International Psychogeriatrics (2012), 24:10, 1561–1570 © International Psychogeriatric Association 2012
doi:10.1017/S104161021200049X

Effects of general medical health on Alzheimer's progression: the Cache County Dementia Progression Study

Jeannie-Marie S. Leoutsakos,[1] Dingfen Han,[1] Michelle M. Mielke,[1] Sarah N. Forrester,[1] JoAnn T. Tschanz,[2,3] Chris D. Corcoran,[2,4] Robert C. Green,[6] Maria C. Norton,[2,3,5] Kathleen A. Welsh-Bohmer[7] and Constantine G. Lyketsos[1]

[1] *Department of Psychiatry, Division of Geriatric Psychiatry and Neuropsychiatry, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA*
[2] *Center for Epidemiologic Studies, Consumer and Human Development, Utah State University, Logan, Utah, USA*
[3] *Department of Psychology, Consumer and Human Development, Utah State University, Logan, Utah, USA*
[4] *Department of Mathematics and Statistics, Consumer and Human Development, Utah State University, Logan, Utah, USA*
[5] *Department of Family, Consumer, and Human Development, Utah State University, Logan, Utah, USA*
[6] *Division of Genetics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA*
[7] *Department of Psychiatry and Behavioral Sciences and the Joseph and Kathleen Bryan Alzheimer's Disease Research Center, Duke University, Durham, North Carolina, USA*

ABSTRACT

Background: Several observational studies have suggested a link between health status and rate of decline among individuals with Alzheimer's disease (AD). We sought to quantify the relationship in a population-based study of incident AD, and to compare global comorbidity ratings to counts of comorbid conditions and medications as predictors of AD progression.

Methods: This was a case-only cohort study arising from a population-based longitudinal study of memory and aging, in Cache County, Utah. Participants comprised 335 individuals with incident AD followed for up to 11 years. Patient descriptors included sex, age, education, dementia duration at baseline, and APOE genotype. Measures of health status made at each visit included the General Medical Health Rating (GMHR), number of comorbid medical conditions, and number of non-psychiatric medications. Dementia outcomes included the Mini-Mental State Examination (MMSE), Clinical Dementia Rating – sum of boxes (CDR-sb), and the Neuropsychiatric Inventory (NPI).

Results: Health status tended to fluctuate over time within individuals. None of the baseline medical variables (GMHR, comorbidities, and non-psychiatric medications) was associated with differences in rates of decline in longitudinal linear mixed effects models. Over time, low GMHR ratings, but not comorbidities or medications, were associated with poorer outcomes (MMSE: $\beta = -1.07$ $p = 0.01$; CDR-sb: $\beta = 1.79$ $p < 0.001$; NPI: $\beta = 4.57$ $p = 0.01$).

Conclusions: Given that time-varying GMHR, but not baseline GMHR, was associated with the outcomes, it seems likely that there is a dynamic relationship between medical and cognitive health. GMHR is a more sensitive measure of health than simple counts of comorbidities or medications. Since health status is a potentially modifiable risk factor, further study is warranted.

Key words: Alzheimer's disease, comorbidity, GMHR, disease progression, rate of decline, medical care, cohort study

Introduction

Alzheimer's disease (AD) is characterized by cognitive and functional decline and the presence of neuropsychiatric symptoms, but there is a substantial amount of variability in rates of decline among individuals with AD (Folstein *et al.*, 1975; Aguero-Torres *et al.*, 1998; Cortes *et al.*, 2008; Tschanz *et al.*, 2011). Knowing which factors influence rate of decline will be useful for understanding disease progression and treatment, as well as for resource planning and prognosis. Previously reported demographic factors associating with rate of decline include age (Wilkosz *et al.*, 2010), age of dementia onset (Xie *et al.*, 2009), sex (Tschanz *et al.*, 2011), and education and occupational complexity (Wilson *et al.*, 2004; Andel *et al.*, 2006).

Correspondence should be addressed to: Dr. Jeannie-Marie S. Leoutsakos, PhD, MHS, Assistant Professor, Department of Psychiatry, Division of Geriatric Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Bayview – Alpha Commons Building 4th Floor, Baltimore, MD 21224, USA. Phone: +1 410-550-9884; Fax: +1 410-550-1407. Email: jeannie-marie@jhu.edu. Received 5 Jan 2012; revision requested 29 Jan 2012; revised version received 22 Feb 2012; accepted 23 Feb 2012. First published online 12 June 2012.

Brain imaging predictors of decline include cerebral atrophy and white matter hyperintensity burden (Mungas *et al.*, 2002; Brickman *et al.*, 2008). Cerebrospinal fluid (CSF) biomarkers of tau and amyloid have also been shown to predict rate of decline (Buerger *et al.*, 2005; Kester *et al.*, 2009). Presence of one or more APOE $\varepsilon 4$ alleles has been associated with greater decline in some studies (Martins *et al.*, 2005; Bracco *et al.*, 2007) but not all (Hoyt *et al.*, 2005).

While these findings are interesting, these risk factors are not *modifiable.* For example, knowing that age is associated with faster decline is not of practical, immediate significance because we cannot control whether or not people get older. Considering the enormous burden of AD (Alzheimer's Association, 2010), identifying modifiable risk factors for more precipitous decline would have substantial public health impact (Colantuoni *et al.*, 2010). One potentially modifiable predictor of rate of decline is health status. In one cross-sectional study, greater medical comorbidity was significantly associated with more severe AD after controlling for age and other covariates (Doraiswamy *et al.*, 2002). In another very large cross-sectional study comparing individuals with AD to demographically matched controls, individuals with AD had significantly more medical comorbidity and higher medical expenditures (Kuo *et al.*, 2008). In an earlier nested case-control study in Cache County comparing individuals with AD to those without, individuals with AD were taking more medications, were more likely to have a serious illness, and had worse General Medical Health Ratings (GMHR; Lyketsos *et al.*, 2005). In a different small cohort study, fast progressors had significantly more medical diagnoses (6.0 vs. 3.9) than slow progressors (Boksay *et al.*, 2005). However, in a larger study of 289 participants from Alzheimer's Disease Research Center (ADRC), individuals taking five or more medications at baseline declined more slowly than those taking fewer (Storandt *et al.*, 2002). To date, there have been no longitudinal, population-based studies of the relationship between health status and AD progression.

