12-1-2017

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HHS Public Access

Author manuscript

J Am Geriatr Soc. Author manuscript; available in PMC 2018 December 01.

Published in final edited form as:

J Am Geriatr Soc. 2017 December ; 65(12): 2627–2633. doi:10.1111/jgs.15077.

Cognitive trajectory changes over 20 years prior to dementia diagnosis: a large cohort study

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Abstract

Objective—Longitudinal studies have shown an increase in cognitive decline many years prior to clinical diagnosis of dementia. We sought to estimate changes, relative to “normal” aging, in the trajectory of a global cognitive function test - the Cognitive Abilities Screening Instrument (CASI).

Design—A cohort of cognitively intact elderly participants, assessed biennially for dementia for up to 20 years.

Setting—Community dwelling elderly enrolled in a health maintenance organization.

Participants—Four thousand three hundred fifteen participants aged 65 and older who had no dementia diagnosis at baseline and had at least 2 visits with valid CASI test score.

Measurements—Average longitudinal trajectories, including changes in trajectory prior to clinical diagnosis in those who would be diagnosed with dementia, were estimated for CASI item response theory (IRT) scores. The impact of sex, education level, and *APOE* genotype on cognitive trajectories was assessed.

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We have no conflicts of interest or financial disclosures to report.

Author Contributions: Concept and design: Li, Thompson and Shofer.
Acquisition of data: Larson, Crane, McCormick and Bowen.
Data analysis: Shofer and Gibbons.
Drafting manuscript: Li, Shofer and Thompson.
Interpretation of data, critical revision of manuscript, and final approval of manuscript: Li, Larson, Shofer, Crane, Gibbons, McCormick, Bowen, and Thompson.

Results—Increased cognitive decline relative to "normal" aging was evident in CASI IRT at least 10 years prior to clinical diagnosis. Male gender, lower education, and presence of ≥1 *APOE* ε4 alleles were associated with lower average IRT scores. In those who would be diagnosed with dementia, a trajectory change-point was estimated at an average of 3.1 years (95% confidence interval 3.0, 3.2) prior to clinical diagnosis, after which cognitive decline appeared to accelerate. The change-point did not differ by sex, education level, or *APOE* ε4 genotype. There were subtle differences in trajectory slopes by sex and *APOE* ε4 genotype, but not by education.

Conclusion—Decline in average global cognitive function was evident at least 10 years prior to clinical diagnosis of dementia. The decline accelerated about 3 years prior to clinical diagnosis.

Keywords

dementia; cognitive function; trajectory changes; change-point

Introduction

Neurodegenerative changes begin years before the clinical diagnosis of Alzheimer's disease (AD)[1-3] and there is great interest in identifying early clinical manifestations of underlying brain changes for early intervention. Several large community-based studies[4-7] reported cognitive decline starting as early as 15-16 years prior to dementia diagnosis, followed by acceleration of decline closer to diagnosis.[4-6] We will refer to the initiation of accelerated decline as a trajectory "change-point". Estimates of timing of the change-point vary widely in different populations and with different measures of cognition, with studies indicating an accelerated decline in cognitive trajectory commencing at 1 to 17 years prior to AD or dementia diagnosis.[3, 8-16]

Estimates of the effect of education and presence of *APOE* ε4 alleles on cognitive trajectory during the preclinical stage of disease are inconsistent. Two studies[3, 11] found that those with higher education experienced on average a later change-point in their trajectory with subsequent faster decline. However, other studies have shown that education appears to influence the level of cognitive function but not the rate of decline.[17, 18] Similarly, estimates of the effect of *APOE* genotype are inconsistent, with some studies indicating that subjects with ≥1 *APOE* ε4 alleles had a more rapid progression during the preclinical stage of AD.[15, 19-21] Finally, sex is an important biological variable, yet its impact on cognitive trajectory has been considered in only a few studies.[3, 22] The majority of longitudinal studies of cognitively normal adults either did not consider sex[9] or adjusted for it as a covariate,[4-7, 23] without considering further its impact on cognitive trajectory.

In this study, we used longitudinal data from a cohort of initially non-demented participants in the Adult Changes in Thought (ACT) study with up to 20 years of follow-up. Cognitive function was assessed using the CASI,[24] a global cognitive test that has been used in large epidemiological cohort studies for detecting dementia.[25-27] We aimed to estimate whether, relative to "normal" aging, there were changes in the CASI trajectory prior to dementia diagnosis and, if so, when these changes occurred. We defined "normal" aging to be the cognitive trajectory of individuals not diagnosed with dementia during follow-up. Our approach allowed us to assess, in subjects who would later be diagnosed with dementia, not

only early changes in cognitive trajectory relative to normal aging, but also the presence and timing of a change-point at which accelerated cognitive decline commenced and the magnitude of the changes in cognitive score before and after the change-point. We further assessed how the cognitive trajectory varied by sex, education and presence of ≥1 *APOE* ε4 allele.

