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Measuring Alzheimer Disease Progression with Transition Probabilities: Estimates from NACC-UDS

D.E. Spackman[1,*], **S. Kadiyala**[2], **P.J. Neumann**[3], **D.L. Veenstra**[2], and **S.D. Sullivan**[2]

[1]Centre for Health Economics, University of York, York, UK

[2]Department of Pharmacy, University of Washington, Seattle, WA, USA

[3]Center for the Evaluation of Value and Risk in Health, Tufts Medical Center, Boston, MA, USA

Abstract

Objectives—Estimate the probabilities, for Alzheimer's disease (AD) patients, of transitioning between stages of disease severity (mild, moderate, severe, dead) and care settings (community, institutional).

Methods—Data were compiled by the National Alzheimer Coordinating Center. The main analyses were limited to 3,852 patients who were >50 years old, diagnosed with possible/probable AD and had at least two center visits. A multinomial logistic model accounting for patient and center level correlation was used to calculate transition probabilities between stages of the Clinical Dementia Rating (CDR). Separately we calculated the probabilities of being institutionalized based on CDR stage. Both analyses controlled for baseline age, time between visits, sex, marital status, whether white, whether Hispanic and number of years of education.

Results—The annual probabilities of dying for patients in mild, moderate and severe health states were 5.5%, 21.5% and 48.0%, respectively, while the annual probabilities for institutionalization were 1.2%, 3.4% and 6.6%, respectively. The majority of mild and moderate patients remain in the same health state after one year, 77.4% and 50.1% respectively. Progressing patients are most likely to transition one stage, but 1.3% of mild patients become severe in one year. Some patients revert to lower severity stages, 7% from moderate to mild.

Conclusions—Transition probabilities to higher CDR stages and to institutionalization are lower than those published previously, but the probability of death is higher. These results are useful for understanding AD progression and can be used in simulation models to evaluate costs and compare new treatments or policies.

[*] Address correspondence to this author at the University of York, Centre for Health Economics, Alcuin 'A' Block Heslington, York, YO10 5DD, UK; Tel: +44(0)1904 321422; Fax: +44(0)1904 321402; eldon.spackman@york.ac.uk.

CONFLICT OF INTEREST

None declared.

SUPPLEMENTAL MATERIAL

1. Mean cognition, physical functioning and behavior, as measured by the MMSE, FAQ and NPIQ, by CDR stage.
2. Pharmaceutical use by CDR stage and the odds of using each pharmaceutical if a patient is diagnosed with AD, controlling for age, age-squared, sex, whether white, whether Hispanic, years of education, marital status and other cognitive impairment.
3. A comparison of annual transition probabilities by selected demographic factors to show fast and slow transi-tioners.

Keywords

Alzheimer disease; Natural history study; Progression; Transition probabilities

INTRODUCTION

Alzheimer disease is a progressive illness. The brain becomes increasingly damaged over time and symptoms become increasingly debilitating. Patients experience disease in their own way but understanding progression of disease allows patients and caregivers to prepare for future changes and the accompanying challenges.

From a policy perspective, disease progression informs upcoming changes in resource use and costs and allows comparisons to be made with new interventions. With the hope that new biologics or possibly other future treatments change the progression of AD it is important to understand the current disease progression to be able to assess the potential incremental benefit of new treatments.

Tacrine was the first cholinesterase inhibitor (CI) approved by the FDA in 1993 to treat cognitive symptoms [1] and was not widely prescribed. Since, treatment for AD has changed substantially with five new CI [2, 3] and other new treatments to ease behavioral symptoms [4, 5]. Current treatment plans also include management of comorbidities and counseling. Elderly patients use many new medications for other conditions that may change AD treatment or progression.

Neumann *et al.*, calculated probabilities of transitioning between disease stages, and to institutionalization and death [6]. They used data from the Consortium to Establish a Registry for Alzheimer' Disease (CERAD), a longitudinal study of 1145 dementia patients from 22 major medical centers in the United States from 1986 to 1995. Their results have been widely cited and used in modeling the cost-effectiveness of AD interventions [6–10]. However, these transition probabilities no longer represent patients receiving modern AD care.

The transition probabilities estimated in this analysis will allow researchers, practitioners, and policy makers to better understand AD progression, and will permit cost-effectiveness modelers to appropriately model progression for patients receiving the current standard of care.