This paper aims to characterize the course of health status (as measured by GMHR, number of non-psychiatric prescription medications, and number of medical comorbidities), to determine whether baseline health status is predictive of cognitive, functional, and behavioral change, and to examine relationships between time-varying measures of those three domains and time-varying measures of health status. This last aim is particularly important because it speaks to our ability to alter the course of dementia-related decline through increased attention to patients' medical health. The Cache County Dementia Progression Study (DPS), with its well-characterized, community-based sample of participants, followed longitudinally before and after dementia onset, is an ideal setting to address these questions.

Methods

The Cache County Dementia Progression Study began in 2002, and is a follow-up study of incident cases of dementia identified from the Cache County Study on Memory in Aging (CCSMA) (Tschanz *et al.*, 2011). The CCSMA is a longitudinal, population-based study examining the prevalence, incidence, and risk factors for dementia in Cache County, Utah (Breitner *et al.*, 1999). In its first wave in 1995, the CCSMA enrolled 90% of the 5,677 county residents who were aged 65 years or older. Three subsequent "incidence" waves were completed: 1999, 2003, and 2006. Nineteen incident AD cases were identified during wave 1, 108 in wave 2, 156 in wave 3, and 52 in wave 4. CCSMA participants diagnosed with incident dementia were followed prospectively by the DPS, approximately every six months, until death or administrative censoring. As such, DPS, though a case-only follow-up, can also be considered population-based. These analyses include DPS participants with a diagnosis of possible or probable AD.

Participants and dementia diagnoses

Details on the methods used in CCSMA are published elsewhere (Breitner *et al.*, 1999; Lyketsos *et al.*, 2000). In brief, dementia cases from CCSMA were ascertained via a multi-stage procedure (Breitner *et al.*, 1999). First, participants were screened for cognitive disorders using the Modified Mini-Mental State Examination (Teng and Chui, 1987), which was further adapted for use in epidemiological studies (Tschanz *et al.*, 2002). Individuals who screened positive, along with a weighted, stratified subsample, were further screened using an informant-based telephone interview (Kawas *et al.*, 1994). Participants who screened positive on the interview then underwent a clinical assessment (CA) by a trained research nurse and psychometrician, which included a structured physical and neurological exam and a neuropsychological battery (Tschanz *et al.*, 2000). Additional information on each participant's medical history, cognitive and functional impairment, and psychiatric symptoms was obtained from a knowledgeable informant. Next, a study geriatric

psychiatrist and a neuropsychologist reviewed data from the clinical assessment and preliminary diagnoses of dementia were made using DSM-III-R criteria (American Psychiatric Association, 1987). The age of onset was estimated as the age the individual met DSM-III-R dementia criteria. Individuals with preliminary dementia diagnoses were then examined in person by a geriatric psychiatrist and underwent neuroimaging and laboratory studies for a differential diagnosis of dementia. A panel of experts with expertise in neurology, geriatric psychiatry, neuropsychology, and cognitive neuroscience then reviewed all data and assigned diagnoses of probable or possible AD according to the National Institute of Neurological Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) criteria (McKhann *et al.*, 1984). Incident cases of dementia identified at CCSMA waves 1–4 were invited to join the DPS. Institutional review boards at Utah State, Duke, and the Johns Hopkins universities reviewed and approved all study procedures.

Demographics

Education and gender were determined at wave 1 of the CCSMA. Apolipoprotein E (APOE) genotype was determined at that time from buccal DNA using previously published methods (Breitner *et al.*, 1999).

Measures of dementia progression and medical comorbidity

Trained neuropsychological technicians administered the Mini-Mental State Examination (MMSE), a measure of global cognitive functioning (Folstein *et al.*, 1975). Scores were adjusted for items missing due to sensory or motor impairment (Breitner *et al.*, 1999). The Clinical Dementia Rating (CDR; Hughes *et al.*, 1982) measures functional ability in the following six domains: memory, orientation, judgment/problem-solving, community affairs, participation in home/hobbies, and personal care. We used the extended version (Dooneief *et al.*, 1996), which rates subjects on an ordinal scale ranging from 0 (no impairment) to 5 (terminal), producing a summed score ranging from 0–30. The ratings from 0–3 have the same interpretation as the traditional CDR, but the additional two categories, profound and terminal, extend the floor of the measure. Such an extension is important for DPS, which follows subjects to death. CDR was administered by a trained research nurse at each visit, taking into account a caregiver's report of symptoms as well as the participant's performance on neuropsychological tests. The Neuropsychiatric Inventory (NPI; Cummings, 1997) assesses neuropsychiatric symptoms (NPS) that commonly occur in dementia, including delusions, hallucinations, agitation/aggression, depression, apathy, elation, anxiety, disinhibition, irritability, and aberrant motor behavior. The instrument first screens for symptoms in each domain. If positive, NPI rates the individual by frequency (0–3) and severity (0–4). Individuals currently on antipsychotic medication for either hallucinations or delusions automatically received severity scores of 4 for that domain. Those two scores are then multiplied to obtain scores for each domain (0–12), and summed across all 10 domains for a total score ranging from 0 to 120.