Methods

Participants

The ACT study design has been described elsewhere.[27] Briefly, the initial cohort of 2,581 community-based participants was randomly selected in 1994-1996 from Seattle area members of Group Health Cooperative (Kaiser Permanente Washington as of 2017). The base population was over 20,000 enrollees aged ≥ 65 years without dementia whose demographics were representative of surrounding counties. In 2000-2002, an expansion cohort (n=811) was added using the same sampling methods except oversampling clinics with higher proportions of minorities. Since 2005, a continuous enrollment strategy has been used to maintain a cohort of over 2,000 participants. The criteria for enrollment were a CASI score of ≥ 86 or absence of evidence of dementia after additional examination. Demographic characteristics, medical history, and suspected AD risk factors were obtained at the time of entry to the study and updated at every study visit. Of the 5,081 ACT participants as of May 2015, 4,315 had at least one follow-up with a valid CASI score. For participants with incident dementia identified by the ACT study, we included data from all visits prior to diagnosis. For those subjects who were not diagnosed with dementia during follow-up, their records were censored in the analyses at their next to last visit to reduce misclassification of those who might subsequently have a diagnosis of dementia.

The study followed appropriate informed consent and had local IRB approval.

Cognitive assessment with the CASI

The CASI is a 40-item global cognitive test that assesses a broad range of cognitive domains, with total score of 0 - 100.[24] CASI was administered at baseline and at each biennial follow-up visit and served as the screening tool for detecting dementia.

We used Item Response Theory (IRT) scores to address limited sensitivity at higher levels of cognitive functioning and nonlinear measurement properties of the CASI. In IRT, the construct of interest is regarded as a latent trait and each individual's responses to the individual items of the test are regarded as manifestations of this trait, which can be thought of as the “ability” of that individual at the time of testing. Two individuals with the same total (standard) CASI test score may have different IRT scores depending on the specific items they answered correctly. Unlike standard total test scores, IRT scores have linear scaling properties, i.e., a unit change in IRT corresponds to the same change in the underlying trait, regardless of the level of the trait.[25, 28-30] Scores were scaled to have approximately mean 0 and standard deviation (SD) 1 at the 5th biennial visit, so CASI IRT can be thought of as being measured in approximately SD units.[31] Figure S1 in Supplementary Material shows CASI IRT versus standard CASI scores for all individuals at

baseline and at their last visit, by dementia status at the time of censoring. In this study, we focus our primary analysis on estimating the average longitudinal trajectory of the CASI IRT score because of its better psychometric and statistical properties.[25, 32]

Diagnosis of dementia

In the ACT study, a CASI score of less than 86 was considered a screen positive for possible dementia. Those who screened positive underwent a standardized dementia diagnostic evaluation, including physical and neurological examination by a study physician and a battery of neuropsychological tests. Relevant laboratory tests and neuroimaging studies were performed or results were obtained from GHC records. Dementia diagnoses were assigned at consensus diagnostic conferences. All-cause dementia and its subtypes were determined based on the Diagnostic and Statistical Manual, 4th edition.[33] Apolipoprotein E (*APOE*;GenBank, M12529) genotype was determined by a restriction digest method.[34]

Statistical analysis

Quantitative (/categorical) characteristics of study participants by dementia status were summarized by means, standard deviations and ranges (/frequencies). We used mixed effects linear regression to estimate mean longitudinal CASI IRT trajectories, using the records of all 4,315 subjects who had at least one follow-up with a valid CASI score. In individuals without diagnosis of dementia during follow-up, the mean CASI IRT score was assumed to change at a constant rate over time (age), where this trajectory represents “normal” aging. Linear cognitive trajectories have been demonstrated in a variety of settings.[8, 9, 35] For those who were diagnosed with dementia during follow-up, the model for mean CASI IRT additionally included a piece-wise linear trajectory consisting of linear change with time to diagnosis until a change-point (at a time prior to diagnosis), after which there was possibly a different rate of linear change. Hence, the longitudinal trajectory model for those not diagnosed with dementia has a single slope parameter, corresponding to normal aging. For those who were diagnosed with dementia, their trajectories have two additional slope parameters, before and after an estimated change-point, representing the change in trajectory, relative to normal aging, as these individuals advance towards dementia diagnosis.