MATERIAL AND METHODS

Participants

We used the Uniform Data Set (UDS) from the National Alzheimer Coordinating Center (NACC). The UDS contains demographic, clinical and specimen data from Alzheimer disease centers (ADCs) across the US. All ADCs enroll and follow patients annually with a standardized protocol and provide pooled data for research through the NACC. The UDS is not considered a population-based sample because of non-random enrollment of patients by participating ADCs. We limited data analysis to those patients who were 50 years of age or older. This study was approved by the University of Washington IRB.

Measures

Binomial variables were used to indicate whether a patient was institutionalized, white, married or Hispanic. Patients classified as institutionalized included those who resided in

assisted living, boarding homes, adult family homes, skilled nursing facilities or nursing homes. We classified patients as married if they reported being married or living as married.

We measured education as the number of years of schooling. Baseline age was calculated as the difference in the birth year and the date of the initial visit. The day and month of birth and death were not included in the data set and assumed to be July 1. Thus, baseline ages are only approximate, as are time between visits.

We used the global Clinical Dementia Rating (CDR) scale to determine the stage of AD patients. CDR scores have been found to correlate well with other measures and to predict institutionalization and death [11]. CDR has also been correlated with patient quality of life and costs [12]. The lowest scores on the CDR (0.5 and 1) were combined and classified as mild as has been done previously [13]. Those that scored 2 or 3 were classified as moderate or severe, respectively. The previous CDR was calculated as the CDR stage at the last visit e.g. those classified as 'previously moderate' are those patients that were moderate at the previous visit.

Other measures were used to describe the population analyzed. The Mini Mental state examination (MMSE) is commonly used to measure cognitive impairment [14–16]. The Functional Activities Questionnaire (FAQ) is used in clinical situations for the assessment of functional deficit for the elderly [17]. To adjust for the number of tasks that were attempted by each individual we added the score for each task and divided by the number of tasks attempted. Individuals with full physical functioning score 0 while those dependent in each of the tasks attempted score 3. The Neuropsychiatric Inventory (NPI) was developed to assess the severity, frequency and caregiver distress of 12 different neuropsychiatric disturbances common in dementia [18–21]. Only the severity score of the NPI is contained within the UDS.

Pharmaceutical use in the 2 weeks prior to each ADC visit of 100 treatments of interest is collected in the NACC-UDS. Treatments of interest include all AD drugs, anti-psychotics and others, for a complete list see (https://www.alz.washington.edu/NONMEMBER/UDS/DOCS/VER2/ivpfillable.pdf).

Statistical Analyses

We first describe the population by CDR stages. We calculated the mean MMSE, NPI and FAQ scores by CDR stage to show the cognitive, behavioral and physical functioning differences. We also determined pharmaceutical use by diagnosis and CDR stage. To estimate the likelihood of pharmaceutical use we used logistic regression. We tested the association between pharmaceutical use in the last two weeks and AD diagnosis controlling for age, age-squared, sex, whether white, whether Hispanic and other cognitive impairment. For those pharmaceuticals that were significantly associated with AD diagnosis we calculated the percent of AD patients that used each treatment of interest by CDR stage.

We then calculated the association between previous and current CDR stages. We used multinomial logistic models with random effects to account for the individual and center level correlation. We adjusted for demographic characteristics of the patients including: sex, race, Hispanic, marital status, number of years of education and age. Since the duration between observations was not equal we adjusted for the exact time (days) between visits.

We also calculated the association between previous CDR stage and nursing home placement using logistic models and controlling for patient and center level correlations and the above mentioned demographics.

The coefficients from the multinomial and logistic regressions were used to derive the predicted probabilities [22, 23]. The point estimates and 95% confidence intervals were calculated using the delta method [24]. For the main transition probability tables we used the population means for each of the covariates. We estimated other transition probabilities for different populations to show the range of results.

We compared the transition probabilities we estimated to those estimated by Neumann *et al.*, 2001. We calculated the percent of patients in each stage over time from the transition probabilities as was done by Neumann *et al.*, 2001. We present 3 different scenarios, first we duplicate the results using the transition probabilities reported in Neumann *et al.*, 2001, secondly we use the transition probabilities estimated from our statistical model using the mean patient characteristics from the NACC-UDS data, and third, we use the transition probabilities estimated from our statistical model using the patient characteristics from the CERAD population.

RESULTS

At the time of collection the UDS contained 17,736 patients from 32 different ADCs who had completed initial visits and met our inclusion criteria. Of these, 7,050 patients were diagnosed with possible or probable AD and 3,918 AD patients had more than one observation. Our main analyses were limited to 9,730 observations of 3,852 patients 50 years or older, with possible or probable AD, who had more than one observation and complete data for our covariates of interest.