At each visit, participants were asked whether they had used any prescription medications in the previous two weeks. If they answered yes, they were asked to produce the medication containers and, for each, the name, indication, strength, dosage form, age at first use, and duration of use were recorded. The list of medical comorbidities or events specifically assessed by targeted questions included asthma, emphysema, bronchitis, pneumonia, transient ischemic attack, cerebrovascular accident, myocardial infarction, Parkinson's disease, epilepsy, hypertension, hypercholesteremia, diabetes, coronary artery bypass graft, angioplasty, headache, chronic pain, head injury, brain injury, arthritis, ulcers, constipation, thyroid conditions, cancer, and angina. The first four were assessed only at baseline; the remaining conditions were also reassessed at each follow-up visit.

The General Medical Health Rating (GMHR) is a rapid bedside global rating of health status in dementia patients (Lyketsos *et al.*, 1999). Ratings are derived through an interview with the patient and their caregiver, including current and past medical history and a review of systems. To receive a rating of 4 (excellent), patients typically have no unstable illnesses, no more than two stable illnesses, and are on no more than two medications. To receive a rating of 3 (good), patients typically have one unstable but treated illness, no more than four stable illnesses, and are on no more than four medications. To receive a rating of 2 (fair), patients typically have no more than three unstable illnesses. Very ill patients receive a rating of 1 (poor). It is important to note that these are only rules of thumb, and the clinician's overall general impression plays a significant role in determination of the rating. The GMHR has demonstrated excellent inter-rater reliability (weighted kappa (κ) = 0.93) and has been shown to be a stronger predictor of mortality than either age or dementia severity (Lyketsos *et al.*, 1999).

Statistical analysis

Descriptive analyses of demographics, medical variables, and outcomes were performed to test distributional assumptions of the proposed analyses. Time was measured in years from the baseline visit. All longitudinal regression models included random effects for both intercept and time (Laird, 1982). We chose random effects models over the method of generalized estimating equations (GEE), as the latter entails an assumption that all loss to follow-up occurs completely at random. In the present study, we expected loss-to-follow-up to be more likely among individuals who are older or in poorer health, and therefore not completely at random. In reporting findings from these models, when we refer to "decline," this will refer to worsening of symptoms, not necessarily numerical decreases in scale scores, as increases in both CDR and NPI scores imply greater severity.

The first set of analyses examined change in MMSE, Clinical Dementia Rating – sum of boxes (CDR-sb), and NPI total as a function of baseline GMHR rating. GMHR at baseline was included as a set of two binary covariates (4 – excellent, 3 – good, 2/1 – fair/poor). GMHR values of 1 and 2 were combined due to the very small number of individuals with ratings of 1. A value of 4 (representing excellent health) was the reference group. Interactions between GMHR and time (measured in years) were also included. For example, the interaction between time and the GMHR = 3 indicator variable represents the expected difference in rate of change between two individuals, one with a baseline GMHR of 3 and another with a baseline GMHR of 4. Previous DPS analyses had demonstrated that the trajectories of many individuals were not straight lines, but instead typically appeared to curve downward over time (Tschanz *et al.*, 2011). To model this downward curvature appropriately, we included a quadratic (time-squared/time^2) term and terms for its interaction with GMHR in each of the models. We used likelihood ratio tests to compare models with and without these quadratic terms (Casella, 2002). Previous DPS analyses have reported associations between MMSE, CDR-sb, and NPI totals and the following variables: baseline age, male sex, years of education, dementia duration at baseline visit, and presence of one or more APOE $\varepsilon 4$ alleles. These variables were therefore included in all models. Analogous models were also fit using number of baseline comorbid medical conditions, number of baseline non-psychiatric prescription medication, and both, rather than GMHR.

The second set of models used time-varying measurements of health status as predictors of change in each outcome. Using time-varying covariates allows for estimation of the effects of those measurements on the outcome variables as measured at each visit (e.g., not lagged) rather than on overall rate of decline. As before, linear and quadratic time terms were included, but interactions between the time variables and the health measures were not included. Analyses were conducted using STATA Version 11.1 (Stata Corp LP, 2009).

We conducted post-hoc power analyses based on the formulae of Jung and Ahn (2003), because they account for missing data due to attrition. Based on these formulae and attributes of our observed data, we would expect to have 80% power to detect a between-GMHR group difference in rate of decline of 0.79 MMSE points per year. Details of the power calculations are available from the first author on request.

Results

All 335 individuals with incident possible or probable AD and without a vascular dementia component who were identified as part of the four waves of CCSMA were included in these analyses. The means and standard deviations of the baseline scores on the three outcomes were MMSE: 21.96 (4.62), CDR-sb: 5.93 (3.39), and NPI: 4.66 (9.25). Of the 335 participants, 70 (21%) were still active (alive and completing visits) at the time of close of the study. During the study, 217 (65%) individuals died and 48 (14%) moved away or withdrew from the study. Of the 335 participants, 105 (31.3%) had only one study visit. Among the 230 with at least one follow-up visit, the total number of visits ranged from 2 to 13 with a median of 4. The lengths of observation ranged from 0.65 to 11.18 years with a median of 3.07 years. Table 1 shows mean number of years of follow-up by presence or absence of each dichotomous baseline variable or tertile of each continuous variable. As anticipated, both GMHR and age were significantly associated with length of follow-up time. There was no clear relationship between length of follow-up and education, dementia duration, number of medical comorbidities, or medications at baseline.

There was considerable variability (both up and down) in GMHR over time within individuals. At the second visit, of the 226 subjects for whom we had GMHR ratings at both visits 1 and 2, 135 (60%) had the same rating as they had at visit 1, 26 (12%) had gotten worse, and 65 (28%) had improved. At the third visit, of the 149 subjects for whom we had GMHR ratings at both visits 2 and 3, 100 (67%) had the same rating as they had at visit 2, 32 (21%) had gotten worse, and 17 (11%) had improved.

