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Changes in frailty predict changes in cognition in older men: the Honolulu-Asia Aging Study

J.J. Armstrong, PhD¹, J. Godin, PhD², L.J. Launer, PhD³, L.R. White, MD⁴, A. Mitnitski, PhD¹, K. Rockwood, MD¹, and M.K. Andrew, PhD, MD^{1,2}

¹Geriatric Medicine Research Unit, Department of Medicine, Dalhousie University, Nova Scotia, Canada

²Geriatric Medicine Research Unit, Nova Scotia Health Authority, Nova Scotia, Canada

³Laboratory of Epidemiology and Population Sciences, National Institute on Aging, Bethesda, Maryland, USA

⁴Pacific Health Research & Education Institute, Honolulu Hawaii, USA

Abstract

Objectives—As cognitive decline mostly occurs in late life, where typically it co-exists with many other ailments, it is important to consider frailty in understanding cognitive change. Here, we examined the association of change in frailty status with cognitive trajectories in a well-studied cohort of older Japanese-American men.

Methods—Using the prospective Honolulu-Asia Aging Study (HAAS), 2817 men of Japanese descent were followed (aged 71–93 at baseline). Starting in 1991 with follow-up health assessments every two to three years, cognition was measured using the Cognitive Abilities Screening Instrument (CASI). For this study, health data was used to construct an accumulation of deficits frailty index (FI). Using six waves of data, multilevel growth curve analyses were constructed to examine simultaneous changes in cognition in relation to changes in the frailty index (FI), controlling for baseline frailty, age, education, and APOE-ε4 status.

Results—On average, CASI scores declined by 2.0 points per year (95% confidence interval 1.9–2.1). Across six waves, each 10% within-person increase in frailty from baseline was associated

Corresponding Author: Kenneth Rockwood, Suite 1421 Veterans' Memorial Building, 5955 Veterans' Memorial Lane, Halifax, NS. B3H 2E1, Kenneth.Rockwood@dal.ca; Fax: (902) 473-4908.

Contributors

JJA drafted and revised the manuscript for content, conducted data analyses, and prepared the results. JG constructed the figure and helped with the analyses and interpretation of data. LJA and LRW assisted with acquisition of data and revising of the manuscript. AM helped with the analyses and interpretation of the data. MKA assisted with revising the manuscript for content. KR supervised the research and revised the manuscript. All authors contributed to the interpretation of the results and worked on and agreed on the final version of the manuscript.

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with a 5.0 point reduction in CASI scores (95% confidence interval 4.7–5.2). Baseline frailty and age were associated both with lower initial CASI scores and with greater decline across the five follow-up assessments ($p < 0.01$).

Conclusions—Cognition is adversely affected by impaired health status in old age. Using a multidimensional measure of frailty, both baseline status and within-person changes in frailty were predictive of cognitive trajectories.

Keywords

Frail elderly; Cognition; Aging; Cohort studies; Risk factors

INTRODUCTION

Despite considerable advances in understanding the epidemiology of cognitive impairment, age remains the most potent risk factor for dementia.[1] This is an important signal, but what to make of it is unclear. Often age is seen simply as a non-modifiable risk factor.[2] One consequence has been a search for “pure” Alzheimer disease in younger people, and for early-onset disease arising from single gene mutations.[3] Support for this view is not unanimous. Some critics argue that the generalizability of insights from studies in early-onset disease, seen in no more than 1% of dementia patients, is suspect for the other 99%.[4] Others argue that in not addressing aging, the opportunity to understand how Alzheimer disease works is being lost: it cannot be for nothing that this is mostly seen in old age.[5–7]