From our descriptive analyses we find that patients are relatively mild and the majority are relatively new to the cohort (Table 1). Those mild, moderate or severe on the CDR had an average MMSE of 22.8, 14.6 or 5.3, respectively. Patients at higher stages on the CDR also had more physical and behavioral problems as measured by the FAQ and NPI (Supplementary Material 1).

Patients reported having taken an AD drug in the previous two weeks at 70.2% of their ADC visits (Supplementary Material 2).

The coefficients from the multinomial regressions represent the likelihood of transitioning into moderate, severe or dead states as compared to the mild state for a one unit increase in the independent variable of interest. In our analysis there are three odds ratios reported for each independent variable, one comparing the probability of being in a moderate state to a mild state, one comparing the probability of being in a severe state to a mild state and one comparing the probability of dying to being in a mild state. The OR 35.29 in the first row suggests that a patient currently in the moderate CDR stage is 35 times more likely to have been previously in a moderate health state at the last time of assessment rather than to have been previously in a mild health state. The coefficient for the previous CDR stage is positive and significant in all cases which suggests that being in a higher CDR stage at the previous visit is associated with being in a higher CDR stage or dead (Table 2). Demographic variables including age, whether white, whether Hispanic and years of education are significantly associated with dying. Older patients are 6% more likely to die than be in a mild state; white patients are 53% more likely than non-white patients to die than be in a mild state, all else equal.

The results of our logistic regression suggest that previous CDR stage is strongly associated with whether a patient is institutionalized (Table 3).

Age, whether white, whether Hispanic and marital status are also statistically significant factors and suggest that older, white, non-Hispanic, unmarried patients are more likely to be institutionalized, all else equal.

These transition probabilities suggest that patients are most likely to stay in the same stage year to year, 77% estimated to stay mild, 50% estimated to stay moderate and 49% estimated to stay severe. The next most likely transition is to the next higher stage of AD. There are also a small number of patients that transition to lower (i.e. less severe) stages; moderate patients are estimated to transition to mild in 7% of cases and about 3% of severe patients are estimated to regress. There were a small number of patients that transitioned from severe to mild but this result was not statistically significant (95% CI −0.002,0.006) The annual probabilities of dying for patients in mild, moderate and severe health states were 5.5%, 21.5% and 48.0%, respectively. The annual probabilities to institutionalization were 1.2% from mild, 3.4% from moderate and 6.6% from severe, although the transition from mild was not statistically significant (Table 4).

The model estimates very different likelihoods of transitioning between 60 year old, white, Hispanic females with 22 years of education and married compared to 80 year old, non-white, non-Hispanic males with 12 years of education and unmarried (Supplementary Material 3). Transition probabilities for non-Hispanic whites, non-Hispanic blacks and Hispanics predict median time to death as 5.4 years, 6.6 years and 8.4 years, respectively.

We compared the transition probabilities to those reported by Neumann *et al.*, 2001 (Fig. 1). We found that patients were more likely to be mild or die using our data and model.

DISCUSSION

In this analysis we compute and report transition probabilities for AD patients. To do so we use a multivariate model and average population characteristics from the NACC-UDS. We also report regression coefficients that can be used to calculate transition probabilities for other populations of interest and we show how population characteristics change transition probabilities using an example of slow and fast transitioners.

We found that only the patients' previous AD stage was significantly associated with their current AD stage. Age, gender, race and ethnicity do not significantly affect the likelihood of transitioning between AD stages in our analysis. We found that demographic factors and stage of disease severity are associated with dying and institutionalization.

The transition probabilities calculated in this analysis are useful for understanding AD progression and can be used in simulation models to evaluate costs and quality of life and compare new treatments or policies. Transition probabilities are commonly used by health economists to inform Markov models whereby costs and quality of life are assigned to health states and overall health and economic outcomes are estimated by tracking the time spent in different health states, as informed by the transition probabilities.

The NACC-UDS represents a large population from across the US. We found the AD population to be similar to other studies, although more educated [25, 26]. Our results are supported by others who have found that age, education, gender, race, ethnicity and marital status affect the mortality of AD patients [27–29]. In a systematic review of the effect of education on AD mortality Paradise *et al.*, 2009 [30] conclude, contrary to our findings, that education does not lead to a difference in time to death after diagnosis.