The model included intercept-level adjustment for the following covariates: dementia status, sex, education (college degree vs. no college degree) and baseline age cohort (>75 years vs. ≤ 75 years at baseline) and random effects for study participant and the individual level trajectory slopes corresponding to normal aging. The primary analysis considered a common trajectory change-point for all individuals who were subsequently diagnosed with dementia. Sex, college education and baseline age cohort were assumed to affect the overall level of mean CASI IRT, but not the slopes and change-point of the longitudinal trajectory. Secondary analyses included interactions of the change-point and associated slope coefficients with (separately) college education, sex and presence of ≥1 *APOE ε4* allele.

Model parameters were estimated by maximizing the likelihood using non-linear optimization. We tested specific hypotheses using likelihood ratio tests with 5% level of significance.

We performed several sensitivity analyses. We repeated the primary trajectory analyses using standard CASI and the transformation ln (101-CASI), which has been used previously to address the skewness of the distribution of standard CASI scores.[11] We also repeated the analysis including the last visit for subjects not diagnosed with dementia during follow-up. To assess the assumption of a (piece-wise) linear trajectory, we also estimated the time-to-dementia and normal aging trajectories with fractional polynomials (FPs).[36] In our study population, *APOE* genotype data were not available for 599 participants (14%). In further sensitivity analyses, all individuals with missing *APOE* ε4 status were assumed to be either ε4 negative or ε4 positive.

Analyses were carried out using R 3.3.2.[37]

Results

Characteristics of participants with and without dementia diagnosis

Table 1 shows study characteristics by eventual dementia status. Of 1,040 subjects who were diagnosed with dementia during follow-up, 636 had AD, 109 had vascular dementia, 185 had mixed dementia, and 110 had other types of dementia. Compared to those not diagnosed with dementia during follow-up, those who developed dementia were less likely to be college educated, more likely to have ≥1 *APOE* ε4 allele, were older at enrollment and at last follow-up visit, and had lower mean CASI scores at enrollment and follow-up (all p-values < 0.01).

Estimated CASI IRT trajectories and change-points

Figure 1A, B presents observed longitudinal CASI IRT scores by dementia diagnosis in individual participants during the study period with non-parametric smoothed trajectories. The smoothed trajectory for normal aging (those without diagnosis of dementia) is approximately linear. On visual inspection, the smoothed CASI IRT trajectory in those who would be diagnosed with dementia is lower than the trajectory of normal aging throughout follow-up and exhibits an accelerated decline at about 3 years prior to diagnosis.

Coefficient estimates for the CASI IRT primary trajectory model are summarized in Table 2. The estimated trajectory change-point (95% confidence interval (CI)) was at 3.1 (3.0, 3.2) years prior to diagnosis. The pre-change-point CASI IRT slope in those who would be diagnosed with dementia was significantly greater than the slope for normal aging: prior to the change-point, the mean annual decline in CASI IRT was more than double (0.041) the estimated annual decline associated with normal aging (0.015). After the change-point, the estimated annual decline in subjects who would be diagnosed with dementia increased markedly. Figure 1C, D shows CASI IRT spaghetti plots for individual subjects, and the estimated mean trajectories corresponding to normal aging and for those diagnosed with dementia at age 85, using the (piece-wise) linear trajectory models and FPs. The FP curves correspond closely to the estimated trajectories from the linear change-point models and also suggest a change-point at about 3 years prior to diagnosis.

Results of other sensitivity analyses were substantively in agreement with those of the primary analysis and are provided in Supplementary Tables S1 and S3.

Differences in CASI IRT, relative to normal aging, in subjects with dementia diagnosis

We compared estimated mean CASI IRT scores from the primary model at 2, 5, 10, and 15 years prior to dementia diagnosis to mean scores for individuals of the same age, age cohort, sex and education without dementia diagnosis (normal aging) (Table 3). The mean CASI IRT scores in those with subsequent dementia diagnosis were significantly lower ($p < 0.01$) than mean scores for those without diagnosis over the 15 years prior to diagnosis. Participants who would be diagnosed with dementia 10 years later are estimated to have mean CASI IRT 0.21 units lower than participants of the same age, age cohort, sex and education who were not diagnosed with dementia during follow-up.

Effect of sex, education and *APOE* genotype on CASI IRT trajectory

The average IRT and standard CASI scores differed significantly by sex, education and presence of ≥1 *APOE* ε4 alleles. Based on the primary trajectory model, males had mean CASI IRT scores 0.16 (95% CI 0.13, 0.19) units lower than females (adjusting for age, age cohort and education). Those without a college education had adjusted mean CASI IRT scores 0.29 (95% CI 0.26, 0.33) units lower than those with a college education. Including ≥1 *APOE* ε4 alleles as an intercept adjustment in the primary model, those with ≥1 *APOE* ε4 alleles had adjusted mean CASI IRT 0.05 (95% CI 0.01, 0.08) lower than those with no *APOE* ε4 alleles.