Advanced age alone cannot fully account for the incidence of dementia, if only because age is notably heterogeneous in conveying risk. Although closely tied to the chance of dying, especially after age 40, even amongst people of the same chronological age, mortality risk varies considerably.[8] Recognition of this variability was at the heart of the notion of “frailty”, introduced as a term in age-mortality regression modeling to describe people at an increased risk compared with their age peers.[8] The concept has been elaborated since to describe a clinical phenomenon[9] that appears to be especially relevant to understanding the risk of cognitive impairment.[10] (This is distinct from the two sometimes being grouped in an entity (“cognitive frailty”) that is said to represent a “single complex phenotype”, and has been considered separately.[11]) The overarching concept of frailty integrates many of the effects of biological and environmental interactions that give rise to the increased risk seen with age. This is an explicit motivation of one approach to measuring frailty, which is by quantifying the extent to which individuals have accumulated health deficits.[12]

To measure frailty, the Frailty Index (FI) was designed as a *state variable* that integrates multiple sources of health information. In this way, it quantifies the package in which come “the problems of old age”. [5] The FI has been shown to be a reliable predictor of adverse outcomes in a variety of older populations from around the world (e.g., Canada,[13] USA, [14] China,[15] Sweden[16], and the EU[17]).

Several epidemiological studies having identified significant associations between frailty and cognitive impairment.[7,18–21] Even so, most studies linking cognition to frailty have been either cross-sectional or cross-lagged[11], which ignores the dynamic nature of both

cognition and frailty,[22,23] and which obliges using longitudinal data. Here, we employ multilevel growth curves to study how change in cognition relates to change in frailty, controlling for age, education, and APOE $\epsilon 4$ status. In this way, we can test whether the very strong relationship between dementia and age reflects not simply age, but the many health deficits that go with it.

MATERIALS AND METHODS

Study Population

Data were from the Honolulu-Asia Aging Study (HAAS), a prospective cohort study which began in 1991. The chief aim of HAAS was to examine factors associated with late-life cognition and other conditions related to aging, and the design of the study has been published elsewhere.[24] Briefly, the HAAS consists of men who had been enrolled in the Honolulu-Heart Program (HHP; 1965–1975).[25] In 1991, 80% of the survivors of the original HHP cohort were enrolled in the HAAS (3845 men; age range, 71–93 years), with no age difference in the participants and non-participants. Follow-up examinations took place approximately every 2–3 years, with six follow-up exams over the following 18 years. An overview of the cohort across study can be found in Figure 1. Information at each wave was collected through structured interviews and standardized evaluations. Data collection was approved by the Kuakini Medical Center IRB, with informed consent provided by all participants. Approval for the secondary analyses came from the Research Ethics Committee of the Nova Scotia Health Authority, Halifax, Nova Scotia, Canada.

Here, we examined HAAS waves 1–3 and 5–7. We were obliged to omit Wave 4, which lacked sufficient variety of health assessment items, so that an accumulation of deficits frailty index could not be calculated. We excluded men with less than two cognitive assessments ($n=1011$) and those missing APOE $\epsilon 4$ information ($n = 281$), baseline frailty ($n = 44$), and years of education ($n=155$). After these exclusions, 2817 men were included in the analyses. Differences between included and excluded participants can be found in Table 1.

Outcome measure

The CASI[26] was used to assess cognitive function at each study wave and is considered a comprehensive measure of global intellectual function designed for use in cross-cultural studies. The CASI is scored on a 100 point scale and is a combination of the Hasegawa Dementia Screening Scale, the Folstein Mini-Mental State Examination,[27] and the Modified Mini-Mental State Examination (3-MS).[28] The CASI has been used to examine cognitive performance over time[29–31], but never in relation to frailty.

Frailty Index

We calculated a frailty index (FI)[32] based on the accumulation of deficits using a standard procedure.[33] Variables were selected as health deficits if they were associated with health status, accumulate with age, and have prevalence greater than 1% but less than 80% in the sample. For consistency, we only included frailty items that could be found across the majority of waves (Table 2). Each variable was dichotomized (0 for deficit absent; 1 for

present). These deficits were then summed and divided by the total number of deficits considered (max = 34; Table 2). Thus, a participant with no missing measurements and 17 deficits would be given a FI score of 0.50. No FI was calculated for study participants with more than 20% missing deficit data (N=44). Compared to those with complete data, those with missing FIs were not significantly different in age or time to death, but were significantly different in their CASI scores. A more detailed description of the FI in the HAAS has been published[34]; note that here the FIs do not contain any deficits that are directly related to cognition (e.g., difficulty in paying bills was removed). For ease of interpretation, FI scores were transformed by multiplication (x10) with model results representing 10% increases in FI scores. When examining longitudinal data using multilevel growth curves, it is important to disaggregate between- and within-person effects. Here, baseline frailty was added into the growth curve models to account for between-person differences at baseline. Within-person effects of frailty were estimated by calculating frailty change from baseline at all follow-up assessments and was entered into the multilevel growth curve models as a time-varying covariate.