The transition probabilities estimated suggest that a small number of patients improve their CDR score over time. This was also found by Neumann *et al.*, who concluded these

improvements were likely due to factors, such as variations in clinical assessment, the presence of depression or psychosis, or adjustments in medications that may mask actual disease stages. From this analysis we were unable to determine whether this result was measurement error or a true effect. A future analysis could consider this question more closely by also comparing other measures of AD.

Comparing our estimated transition probabilities to those in Neumann *et al.*, part of the difference in the transitions is due to the difference in the patient characteristics between CERAD and NACC-UDS. To adjust for this difference we calculated transition probabilities using the patient characteristics of the CERAD population (Table 5).

Since the percent married was unknown we used the 66% as in NACC-UDS. Using the NACC-UDS predictive model and CERAD population characteristics the resulting transition probabilities were not greatly different from the predictive model using the NACC-UDS population characteristics but were slightly more similar to those of Neumann *et al.*, Fig. (1). This is probably not a surprising result since the population characteristics used in the model had relatively small coefficients when estimating transitions between stages, but were larger and more significant when estimating institutionalization and death (Table 2). This result suggests that the difference between the two studies is something other than the population characteristics used in the model.

This difference in transition probabilities could be due to a shift in CDR staging over time. However, a recent study suggests that CDR drift is minimal and that the CDR demonstrates general stability for assessment of dementia over time [31]. The probability of death may differ due to the limited follow-up in the NACC-UDS and the high dropout rate in CERAD.

Modeling the NACC-UDS transition probabilities we found that 50% of the population was dead in approximately 5.5 years where as using the CERAD transitions it took approximately 8.5 years. The median time to death as predicted by the NACC-UDS transition probabilities are more similar to other published estimates than the CERAD transition probabilities. Helzner *et al.*, 2008 [27] reported that median post-diagnosis survival for white non-Hispanics was 3.7 years, 4.8 years for black /African American and 7.6 years for Hispanics. We used our model to predict the probability of death in each of these populations and found a median survival for each group 1–2 years longer. This difference may be due to an under estimation of death in the NACC-UDS since death collection is ongoing and often delayed.

Patients transitioned to an institution more slowly in the NACC-UDS cohort than in CERAD. In following the assumption made by Neumann *et al.*, we assumed that once a patient was institutionalized they stayed institutionalized although there were a small number of patients in the data set that transitioned back to the community. The low number of institutionalizations could be due to a less severe population or difficulty in following up with participants in nursing home. However we tried to control for the severity by including the previous CDR stage. Another difference between our study and Neumann *et al.*, is the definition of institutionalization. CERAD did not gather information on entry into assisted living, but included only those who transitioned into nursing homes [32]. According to the National Center for Health Statistics nursing home residents have declined in the last 10 years. Of those 65 years or older the age-adjusted nursing home residents were 46.4 per 1000 in 1995 compared to 34.8 per 1000 in 2004.[33] There may be many reasons for this difference including financial and cultural changes or the benefit of new treatments. Mittelman *et al.*, 2006 show that caregiver counseling and support group participation may delay nursing home admissions [34, 35]. Others have shown that for AD patients, anti-

cholinesterase inhibitors and memantine may also delay time to nursing home placement [36, 37].

Many cost-effectiveness analyses have relied on the cost offsets of slowing nursing home progression due to treatment to show cost-effectiveness. These cost offsets will be less substantial if patients are being admitted less frequently. This result also suggests that it will be more important in the future to understand the effects of AD on family and caregivers as the responsibility shifts away from nursing homes.

The comparisons to Neumann *et al.*, suggest that patients today are transitioning more slowly between disease stages and to institutionalization but dying more quickly. Given the difference in availability of pharmaceuticals between CERAD and NACC-UDS it may be tempting to suggest that the difference in transitions is due to treatment differences. However, although this is a possibility, we do not have sufficient information on patients' treatments to make any conclusions as to the cause of the change in transition probabilities. Although a large number of patients report using pharmaceutical treatments, many other counseling and support group interventions are available and not recorded in this data set. It might be the case that those who are more likely to take pharmaceutical treatments are also more likely to seek non-pharmaceutical care. It is also possible that transition probabilities are being affected by non-AD treatments or differences in life style such as healthy eating or less smoking. Our analysis could not control for these differences. The comparison of transition probabilities might also suggest that the benefits of current treatments are being offset by increased mortality. However we believe this is unlikely as our results are more in line with other studies of mortality in AD and believe we are more likely overestimating survival time for AD patients due to the time delay in reporting death.