Table 1. Follow-up time by baseline variables

BASELINE VARIABLES		N	MEAN (SD) OF FOLLOW-UP TIME	t or F
Gender	Male	220	2.38 (2.61)	$t(333) = 0.17$, $p = 0.86$
	Female	115	2.43 (2.36)	
APOE4	0	182	2.35 (2.54)	$t(331) = 0.46$, $p = 0.64$
	1+	151	2.48 (2.59)	
GMHR	1 or 2	110	1.81 (1.92)	$F(2,325) = 4.97$, $p = 0.008$
	3	181	2.75 (2.78)	
	4	37	2.66 (2.80)	

	Mean (SD) of follow-up time by tertile				
	Mean (SD)	Tertile 1	Tertile 2	Tertile 3	
Age	85.96 (6.29)	3.29 (2.83)	2.47 (2.62)	1.41 (1.74)	$F(2,332) = 16.59$, $p < 0.001$
Education	13.24 (3.0)	2.39 (2.57)	2.34 (2.40)	2.46 (2.65)	$F(2,332) = 0.04$, $p = 0.10$
Dementia duration	1.69 (1.25)	2.07 (2.28)	2.63 (2.63)	2.51 (2.73)	$F(2,332) = 1.52$, $p = 0.22$
Medical comorbidities	3.17 (1.98)	2.60 (2.72)	2.23 (2.53)	2.26 (2.27)	$F(2,332) = 0.81$, $p = 0.45$
Non-psychiatric medications	5.96 (4.55)	2.54 (2.75)	2.30 (2.37)	2.56 (2.62)	$F(2,332) = 0.36$, $p = 0.70$

APOE = Apolipoprotein E; GMHR = General Medical Health Rating.

Table 2. Baseline GMHR, non-psychiatric medications, comorbidities, and AD outcomes

	MMSE	CDR-sb	NPI-TOTAL
Baseline GMHR model			
Time	−1.82 (0.38)* $p < 0.001$	1.51 (0.28) $p < 0.001$	2.23 (0.82) $p < 0.01$
GMHR = 1 or 2	−1.26 (0.84) $p = 0.13$	1.50 (0.58) $p = 0.01$	4.78 (2.66) $p = 0.07$
GMHR = 3	0.55 (0.78) $p = 0.48$	−0.41 (0.54) $p = 0.45$	2.37 (2.48) $p = 0.34$
GMHR = 1/2 × time	0.23 (0.46) $p = 0.61$	−0.51 (0.34) $p = 0.13$	0.93 (1.05) $p = 0.38$
GMHR = 3 × time	−0.10 (0.42) $p = 0.82$	−0.06 (0.30) $p = 0.84$	0.11 (0.90) $p = 0.90$
Baseline age	−0.12 (0.04) $p < 0.01$	0.06 (0.03) $p = 0.05$	−0.14 (0.12) $p = 0.25$
Male	−1.07 (0.52) $p = 0.04$	−0.65 (0.35) $p = 0.07$	0.14 (1.51) $p = 0.92$
Education	0.24 (0.08) $p = 0.004$	0.03 (0.06) $p = 0.65$	0.02 (0.24) $p = 0.94$
Dementia duration	−1.18 (0.20) $p < 0.001$	1.04 (0.14) $p < 0.0001$	1.65 (0.58) $p < 0.01$
APOE-4 alleles	0.70 (0.50) $p = 0.16$	−0.05 (0.34) $p = 0.88$	2.05 (1.46) $p = 0.16$
Baseline medications and comorbidities model			
Time	−2.16 (0.33)* $p < 0.001$	1.5 (0.26) $p < 0.001$	4.13 (1.07) $p < 0.001$
Time^2	0.00 (0.04) $p = 0.97$	0.02 (0.03) $p = 0.41$	−0.29 (0.13) $p = 0.25$
Medications	0.02 (0.06) $p = 0.79$	0.01 (0.04) $p = 0.86$	0.09 (0.22) $p = 0.67$
Comorbidities	0.09 (0.14) $p = 0.51$	−0.11 (0.10) $p = 0.28$	0.25 (0.50) $p = 0.61$
Med. × time	0.03 (0.04) $p = 0.41$	−0.02 (0.03) $p = 0.49$)	0.08 (0.14) $p = 0.57$
Med. × time^2	0.00 (0.01) $p = 0.73$	0.00 (0.01) $p = 0.99$	−0.02 (0.02) $p = 0.38$
Comorb. × time	0.13 (0.09) $p = 0.15$	−0.11 (0.07) $p = 0.15$	−0.28 (0.30) $p = 0.35$
Comorb. × time^2	−0.02 (0.01) $p = 0.04$	0.010 (0.10) $p = 0.16$	0.05 (0.04) $p = 0.25$
Baseline age	−0.13 (0.04) $p = 0.001$	0.61 (0.03) $p = 0.03$	−0.02 (0.12) $p = 0.88$
Male	−1.08 (0.53) $p = 0.04$	−0.53 (0.36) $p = 0.15$	−0.32 (1.49) $p = 0.83$
Education	0.26 (0.08) $p = 0.002$	−0.01 (0.06) $p = 0.80$	−0.10 (0.23) $p = 0.66$
Dementia duration	−1.20 (0.20) $p < 0.001$	1.122 (0.14) $p < 0.000$	1.83 (0.55) $p = 0.001$
APOE-4 alleles	−0.64 (0.51) $p = 0.21$	−0.13 (0.35) $p = 0.71$	2.21 (1.41) $p = 0.12$

*β coefficient (standard error), p-value.
MMSE = Mini-Mental State Examination; CDR-sb = Clinical Dementia Rating – sum of boxes; NPI = Neuropsychiatric Inventory; GMHR = General Medical Health Rating; APOE = Apolipoprotein E.