Covariates

Due to their known relationships with late-life cognition, three control variables were included in the models: age at baseline, years of education, and APOE ϵ 4 status. Age and education were measured in years. APOE ϵ 4 status was coded as a binary variable: no ϵ 4 vs. any ϵ 4. Hardy-Weinberg equilibrium using the genotype distribution was tested by chi-square test. These variables were considered time invariant.

Model Specification and Analysis

The objectives of the analyses were: (1) to assess the extent to which cognitive trajectories are patterned by between-person differences in frailty; and (2) to assess whether within-person changes in frailty are associated with within-person changes in cognition. All analyses were performed in SPSS 22.0 using the Mixed Linear Modeling (MLM) procedure. This procedure was used to generate multilevel growth curve models using repeated measurements of the CASI to estimate a growth trajectory in cognitive test scores. The starting point of the trajectory is the intercept, representing average cognition (CASI score) at baseline for the average participant with no APOE ϵ 4 alleles or health deficits (zero-state). The slopes estimate rates of change in CASI scores. The analytic strategy employed a series of nested models, as outlined Shaw and Liang,[35] to address the two objectives of the study. Data were assumed to be missing at random (MAR) over the six waves of the HAAS. Data are MAR when any associations between a variable with missing data and the missingness itself is accounted for by other variables in the data set.[36] Although there is no way to test whether the data are MAR, given the range of variables included in our analyses (i.e., age, education, time, frailty, cognition, APOE), we believe that the MAR assumption is tenable. The metric of change in this study was time, with the baseline assessment date as time zero and time between examinations measured in days. This approach accounts for differences between individuals in the time spans between examinations.

We started with a random intercept model to calculate the Intraclass Correlation Coefficient (ICC),[37] which is used here as an estimate of the amount of variation in CASI scores that

can be attributed to inter-individual differences. The next model was developed to determine the average pattern of change in cognition by examining the trajectories in CASI scores over time, without the influence of any covariates. In Model 3, time-constant predictor variables (age, education, APOE, baseline frailty) are added to the model and their effects on the cognitive trajectories are evaluated (Objective #1). Both age and education were grand mean centered (a zero score represents the average) so the intercept and slopes are representative of the pattern for the average aged and average educated men in the study, with no APOE $\epsilon 4$ alleles. We chose not to grand mean center baseline frailty in the models as the zero-state (i.e., the lowest frailty index score) is of interest. Individuals in the zero-state represent the fittest group, and are the ideal comparison here.[34] By examining the healthiest individuals, we can understand the impact of covariates controlling for the impact of health state. In other words, the outcomes of the fittest group represent the background/ambient changes experienced by this group.[38]

In the next step, we continued to build upon the model by adding change in frailty from baseline (Objective #2). This final model tested whether within-person changes in frailty were associated with within-person changes in cognition, after accounting for between-person differences. Statistics including -2 Log Likelihood (-2LL) Akaike Information Criterion (AIC), and Bayesian Information Criterion (BIC) were used to assess model fit. Chi-square likelihood-ratio tests were used to assess differences between nested models. QQ-plots and scatterplots were used to check the assumptions that residuals and random effects are centered at zero, normally distributed, and independent.