We believe the current study can be improved by the addition of information on other non-pharmaceutical treatments for AD and with the addition of more longitudinal data. Fortunately the NACC-UDS is ongoing and will likely contain adequate follow-up to enrich the current findings within the next few years.

CONCLUSION

The transition probabilities reported here provide an estimation of progression through AD for those on current standard of care and may act as the comparator to new treatments. The reported regression results also allow researchers to calculate transition probabilities for specific populations. Even without new treatments in AD, these transition probabilities may be used in CEAs to determine the value of screening, different methods of diagnosis and other programs for AD patients and their caregivers. Future work may focus on estimating specific treatment effects on transition probabilities for AD patients using standard of care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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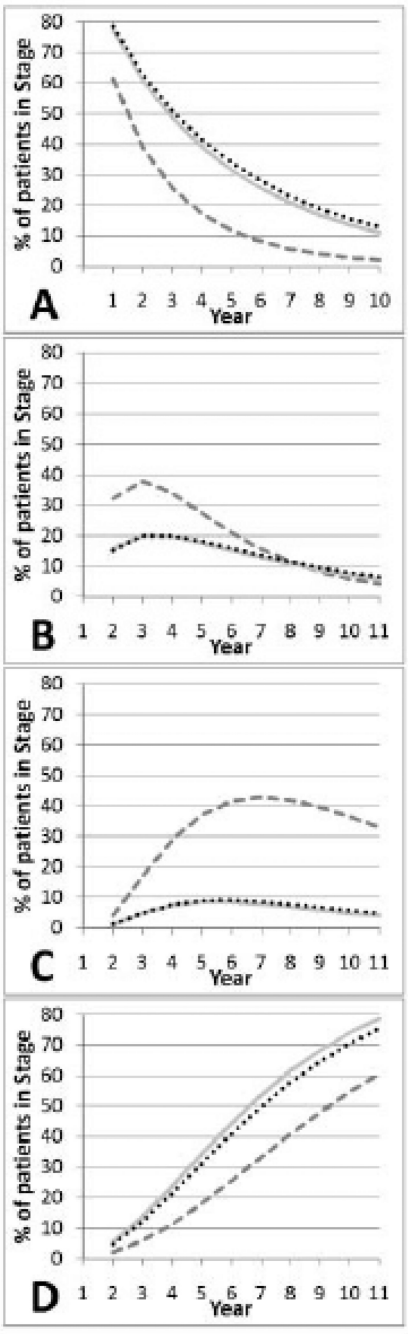

Fig. 1.
A comparison of CDR stage distribution over time between CERAD*, NACC-UDS† and the Model‡

Table 1

Description of Population Analyzed

Time in years between visits mean (sd)	1.09(0.35)	n=5558
Base Age mean (sd)	77.31(9.12)	n=3852
Years of Education mean (sd)	14.24(3.74)	n=3852
FAQ mean (sd)	1.81(0.94)	n=5125
NPI mean (sd)	4.7(4.67)	n=5013
MMSE		n=5023
MMSE score (sd)	19.52(7.35)	
Physical Problem	5.9%	
Cognitive/ Behavioral Problem	57.5%	
Other	30.3%	
Verbal Refusal	6.4%	
Number of observations per patient		n=3852
Two	55.5%	
Three	36.5%	
Four	7.9%	
Five	0.1%	
Sex		
Male	47.8%	
Female	52.2%	
Diagnosis		
Probable AD	79.9%	
Possible AD	20.1%	
Residence at baseline		n=3852
Single Family	83.3%	
Retirement community	5.5%	
Assisted living/ boarding home/ adult family home	5.6%	
Skilled nursing facility/ nursing home	4.0%	
Other	1.5%	
Unknown	0.2%	
Living Situation at baseline		n=3852
Lives alone	15.5%	
Lives with spouse or partner	62.3%	
Lives with relative or friend	13.0%	
Lives with group	3.5%	
Other	5.5%	
Unknown	0.1%	
Marital status		
Married	65.0%	n=3852

Widowed	25.1%	
Divorced	5.9%	
Separated	0.6%	
Never married	2.4%	
Living as married	1.1%	
Other	0.1%	
Unknown	0.0%	
Race		n=3852
White	82.6%	
Black or African American	12.1%	
American Indian or Alaska Native	0.3%	
Native Hawaiian or Other Pacific Islander	0.1%	
Asian	1.7%	
Other	3.2%	
Unknown	0.0%	
Hispanic	7.4%	n=3852