Ordinal logistic regression models demonstrated modest, but statistically significant associations between baseline GMHR and number of co-morbidities ($p < 0.001$, pseudo-$r^2 = 0.08$) and number of non-psychiatric prescription medications ($p < 0.001$, pseudo-$r^2 = 0.03$). Pseudo-r^2 values represent scaled improvements in log likelihood values of the models with predictors as compared to a model with only an intercept (Agresti, 1999).

Table 3. Time-varying GMHR, non-psychiatric medications, comorbidities, and AD outcomes

	MMSE	CDR-sb	NPI-TOTAL
	Time-varying GMHR model		
Time	−1.65 (0.16)* $p < 0.001$	1.19 (0.13) $p < 0.001$	4.01 (0.56) $p < 0.001$
Time^2	−0.04 (0.02) $p = 0.03$	0.04 (0.02) $p = 0.01$	−0.25 (0.08) $p = 0.001$
GMHR = 1 or 2	−1.07 (0.42) $p = 0.01$	1.79 (0.34) $p < 0.001$	4.57 (1.80) $p = 0.01$
GMHR = 3	0.01 (0.34) $p = 0.98$	0.26 (0.28) $p = 0.35$	1.83 (1.49) $p = 0.22$
Baseline age	−1.22 (0.04) $p = 0.002$	0.05 (0.03) $p = 0.10$	−0.09 (0.12) $p = 0.43$
Male	−1.06 (0.52) $p = 0.04$	−0.70 (0.35) $p = 0.05$	−0.16 (1.49) $p = 0.91$
Education	0.24 (0.08) $p = 0.004$	0.03 (0.06) $p = 0.59$	−0.01 (0.24) $p = 0.98$
Dementia duration	−1.22 (0.19) $p < 0.001$	1.07 (0.13) $p < 0.001$	1.76 (0.57) $p = 0.002$
APOE-4 alleles	−0.69 (0.50) $p = 0.16$	−0.08 (0.34) $p = 0.82$	2.34 (0.44) $p = 0.11$
	Time-varying medications and comorbidities		
Time	−1.60 (0.17)* $p < 0.001$	1.05 (0.13) $p < 0.001$	3.75 (0.54) $p < 0.001$
Time^2	−0.05 (0.02) $p = 0.02$	0.06 (0.02) $p < 0.001$	−0.26 (0.07) $p < 0.001$
Medications	0.01 (0.04) $p = 0.86$	0.01 (0.03) $p = 0.78$	0.80 (0.15) $p = 0.61$
Comorbidities	−0.05 (0.08) $p = 0.57$	−0.03 (0.07) $p = 0.66$	−0.11 (0.32) $p = 0.73$
Baseline age	−0.13 (0.04) $p = 0.001$	0.06 (0.03) $p = 0.02$	−0.02 (0.12) $p = 0.84$)
Male	−0.91 (0.53) $p = 0.09$	−0.68 (0.37) $p = 0.06$	−0.32 (1.47) $p = 0.83$
Education	0.24 (0.08) $p = 0.004$	−0.01 (0.06) $p = 0.91$	−0.12 (0.23) $p = 0.62$
Dementia duration	−1.19 (0.20) $p < 0.001$	1.12 (0.14) $p < 0.001$	1.83 (0.55) $p = 0.001$
APOE-4 alleles	−0.63 (0.51) $p = 0.22$	−0.12 (0.35) $p = 0.73$	2.16 (1.41) $p = 0.12$

*β coefficient (standard error), p-value.
GMHR = General Medical Health Rating; MMSE = Mini-Mental State Examination; CDR-sb = Clinical Dementia Rating – sum of boxes; NPI = Neuropsychiatric Inventory; APOE = Apolipoprotein E.

Table 2 shows results from the first set of models used to determine the effect of baseline GMHR rating on decline. For each of the three outcomes, likelihood ratio tests suggested that quadratic time effects were not needed. Both time and dementia duration were significantly associated with worse scores on all three outcomes. Baseline GMHR ratings of 1 (poor) or 2 (fair) were significantly associated with higher (worse) CDR-sb scores, as compared with individuals with a baseline GMHR rating of 4, implying that, on average, individuals with GMHR ratings of 1 or 2 had CDR-sb scores, which were approximately 1.8 points higher than individuals with GMHR ratings of 4. Older age at baseline was associated with lower MMSE and higher CDR-sb scores. Male sex was associated with lower MMSE, and higher education was associated with higher MMSE. There were no statistically significant interactions between GMHR and time, suggesting that baseline GMHR ratings are not predictive of subsequent rate of decline.

Table 2 also shows models with number of comorbid medical conditions and number of non-psychiatric medications as predictors of change in AD outcomes. The model for NPI total contains only a random effect for the intercept, as the model with random effects for both intercept and time failed to converge. For all three outcomes, likelihood ratio tests showed that the time^2 terms were necessary. Therefore, these terms were retained even when they were not statistically significant individually. Both time and dementia duration were statistically significantly associated with lower scores on all three outcomes. Older age at baseline was associated with lower MMSE and higher CDR-sb scores. Male sex was associated with lower MMSE, and higher education was associated with higher MMSE. With the exception of the interaction between number of comorbid medical conditions and time^2 for MMSE, neither comorbidities nor medications appeared to be associated with differences in rates of decline.

The next set of models, shown in Table 3, used GMHR as a time-varying covariate. All three outcomes were statistically significantly associated with time and time^2. For the MMSE and CDR-sb, individuals declined over time, and the mean rate of decline increased with time. For the NPI, the positive time term but the negative time^2 term suggests that NPI worsens over time, but that this worsening slows, or levels out, over the course of illness. As in the previous models, longer dementia duration was associated with worse ratings on all three outcomes. Male sex was associated with worse MMSE scores but better CDR-sb scores. For all three outcomes, having a GMHR of 1 or 2 (fair or poor) was statistically significantly associated with worse ratings.