RESULTS

Descriptive Analyses

The mean baseline age was 77.1 years (SD = 4.2) and the mean level of education was 10.7 years (SD = 3.2). The mean FI score increased from 0.13 at baseline (SD = 0.08) to 0.22 at Wave 7 (SD = 0.12). On average, the CASI score decreased from baseline (mean = 85.4; SD = 11.2) to Wave 7 (mean = 67.7; SD = 23.3). For APOE status, 19.2% of the participants at baseline were $\epsilon 4$ positive and the baseline cohort was found not to be in Hardy-Weinberg equilibrium ($p=0.02$). The descriptive analyses of the covariates and dependent variable by wave are summarized in Table 4.

Model 1: Unconditional Means Model

The estimates of the residual and intercept covariance were 162.1 (SE=2.74) and 134.6 (SE=5.2), respectively. The intraclass correlation was 0.45, which indicates that 45% of the variation in CASI scores occurred between persons. Conversely, 55% of the variation in CASI scores was due to within-person changes over time. This result indicates that the nested variation in the CASI scores warrants the use of a multilevel modeling growth curve analytic approach.

Model 2: Unconditional Growth Models - Determining Average Trajectory

Based on this model using no covariates, the average initial CASI score was 86.1 (Table 4, Model 2). The negative time estimate ($\beta = -2.0$, 95% CI = $-2.1, -1.9$) indicates that on

average, participants experienced a decline in CASI scores of 2.0 points per year. The covariance estimates indicate that there were significant between-subjects variations in the initial status of the CASI and significant differences in the slopes (trajectories).

Model 3: Growth Curve Models – Adding Time Invariant Predictors

Building on the previous model, age, education, APOE status, and baseline frailty were added as time-constant fixed effects. Interactions of the covariates with time were also added to evaluate their impact on the slope of CASI change. The results (Table 4, Model 3) indicated that after accounting for all covariates, education was found to have a protective effect of 1.0 additional points for every additional year of education above the cohort's mean (11 years). Older age was associated with lower baseline CASI scores ($\beta = -0.63$, 95%CI = $-0.71, -0.54$) and steeper decline over time ($\beta = -0.1$, 95%CI = $-0.17, -0.13$). Baseline frailty was significantly associated with both lower CASI scores at baseline ($\beta = -4.4$, 95%CI = $-4.9, -4.0$) and with steeper decline over the follow-up assessments ($\beta = -0.5$, 95%CI = $-0.7, -0.4$). APOE- $\epsilon 4$ status had a non-significant impact on the intercept of CASI scores ($p=0.06$) but a significant interaction with time ($\beta = -0.6$, 95%CI = $-0.8, -0.4$). Figure 1A uses Model 3 results to depict three hypothetical individuals with varying levels of frailty at baseline. Model fit statistics (AIC and BIC) also substantially decreased, indicating that the addition of the covariates in Model 3 was better fit the data when compared to Model 2.

Model 4: Growth Curve Models – Adding Frailty as a Time-Varying Predictor

In the final model, frailty change from baseline was added as a time-varying covariate. On average, after accounting for age, education, and baseline frailty, change in the frailty index (each 10% increase) was associated with a five point drop in CASI ($\beta = -5.0$, 95%CI = $-5.2, -4.7$). The effects of the time-invariant predictors remained fairly constant with the exception of time, which dropped to -0.7 from -1.2 . Figure 1B uses Model 4 results to illustrate the impact of baseline frailty and change in frailty in three hypothetical individuals.

Across the four models, the residual variances and statistics for overall model fitting ($-2LL$, AIC, BIC) decreased, suggesting that the final model that contained all of the covariates had the best fit with the data, and accounted for more of the variance in cognitive test scores than did the prior models. Chi-square likelihood-ratio tests between each subsequent models indicated significant improvement with each step ($p < 0.05$). Residuals and random effects were normally distributed and centered around zero. The scatterplot indicated a moderately strong correlation between intercept and time, our two random effects. This is not surprising as we would expect participants with high baseline CASI score to decline at a slower rate compared to those with lower scores.