Table 2

The Odds of Each CDR Stage Compared to Mild

CDR Stage Compared To Mild	Independent Variable	OR (95% CI)
Moderate	Previously moderate	35.29 (26.40, 47.17)
	Previously severe	68.38 (9.00, 519.67)
	Time since last visit	1.03 (0.81, 1.32)
	Age	1.01 (1.00, 1.02)
	White	0.94 (0.75, 1.18)
	Hispanic	1.21 (0.88, 1.68)
	Female	1.24 (1.04, 1.48)
	Years of education	0.98 (0.96, 1.01)
	Married	0.90 (0.74, 1.09)
	Constant	0.14 (0.05, 0.35)
Severe	Previously moderate	183.01 (122.25, 273.97)
	Previously severe	15290.22 (2101.38, 111256.10)
	Time since last visit	1.19 (0.85, 1.66)
	Age	1.00 (0.99, 1.02)
	White	0.79 (0.56, 1.11)
	Hispanic	1.02 (0.63, 1.67)
	Female	1.20 (0.90, 1.61)
	Years of education	0.99 (0.95, 1.02)
	Married	0.97 (0.70, 1.34)
	Constant	0.01 (0.00, 0.06)
Dead	Previously moderate	43.39 (31.24, 60.27)
	Previously severe	3522.48 (490.14, 25314.69)
	Time since last visit	0.45 (0.33, 0.62)
	Age	1.06 (1.04, 1.07)
	White	1.53 (1.11, 2.11)
	Hispanic	0.37 (0.22, 0.62)
	Female	0.87 (0.68, 1.10)
	Years of education	0.96 (0.93, 0.99)
	Married	0.92 (0.70, 1.19)
	Constant	0.00 (0.00, 0.01)

Number of Observations = 5558.

Number of Patients = 3852.

Number of NACC center = 32.

Log likelihood = −4271.24.

Variances and covariances of random effects.

level 2 (Patient) 4.36e-21 (1.66e-11).

level 3 (NACC center) 0.085 (0.037).

Table 3

The Odds of Institutionalization Compared to Community Living

Institutionalization	OR (95% CI)
Previously moderate	2.88 (1.69, 4.89)
Previously severe	5.75 (2.65, 12.49)
Time since last visit	2.23 (1.26, 3.93)
Age	1.03 (1.00, 1.05)
White	2.33 (1.28, 4.25)
Hispanic	0.36 (0.16, 0.84)
Female	0.73 (0.49, 1.1)
Years of education	1.03 (0.97, 1.09)
Married	0.24 (0.13, 0.42)
Constant	0.00 (0.00, 0.01)

Number of Observations = 4412*

Number of Patients = 3149.

Number of NACC center = 32.

Log likelihood = −707.18.

Variances and covariances of random effects.

level 2 (Patient) 1.53 (1.51).

level 3 (NACC center) 0.31 (0.16).

* Limited from the main analysis to those who started in community living.

Table 4

Annual Transition Probabilities between Severity Levels and to Death for the Average NACC-UDS Patient *

		t+1				t+1
		Mild	**Moderate**	**Severe**	**Dead**	**Institutionalization**
t	Mild (95%CI)	0.774 (0.75, 0.798)	0.158 (0.139, 0.176)	0.013 (0.009, 0.017)	0.055 (0.046, 0.064)	0.012 (−0.003, 0.028)
	Moderate (95%CI)	0.07 (0.051, 0.089)	0.501 (0.466, 0.536)	0.214 (0.186, 0.243)	0.215 (0.186, 0.244)	0.034 (0.000, 0.069)
	Severe (95%CI)	0.002 (−0.002, 0.006)	0.027 (0.013, 0.04)	0.492 (0.447, 0.536)	0.480 (0.435, 0.525)	0.066 (0.005, 0.128)
	Dead	0	0	0	1	

* Time since last visit=1, Age=77.31, White=0.826, Hispanic=0.074, Female=0.522, Years of education=14.24 and Married=0.660.

Table 5

Population Characteristics from NACC-UDS and CERAD

Model Variables	NACC-UDS	CERAD
Base Age mean (sd)	77.31(9.12)	71.5
Years of Education mean (sd)	14.24(3.74)	12.9
Female	52.2%	53%
Married/ Living as married	66.1%	Unknown
White	82.6%	96%
Hispanic	7.4%	1%