Table 3 shows results from a similar set of models, but with the number of medical comorbidities and number of non-psychiatric medications as time-varying covariates. The

parameter estimates show a similar pattern to the time-varying GMHR analyses in Table 3, with time and time^2 being statistically significantly associated with all three outcomes, and with accelerating decline for both MMSE and CDR-sb, but decelerating decline (amelioration of worsening) for NPI total.

Discussion

In this population-based longitudinal study, health status (as measured by the GMHR) appeared to fluctuate over time rather than to decline monotonically for many of the participants. This may explain why baseline measures of health were not clear predictors of rates of dementia progression, and also suggests that GMHR may be a risk factor that can be altered, thus altering the course of patients' AD-related decline. GMHR at baseline was only associated with CDR-sb scores, and was not associated with rate of decline on any of the three outcomes. Neither number of comorbidities nor number of non-psychiatric medications at baseline was associated with decline on any of the three domains. By contrast, having a GMHR of 1 or 2 at a DPS visit was strongly associated with worse scores in all three domains at that same visit, though this was not true for medications or comorbidities. This suggests that GMHR, whose scoring is only partly based on number of comorbidities and medications, is capturing something above and beyond just simple counts. It further suggests that there is a dynamic relationship between medical and cognitive health, since the effect appears to be immediate and GMHR fluctuates in a substantial portion of the sample.

The literature on the relationship between general medical health and dementia is somewhat sparse. The majority of papers to date describe cross-sectional studies. Of the two previously published cohort studies, one found that fast progressors had significantly *more* comorbidities (Boksay *et al.*, 2005), while the second found that a larger number of medications were associated with *slower* decline (Storandt *et al.*, 2002). We found no association between decline in any domain with either comorbidities or prescriptions, as measured at baseline. Neither study reported on health variables measured longitudinally.

For the most part, our findings confirmed previously reported risk factors for poorer outcomes, including older age and greater dementia duration at baseline. Female sex is generally associated with worse prognosis; we found that female sex was associated with higher MMSE scores but worse CDR-sb scores. Several studies have found an association between higher education and poorer outcomes, but in our sample we found associations with higher scores on MMSE and no associations with either CDR or NPI. Contrary to some published reports, presence of one or more APOE-4 alleles was not significantly associated with any of the outcomes in either the baseline or time-varying models.

The strengths of this study include its population-based cohort and its capture of incident cases, thus allowing for observation over the full course of illness. The high participation rates and longevity of Cache County residents (Tschanz *et al.*, 2011) serve to reduce potential biases as a result of selection or competing risks. Another strength is the wealth of information collected, including measures of dementia progression in three domains, detailed health status assessment, and medication use data.

Potential limitations include the lack of follow-up in approximately one-third of the sample and the association between low GMHR and shorter follow-up time. This association likely resulted in estimates of associations between poor health and faster dementia progression that were biased toward the null hypothesis, as the sicker individuals were less likely to be observed. Hence, our findings of an association between GMHR ratings and dementia progression are probably conservative. Health status is complex and difficult to measure, particularly because it is a dynamic process. Though it has demonstrated excellent reliability and validity, the GMHR is a global measure, which does not allow for differential weightings of conditions that may have a greater or lesser impact on health status as other ratings do. In the majority of follow-up visits, CDR and GMHR ratings were performed by the same nurse, thus introducing the possibility that scores on one instrument influenced scores on the other. This study only enrolled individuals aged $\geq$65 years, therefore these findings may not apply to those with early onset AD. The Cache County population is predominantly white, well-educated, and of northern European descent, thus potentially limiting the generalization of the findings to other populations. Further, the majority of the study sample belong to the Church of Jesus Christ of Latter Day Saints, which prohibits tobacco, caffeine, and alcohol use, thus limiting our ability to assess the effects of these substances on dementia progression. This may also have altered the relationship between dementia progression and medical comorbidities known to be associated with these behaviors, such as cardiovascular disease and certain cancers (Breitner *et al.*, 1999). Despite this potential limitation, atrial fibrillation, systolic hypertension, and angina have been associated with faster decline on MMSE and CDR-sb in this sample (Mielke *et al.*, 2007).

Our findings show that health status, as measured by GMHR, can fluctuate both up and down, and they suggest that the course of decline might be improved through better medical care. This lends additional support to recent recommendations and practice guidelines calling for increased attention to general medical care among individuals with AD (Lyketsos *et al.*, 2006; Rabins *et al.*, 2006; Lyketsos, 2012). One potential barrier to this is the fragmentation and lack of continuity of health care provision in the USA (Bartels, 2003). One solution is the adoption of more collaborative models of care; several recent studies have demonstrated their efficacy in improving some outcomes (Vickrey *et al.*, 2006; Counsell *et al.*, 2007; Callahan *et al.*, 2011) without additional net costs (Counsell *et al.*, 2009).

It is important to note that while we have demonstrated an association between GMHR and dementia progression, we have not demonstrated a causal relationship. Establishing such a relationship in an observational study is difficult, in part because it is not possible to determine the temporal order in cases where both medical and cognitive declines (or gains) occurred between study visits. It is reasonable to suggest that poorer physical health would lead to poorer cognitive/mental health by placing an additional stressor on the brain, but the reverse is also plausible. Poorer cognition and function or increased psychiatric symptoms could lead to physical decline through self-neglect, improper medication administration and monitoring of chronic conditions, such as diabetes or asthma, decreased access to health services, or decreased social and physical activity. It is likely that mechanisms in both directions are at work. Given the paucity of potentially modifiable factors affecting the course of dementia, further study of this relationship is warranted.