DISCUSSION

Using data from a well-known cohort study on aging, we examined cognitive changes in older Japanese American men in relation to age, education, baseline frailty (between-person differences) and within-person changes in frailty. Worse health status (higher FIs) was associated with worse cognition at baseline and a faster rate of cognitive decline over the

study period. This supports the association between frailty and cognition,[7,18–21] and extends that understanding by demonstrating that, not just the individual degree of frailty at baseline, but within-person increases in frailty are associated with substantial cognitive decline. This new finding emphasizes the need for research on the relationship between frailty and age-associated cognitive decline to move beyond static approaches.

These results illustrate that compared with individual risk factors, the cumulative burden of health deficits may have a greater impact on risk of cognitive decline and dementia in the oldest-old.[7,22,38–40] Considering that the FI can be used as a reliable indicator of biological age,[32,40,41] the FI approach provides a means to move away from considering age simply as a non-modifiable risk factor and more to seeing it as a crude measure of cumulative changes over the life course, for which better measures – many captured by the notion of biological age – are available.[6,42]

At the cellular level, aging is considered to result from a range of highly intertwined processes, so that understanding the interplay between them is a critical next step.[43] Similarly at the clinical level, in the last few decades biomedical research has demonstrated how aging enables pathology across most chronic diseases including neurodegenerative disorders. [44] A recent review highlighting the many challenges of translating knowledge in Alzheimer's disease recognized that importance of age, but offered few remedies beyond possibly using senescence-accelerated animal models.[45] By quantifying aging through integrating information across body systems, (in effect by quantifying the package of the problems of old age) the FI can be used to quantify the extent to which physiologic and genetic factors contribute to the whole-body physiologic dysregulation.[41]

Although many studies have linked frailty with cognitive impairment and dementia, fewer have examined causal mechanisms. Frailty and dementia are hypothesized to share a common pathologic basis, including neuropathology[46,47] and in the body's ability to recover from damage.[40,48] Research from the Religious Orders Study and the Rush Memory and Aging Project suggests that the rate of progression of frailty is associated with the accumulation of multiple brain pathologies including Alzheimer disease pathology, macroinfarcts, and nigral neuronal loss. [46,47] How frailty might modify the relationship between brain lesions and global cognitive function has not yet been investigated. With the understanding that there is an inexact correlation between neuropathological lesions and cognitive function in late-life,[49,50] together with the modified rates of incident dementia and the impact of risk factors in frail older adults,[51] examining cohort studies and autopsy data through the lens of accumulated health deficits has the potential to provide new insights into the potent relationship between age and sporadic late-onset Alzheimer's disease.

Many of the studies on frailty and dementia have employed the Fried phenotype of frailty. [52] It is perhaps not surprising that this phenotype should be associated with increased risk, as each of its five components are considered as risk factors for dementia. By considering the accumulation of a broad range of health deficits, multiple studies have demonstrated significant increases in dementia risk are seen in frail older adults.[7,23] Furthermore, in a 2011 study examining a frailty index composed entirely of non-traditional risk factors (e.g., improper denture fit, stomach trouble) in the Canadian Study of Health and Aging, the

resulting index was able to delineate dementia risk and outperformed known risk factors in prediction of dementia onset.[53] Together, regardless of which frailty measure is used, these studies indicate that age-associated decline in health status is a strong risk factor for cognitive decline.

Even though an index approach might seem to lack specificity for determining individual causal mechanisms, it offers several advantages that can make causality clearer, allowing a broader perspective on late-life dementia risk, and offering a pragmatic way to think differently about the impact of age on disease risk.[11,40] The frailty index shows that deficit accumulation is not just a late-life phenomenon.[13] As a consequence of deficit interaction in and of itself – i.e. absent any explicit age dependence[54] – deficits accumulate across the life course at a constant rate – mercilessly, like compound interest.[55] This understanding makes clear why some studies have found midlife factors (hypertension, obesity) to be important in late-life cognitive decline.[56] It also challenges risk factor studies that have only adjusted for age, without considering the variability in health status that is seen with age, or for the studies that report single new risk factors, also without considering such variability. This is why earlier reports from our group – which drew to attention an index of “non-traditional risk factors”[21,53] – was not meant to draw to attention those specific items as new risk factors, but to show that cognitive decline in late life is related to overall health status, and to offer an integrative measure, which is needed if we are to get to grips with how ageing enables disease.[44] Whether the coincidence of cognitive impairment in people with many health deficits constitutes a specific phenotype of cognitive frailty, or whether it shows that past a certain degree of deficit accumulation, the chance of leaving cognitive function intact decline – remains a challenge.[11,57] A related implication is that, if dementia largely arises in frail elderly people as a result of multiple interlocking risk factors over the life course, it is doubtful that a “therapeutic silver bullet” for the disease will be found, despite the enormous amounts of effort and resources being put towards finding effective drug treatments.[58]

