who died in our analysis, we performed secondary analyses in the following two ways. First, we reestimated our model excluding the last observation of the patients who died (i.e., 16 observations dropped). We also reestimated our model excluding these patients entirely (i.e., 42 observations dropped). Results of these models were similar to those reported in this study.

There are several limitations to our study. Patients 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. The patients in our sample also were predominantly white and highly educated. Caution is needed in generalizing the results of this study to patients of other ethnicities, to patients with lower levels of education and income, and to community AD patients. Future research will need to examine AD cost trajectories in samples that are more representative of the general population.

It should be noted that the cost estimates reported in this study are total direct cost associated with caring for patients with AD and not incremental costs due to AD. For example, costs of medications include costs from all medications and not only those from antidementia agents. To estimate the incremental costs due to AD, a comparison longitudinal sample of non-AD patients with otherwise similar characteristics is needed. However, the construction of a non-AD comparison group is beyond the scope of this study. Many studies have documented the high indirect cost of care for patients with AD and documented its association with a number of clinical variables.[8,10,15,21,51,54,55] Most of these studies, like those that examined direct cost of care, are cross-sectional. In future studies, we will examine the trajectories of indirect cost of caring for patients with AD and examine its relationship with important clinical characteristics.

In this study, resource utilization was reported by informants (mostly caregivers) and patients. Self-reported data may be problematic in studies of patients with AD because of the patients' inability to reliably report on service utilization and the necessity of using proxies to obtain information. We are not aware of any studies on the accuracy of caregiver-reported resource utilization data. However, caregivers have been shown to accurately report information on care recipients' medical conditions.[56] Our results may be biased if there are systematic differences between caregivers' reports on medical conditions and resource use. However there is no reason to believe this is the case.

In general, confidence in our findings is strengthened by several factors. A major contribution of the current 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.[24] The patients were followed up prospectively, which eliminates the potential biases inherent in deriving information from retrospective chart reviews. Evaluations were performed annually, which provides multiple assessments of cost and therefore permits more accurate coefficient estimates. Our cohort had a high rate of follow-up participation, with few missing data. Clinical signs of interest were ascertained and coded in a standardized fashion at each visit. Finally, patients were recruited at early stages of the disease and followed for long periods of time. Analysis is not compressed in time, and the cohort describes the full range of progression over time. Longer-term effects on costs are therefore more easily interpreted.

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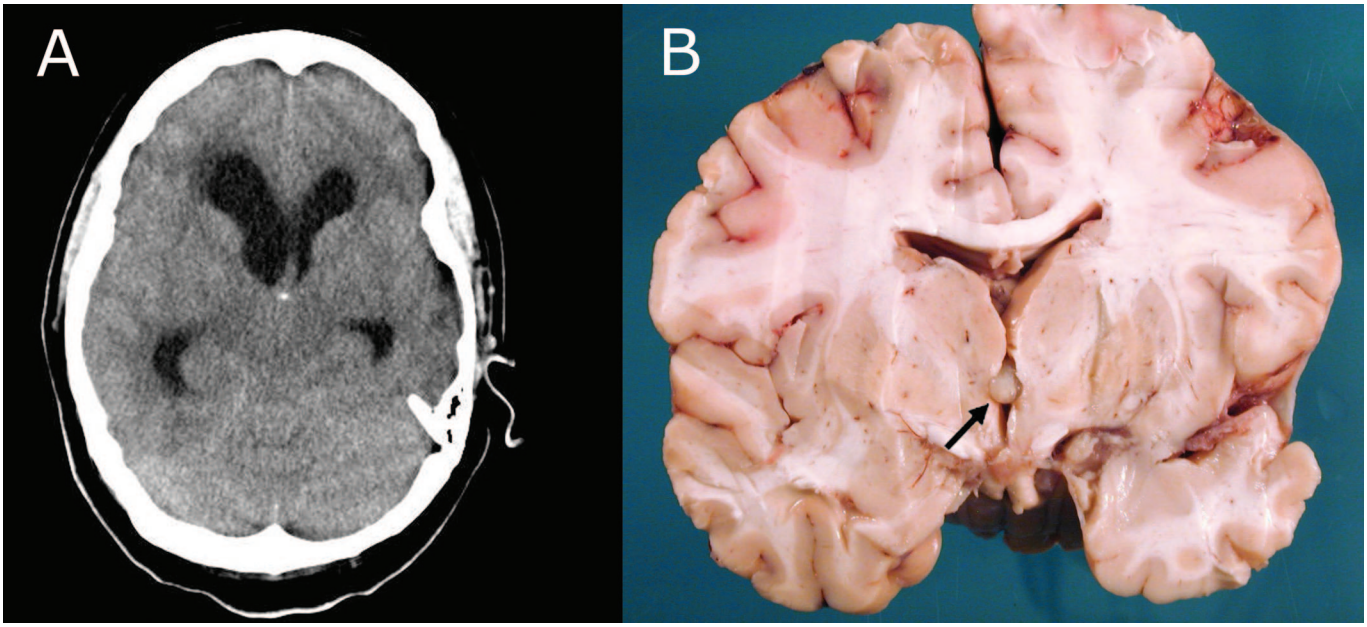

Figure. On admission, a CT scan showed a biventricular hydrocephalus (A). Autopsy showed a colloid cyst of the third ventricle (arrow) (B).

Sudden death after air travel in a patient with colloid cyst

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A 19-year-old previously healthy woman presented with sudden headache and nausea after a transcontinental flight. She rapidly became comatose. A CT scan showed a biventricular hydrocephalus (figure). A ventricular drain was inserted to relieve intracranial pressure, but her clinical condition failed to improve. The patient died 24 hours after admission. The most notable finding at autopsy was a colloid cyst obstructing the foramen of Monro. Few similar cases have been reported.[1,2] We conclude that patients harboring colloid cysts are prone to barotrauma with fatal outcome.

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