Conflict of interest

None.

Description of authors' roles

Dr. Jeannie-Marie S. Leoutsakos had full access to all the data and takes responsibility for data integrity and accuracy of the data analysis, performed and interpreted the analyses, drafted the paper, and gave the approval for final version to be published. Dr. Dingfen Han performed and interpreted analyses, edited the paper for content, and gave approval for final version to be published. Dr. Michelle M. Mielke contributed to design and interpretation of analyses, edited the paper for content, and gave approval for final version to be published. Sarah N. Forrester assisted in the performance of analyses and drafting of the paper, and gave approval for final version to be published. Dr. JoAnn T. Tschanz participated in study design and oversaw data collection, edited the paper for content, and gave approval for the final version to be published. Dr. Chris D. Corcoran contributed to interpretation of analyses, edited the paper for content, and gave approval for final version to be published. Dr. Robert C. Green, Dr. Maria C. Norton, Dr. Kathleen A. Welsh-Bohmer and Dr. Constantine G. Lyketsos participated in study design and analysis interpretation, edited the paper for content, and gave approval for the final version to be published.

Dr. Tschanz and Dr. Lyketsos were the co-senior authors.

Acknowledgments

The work was supported by the following NIH grants: R01AG21136, R01AG11380, R01AG18712, R01HG02213,30AG028377, K24AG027841, and P30AG13846.

References

Agresti, A. (1999). Modelling ordered categorical data: recent advances and future challenges. *Statistics in Medicine*, 18, 2191–2207.

Aguero-Torres, H., Fratiglioni, L. and Winblad, B. (1998). Natural history of Alzheimer's disease and other dementias: review of the literature in the light of the findings from the Kungsholmen Project. *International Journal of Geriatric Psychiatry*, 13, 755–766.

Alzheimer's Association (2010). 2010 Alzheimer's disease facts and figures. *Alzheimer's & Dementia*, 6, 158–194. doi: 10.1016/j.jalz.2010.01.009.

American Psychiatric Association (1987). *Diagnostic and Statistical Manual of Mental Disorders, DSM-III-R*. Washington, DC: American Psychiatric Association.

Andel, R., Vigen, C., Mack, W. J., Clark, L. J. and Gatz, M. (2006). The effect of education and occupational complexity on rate of cognitive decline in Alzheimer's patients. *Journal of the International Neuropsychological Society*, 12, 147–152.

Bartels, S. J. (2003). Improving system of care for older adults with mental illness in the United States. Findings and recommendations for the President's New Freedom Commission on Mental Health. *American Journal of Geriatric Psychiatry*, 11, 486–497.

Boksay, I., Boksay, E., Reisberg, B., Torossian, C. and Krishnamurthy, M. (2005). Alzheimer's disease and medical disease conditions: a prospective cohort study. *Journal of the American Geriatrics Society*, 53, 2235–2236.

Bracco, L. *et al.* (2007). Pattern and progression of cognitive decline in Alzheimer's disease: role of premorbid intelligence and ApoE genotype. *Dementia and Geriatric Cognitive Disorders*, 24, 483–491. doi: 10.1159/000111081.

Breitner, J. C. *et al.* (1999). APOE-epsilon4 count predicts age when prevalence of AD increases, then declines: the Cache County Study. *Neurology*, 53, 321–331.

Brickman, A. M. *et al.* (2008). Measuring cerebral atrophy and white matter hyperintensity burden to predict the rate of cognitive decline in Alzheimer disease. *Archives of Neurology*, 65, 1202–1208. doi: 10.1001/archneur.65.9.1202.

Buerger, K. *et al.* (2005). Phosphorylated tau predicts rate of cognitive decline in MCI subjects: a comparative CSF study. *Neurology*, 65, 1502–1503. doi: 10.1212/01.wnl.0000183284.92920.f2.

Callahan, C. M. *et al.* (2011). Implementing dementia care models in primary care settings: the Aging Brain Care Medical Home. *Aging & Mental Health*, 15, 5–12. doi: 10.1080/13607861003801052.

Casella, G. and Berger, R. L. (2002). *Statistical Inference, Second Edition*. Pacific Grove, CA: Duxbury Press.

Colantuoni, E., Surplus, G., Hackman, A., Arrighi, H. M. and Brookmeyer, R. (2010). Web-based application to project the burden of Alzheimer's disease. *Alzheimer's & Dementia*, 6, 425–428. doi: 10.1016/j.jalz.2010.01.014.

Cortes, F. *et al.* (2008). Prognosis of Alzheimer's disease today: a two-year prospective study in 686 patients from the REAL-FR Study. *Alzheimers & Dementia*, 4, 22–29.

Counsell, S. R. *et al.* (2007). Geriatric care management for low-income seniors: a randomized controlled trial. *JAMA*, 298, 2623–2633. doi: 10.1001/jama.298.22.2623.

Counsell, S. R., Callahan, C. M., Tu, W., Stump, T. E. and Arling, G. W. (2009). Cost analysis of the geriatric resources for assessment and care of elders care management intervention. *Journal of the American Geriatrics Society*, 57, 1420–1426.

Cummings, J. L. (1997). The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. *Neurology*, 48, S10–S16.

Dooneief, G., Marder, K., Tang, M. X. and Stern, Y. (1996). The Clinical Dementia Rating scale: community-based validation of "profound" and "terminal" stages. *Neurology*, 46, 1746–1749.

Doraiswamy, P. M., Leon, J., Cummings, J. L., Marin, D. and Neumann, P. J. (2002). Prevalence and impact of medical comorbidity in Alzheimer's disease. *Journals of Gerontology, Series A: Biological Sciences and Medical Sciences*, 57, M173–M177.

Folstein, M. F., Folstein, S. E. and McHugh, P. R. (1975). "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatry Research*, 12, 189–198.