On average in the HAAS participants, men with higher educational achievement experienced a protective effect on both the baseline CASI score (intercept) and on rate of change in cognition (slopes). Previous research on education’s effect on cognitive trajectories has been mixed, with educational attainment attenuating cognitive decline in some studies, while others have found higher education to have no such effect.[59] The results of this study in the HAAS cohort support the notion that by some set of mechanisms education enhances cognitive processing and brain health, resulting in less decline in late-life.[60]

For the APOE gene, the HAAS cohort was found not to be in Hardy-Weinberg equilibrium. This result is not surprising as the cohort violates some of the assumptions of the principle (i.e., generations are overlapping, mating is likely to be non-random, population size is not infinitely large, participants are able to migrate). In the final growth curve model, APOE-ε4 status (no ε4 vs. any ε4) did not have a significant association with baseline cognition but did have a significant association with time (slope of cognitive change). This is similar to previous findings[61–63] and provides further evidence that APOE ε4 status is significantly associated with steeper rates of cognitive decline. This relationship is likely due to APOE ε4 well-known association with Alzheimer’s disease neuropathology[63]. Further studies that

examine APOE ϵ 4 and neuropathology in the context of frailty are necessary to elucidate the biological mechanisms that underly these relationships, which so far are not clear.[64] This might especially be important given an initial report that ApoE4 might mediate good episodic memory in young people.[65] (The actual link seems more complicated – not always replicable and possibly reflecting important differences in polymorphisms.[66])

The use of multilevel model growth curves and time-varying covariates allowed for the evaluation of both between-person (baseline) and within-person effects of the frailty index on cognitive test scores in the HAAS. Failure to separate between- and within-person effects when modeling repeated measures can lead to imprecise results and potentially inaccurate conclusions.[67] With the growing number of longitudinal studies on human development and aging, correctly unpacking the complex structure of variability that is inherent in multivariate longitudinal data is an important goal for researchers.

Our data should be interpreted with caution. The cohort consists only of men of Japanese origin, limiting the generalizability to the general population. There is a pressing need to understand sex and gender differences in frailty and cognition, which will require further study. Significant differences between participants and those who were excluded from the study may have impacted the results. Excluded participants were older, had a lower level of education, were more frail, and had worse cognition at baseline. These differences may have lead to over- or under-estimation of the effects and also limit the generalizability of the results to healthier older adults. Missing assessment data may have influenced the estimates of the models as the MAR assumption is required to yield unbiased estimates. However, one of the strengths of multilevel growth curve analyses is that it is able to function with cases that have missing data in the repeated measures.[37] Many of the items that compose the FI were assessed via self-report. Self-assessment data used in creating the FIs can be less accurate than data retrieved through clinical or laboratory testing, although such data allow ready generalizability. Self-report is especially a problem when examining aging individuals with growing cognitive impairments and this may have impacted our results. Furthermore, due to the lack of data found in Wave 4 of the study, there is an important time gap between measurements in the middle of the trajectories, which may have had a negative impact on the accuracy of the models.

Multilevel growth curve analyses do not address the stochastic nature of cognition and frailty,[23,68] as any individual improvement and/or stability is masked by the average decline found across the sample.[69] In other words, the heterogeneity found in individual trajectories is concealed when statistical models focus on average trends. Our group has applied multistate transition models elsewhere[23] specifically to account for this problem. Despite this limitation, the application of time-varying covariates within a multilevel growth curve analytic approach provided insight into the impact of change in frailty on cognitive function, over multiple time points, which has not yet been adequately investigated.

Overall, this study highlights the importance of accounting for within-person changes in health status in relation to cognitive outcomes in late life. The results suggest that changes in frailty are closely associated with changes in cognition, even after accounting for baseline frailty, age, education, and APOE ϵ 4 status. Incorporating within-person changes in health

into quantitative models of late-life cognition may further improve our understanding of how and why risk of cognitive decline increases with increasing frailty.

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Figure 1.
Honolulu Heart Project HHP and Honolulu-Asia Aging Study (HAAS) Flowchart.

Figure 2. Growth curves by frailty index levels

Panel A: Predicted cognitive trajectories for hypothetical individuals with average education and age, varied by levels of baseline frailty using results from Model 3 (Time Constant Predictors). **Panel B:** Predicted trajectories for hypothetical individuals with average education and age, varied by baseline FI and change in FI using results from Model 4 (Full Model).

Table 1

Attrition analysis.

	Included in Analyses	Excluded from Analyses	Significance of Difference (P-value)
Age (mean)	77.1	80.1	<.001
Education (mean)	11.0	10.0	<.001
APOE-ε4 Status (% with ε4)	19%	17%	0.15
FI Baseline (mean)	0.13	0.19	<.001
Baseline CASI (mean)	85.4	72.6	<.001

Table 2
Items used to construct Frailty indices and their prevalence (%) across the six waves of the HAAS.

	WAVE					
	1	2	3	5	6	7
Difficulty walking 1/2 mile	14.5	25.5	34.3	39.5	39.0	58.7
Difficulty walking up 10 steps	11.2	19.9	24.8	28.6	28.0	48.9
Unable to do heavy work	14.4	23.6	29.0	30.6	35.4	63.2
Difficulty shopping	4.6	9.8	12.7	13.8	18.5	34.8
Difficulty preparing own meals	3.2	7.4	9.3	11.5	15.1	31.0
Difficulty using phone	13.0	22.9	24.9	20.2	22.5	38.8
Difficulty eating	1.0	2.9	5.0	3.5	3.2	9.4
Difficulty dressing	2.8	6.3	9.6	6.9	7.6	22.9
Difficulty bathing	2.4	6.2	9.2	7.5	10.2	23.4
Difficulty getting to toilet	1.3	4.3	6.9	5.5	6.3	15.8
Difficulty lifting	4.7	9.7	13.0	15.4	16.4	32.0
Difficulty reaching out	4.5	8.5	10.8	8.4	8.6	15.7
Difficulty gripping with hands	3.2	7.6	10.4	10.4	10.4	20.6
Heart attack	6.7	2.2	3.4	4.5	4.4	4.4
Stroke, cerebral hemorrhage	8.7	4.2	7.6	13.7	11.8	11.2
Parkinson's disease	1.4	2.2	3.1	3.8	3.0	3.5
Fracture (hip, spine, forearm)	8.2	1.3	2.3	2.5	2.0	N/A
Speech impairment	2.7	2.2	3.6	3.0	2.0	5.5
Arthritis	16.8	N/A	N/A	26.4	31.8	N/A
Diabetes	16.6	16.0	17.7	17.9	17.3	16.4
Angina	6.5	N/A	N/A	3.4	4.7	3.7
Coronary Heart Failure	1.4	N/A	N/A	1.1	2.4	3.5
Cancer	8.3	N/A	N/A	18.3	18.5	N/A
Emphysema	2.6	N/A	N/A	2.7	4.4	N/A
Arrhythmia	N/A	N/A	N/A	8.2	10.8	11.2
Systolic BP reading > 140	62.4	49.4	48.4	42.0	39.7	31.2
Diastolic BP reading > 80	46.5	29.5	21.7	10.7	9.1	6.3

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	WAVE						
	1	2	3	5	6	7	
Sleepy most of the day	7.7	11.2	10.5	N/A	N/A	27.0	
Disorder related to blood clotting	2.2	N/A	2.4	3.4	4.4	N/A	
Hearing problems	21.9	21.9	27.5	38.7	50.8	24.9	
Vision problems	7.1	4.1	4.6	12.4	12.3	4.0	
Depression	1.4	1.7	2.3	3.4	4.0	4.4	
Bleed or bruise easily	38.3	N/A	39.3	47.2	48.3	N/A	
Abnormal Gait	8.5	7.3	14.3	28.4	21.1	N/A	

Abbreviations: N/A = Not available

Descriptive statistics of age, education, Cognitive Abilities Screening Index (CASI), and frailty index (FI) measures across the six waves of the HAAS.