Hoyt, B. D., Massman, P. J., Schatschneider, C., Cooke, N. and Doody, R. S. (2005). Individual growth curve analysis of APOE epsilon 4-associated cognitive decline in Alzheimer disease. *Archives of Neurology*, 62, 454–459. doi: 10.1001/archneur.62.3.454.

Hughes, C. P., Berg, L., Danziger, W. L., Coben, L. A. and Martin, R. L. (1982). A new clinical scale for the staging of dementia. *British Journal of Psychiatry*, 140, 566–572.

Jung, S. H. and Ahn, C. (2003). Sample size estimation for GEE method for comparing slopes in repeated measurements data. *Statistics in Medicine*, 22, 1305–1315.

Kawas, C., Segal, J., Stewart, W. F., Corrada, M. and Thal, L. J. (1994). A validation study of the dementia questionnaire. *Archives of Neurology*, 51, 901–906.

Kester, M. I. *et al.* (2009). CSF biomarkers predict rate of cognitive decline in Alzheimer disease. *Neurology*, 73, 1353–1358. doi: 10.1212/WNL.0b013e3181bd8271.

Kuo, T. C., Zhao, Y., Weir, S., Kramer, M. S. and Ash, A. S. (2008). Implications of comorbidity on costs for patients with Alzheimer disease. *Medical Care*, 46, 839–846.

Laird, N. and Ware, J. H. (1982). Random-effects models for longitudinal data. *Biometrics*, 38, 963–974.

Lyketsos, C. G. (2012). Prevention of unnecessary hospitalization for patients with dementia: the role of ambulatory care. *JAMA*, 307, 197–198. doi: 10.1001/jama.2011.2005.

Lyketsos, C. G. *et al.* (1999). The General Medical Health Rating: a bedside global rating of medical comorbidity in patients with dementia. *Journal of the American Geriatrics Society*, 47, 487–491.

Lyketsos, C. G., Steinberg, M., Tschanz, J. T., Norton, M. C., Steffens, D. C. and Breitner, J. C. (2000). Mental and behavioral disturbances in dementia: findings from the Cache County Study on Memory in Aging. *American Journal of Psychiatry*, 157, 708–714.

Lyketsos, C. G. *et al.* (2005). Population-based study of medical comorbidity in early dementia and "cognitive impairment, no dementia (CIND)": association with functional and cognitive impairment: the Cache County Study. *American Journal of Psychiatry*, 13, 656–664.

Lyketsos, C. G. *et al.* (2006). Position statement of the American Association for Geriatric Psychiatry regarding principles of care for patients with dementia resulting from Alzheimer disease. *American Journal of Geriatric Psychiatry*, 14, 561–572. doi:10.1097/01.JGP.0000221334.65330.55.

Martins, C. A., Oulhaj, A., de Jager, C. A. and Williams, J. H. (2005). APOE alleles predict the rate of cognitive decline in Alzheimer disease: a nonlinear model. *Neurology*, 65, 1888–1893.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D. and Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of department of health and human services task force on Alzheimer's disease. *Neurology*, 34, 939–944.

Mielke, M. M. *et al.* (2007). Vascular factors predict rate of progression in Alzheimer disease. *Neurology*, 69, 1850–1858. doi: 10.1212/01.wnl.0000279520.59792.fe.

Mungas, D. *et al.* (2002). Volumetric MRI predicts rate of cognitive decline related to AD and cerebrovascular disease. *Neurology*, 59, 867–873.

Rabins, P. V., Lyketsos, C. G. and Steele, C. (2006). *Practical Dementia Care*. New York: Oxford University Press.

StataCorp LP (2009). STATA Version 11.1. Texas: StataCorp.

Storandt, M., Grant, E. A., Miller, J. P. and Morris, J. C. (2002). Rates of progression in mild cognitive impairment and early Alzheimer's disease. *Neurology*, 59, 1034–1041.

Teng, E. L. and Chui, H. C. (1987). The Modified Mini-Mental State (3MS) Examination. *Journal of Clinical Psychiatry*, 48, 314–318.

Tschanz, J. T. *et al.* (2000). Dementia diagnoses from clinical and neuropsychological data compared: the Cache County study. *Neurology*, 54, 1290–1296.

Tschanz, J.T., Welsh-Bohmer, K.A., Plassman, B.L., Norton, M.C., Wyse, B.W. and Breitner, J.C. (2002). An adaptation of the modified Mini-Mental State Examination: analysis of demographic influences and normative data: the Cache County study. *Neuropsychology, Neuropsychiatry, and Behavioral Neurology*, 15, 28–38.

Tschanz, J. T. *et al.* (2011). Progression of cognitive, functional, and neuropsychiatric symptom domains in a population cohort with Alzheimer dementia: the Cache County Dementia Progression Study. *American Journal of Geriatric Psychiatry*, 19, 532–542. doi: 10.1097/JGP.0b013e3181faec23.

Vickrey, B. G. *et al.* (2006). The effect of a disease management intervention on quality and outcomes of dementia care: a randomized, controlled trial. *Annals of Internal Medicine*, 145, 713–726.

Wilkosz, P. A. *et al.* (2010). Trajectories of cognitive decline in Alzheimer's disease. *International Psychogeriatrics*, 22, 281–290.

Wilson, R. S. *et al.* (2004). Education and the course of cognitive decline in Alzheimer disease. *Neurology*, 63, 1198–1202.

Xie, S. X., Ewbank, D. C., Chittams, J., Karlawish, J. H., Arnold, S. E. and Clark, C. M. (2009). Rate of decline in Alzheimer disease measured by a dementia severity rating scale. *Alzheimer Disease and Associated Disorders*, 23, 268–274. doi: 10.1097/WAD.0b013e318194a324.