Table 3

	Wave 1 1991-93 N=2817	Wave 2 1994-96 N = 2679	Wave 3 1997-98 N = 1978	Wave 5 2002-03 N = 1173	Wave 6 2004-05 N = 906	Wave 7 2007-08 N = 544
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)
Age	77.1 (4.2)	80.0 (4.2)	82.6 (3.9)	86.4 (3.4)	87.8 (3.2)	90.9 (2.9)
Age range	71-92	74-95	77-98	82-102	84-103	87-106
Education	10.7 (3.2)	10.8 (3.2)	11.0 (3.2)	11.1 (3.1)	11.1 (3.1)	11.2 (3.1)
Interval time	--	2.9 (0.3)	3.2 (0.4)	4.5 (0.5)	1.7 (0.4)	3.6 (0.3)
CASI	85.4 (11.2)	80.3 (15.9)	77.7 (17.5)	75.1 (18.9)	74.7 (19.3)	67.7(23.3)
FI	0.13 (0.1)	0.13 (0.1)	0.16 (0.1)	0.12 (0.1)	0.19 (0.1)	0.22 (0.2)
FI Change	---	0.01 (0.1)	0.04 (0.1)	0.05 (0.1)	0.08 (0.1)	0.12 (0.2)
E4 +ve	19.2%	19.1%	19.1%	19.7%	19.3%	18.3%

Results are reported as means (SDs), ranges, or percentages.

Abbreviations: CASI = Cognitive Abilities Screening Instrument; FI = Frailty Index

Table 4

Parameter estimates and standard errors from the multilevel growth models.

	Model 1 Null Model	Model 2 Time Only Model	Model 3 Time Constant Covariates	Model 4 Full Model
Intercept	78.9 (0.3)	86.1 (0.21)	92.1 (0.33)	91.9 (0.32)
Time		-2.0 (0.05)	-1.2 (0.08)	-0.7 (0.07)
Education			1.0 (0.06)	1.0 (0.05)
Age			-0.63 (0.04)	-0.59 (0.07)
APOE-ε4 Status			-0.84 (0.45) *	-0.83 (0.43) *
FI Baseline			-4.4 (0.22)	-4.7 (0.2)
Time * Education			0.03(0.01)	0.03 (0.01)
Time * Age			-0.1 (0.01)	-0.1 (0.01)
Time * APOE-ε4 Status			-0.6 (0.11)	-0.4 (0.1)
Time * FI Baseline			-0.5 (0.06)	-0.6 (0.05)
FI Change				-5.0 (0.1)
Covariance Parameters				
Residual	162.1 (2.7)	47.8 (1.0)	47.9 (1.0)	43.3 (0.9)
Intercept	134.6 (5.2)	93.0 (3.5)	53.2 (2.4)	50.9 (2.3)
Intercept + Time		12.0 (0.6)	7.4 (0.4)	4.7 (0.3)
Time		4.1 (0.2)	3.4 (0.2)	1.7 (0.1)
Model Fit				
-2 Log Likelihood	82066	76099	74853	72829
AIC	82072	76111	74881	72858
BIC	82094	76154	74982	72967

* not significant at $p = 0.05$ level. All other estimates were significant ($p < 0.05$).

Note: Model 1 is used to calculate the intraclass correlation. Model 2 is used to examine the average cognitive trajectory independent of other factors. Model 3 builds upon Model 2 by adding in the time-constant effects. Model 4 builds further by including a measure frailty change from baseline as a time-varying co-variate.