There were no other major differences in estimated trajectories by sex, education and *APOE* ε4 genotype. (Supplementary Table S2 and Figure S2). When trajectory models were fitted including interactions, the location of the change-point did not differ by (separately) sex, education or having ≥1 *APOE* ε4 alleles ($p > 0.13$). There were statistically significant, but small, differences in post-change-point slope by sex and in pre-change-point slope by presence of APOE ε4 allele.

Discussion

In this community-based study, we found that, on average, compared to normal aging, increased cognitive decline measured by CASI IRT was present at least 10 years prior to clinical diagnosis of dementia, followed by an accelerated decline at about 3 years prior to the diagnosis. Male sex, lower education and presence of ≥1 *APOE* ε4 alleles were associated, on average, with lower cognitive performance, but these factors had less impact on the shape of cognitive trajectory in those who developed dementia.

In persons not diagnosed with dementia, average CASI IRT declined slowly with aging. In contrast, the average early rate of decline in those who were later diagnosed with dementia was more than double that of normal aging, such that differences in average scores were statistically evident up to 15 years prior to clinical diagnosis of dementia. This early decline in cognition measured with a brief cognitive test is largely consistent with recent observations of cognitive changes from other large community-based studies.[5-7]

Our study suggests that acceleration of global cognitive decline assessed by a brief cognitive measure occurred on average about 3 years prior to dementia diagnosis. This is consistent with the finding in another community-based study of accelerated decline 3 years prior to

dementia diagnosis in standard scores from the Mini-Mental State Examination (MMSE).[4] A study using data from a research clinic setting showed a slight earlier change-point in the MMSE, 5 years prior to AD diagnosis.[8] However, the risk profile of these subjects may be different from that in a community-based study such as ours.[38] The timing of the acceleration of cognitive decline prior to dementia diagnosis may also vary with type of cognitive measure.[4, 9, 12, 16]

Previous studies have generally shown no difference in rate of cognitive decline between men and women.[3, 22] Our finding of a lower average cognitive performance in men than in women is consistent with our earlier findings of poorer executive function[39] in men than in women in a different cohort; and consistent with the observation that men had poorer memory and smaller hippocampal volume and that memory and hippocampal volume decline began at earlier ages than brain Aβ deposition.[40] We speculate that this greater cognitive decline in men may be due to increased cerebrovascular disease in men.[41, 42]

Education is an important factor in assessment of cognitive function and potentially affects cognitive trajectory changes, although it has been suggested that the impact is stronger in younger adults.[5, 6, 15, 23, 43-46] Higher education is consistently associated with better cognitive performance [5, 6, 15, 23, 44, 46, 47] but estimates of the effect of education on cognitive trajectory changes are less consistent and may vary by domain.[5, 6, 15, 35, 44, 46, 47] Some studies[3, 15, 44] showed that persons with higher education level have a change-point closer to diagnosis and a more rapid decline of cognitive function after the change-point. However, as in other studies,[23, 46] while we found that the mean CASI score was significantly higher in those with higher education, we did not find a significant effect of college vs no college on the trajectory. The discrepancy with previous findings could be due to the relatively low sensitivity of the CASI, compared to specific measurement of memory or more extensive neuropsychological test batteries used in other studies.[15, 44] Also, the education effect on CASI score might be at a lower threshold,[48] which could not be adequately assessed in our cohort with high average education levels.

Cognitive trajectory change prior to clinical diagnosis of dementia is also determined by the underlying disease process which could vary by *APOE* genotype.[15, 20] Yu et al. reported that the presence of *APOE* ε4 alleles was associated with more rapid cognitive decline measured by the MMSE both before and after the change-point.[15] We observed a slightly faster decline in those with ≥1 *APOE* ε4 alleles prior to, but not after, the change-point. Other longitudinal studies[3, 6, 21] did not identify changes during the pre-dementia stage in the MMSE trajectory by presence of *APOE* ε4. Again, a potential explanation is the low sensitivity of brief cognitive tests in measuring subtle cognitive impairments prior to dementia diagnosis.

Relative to other studies of cognitive decline, a major strength of this study is that our findings are based on a large community-based cohort with long follow-up up to 20 years. Nevertheless, a potential limitation is that in ACT, the CASI was measured every two years rather than yearly, which may delay diagnosis of dementia. Another limitation is that our piece-wise linear trajectory model was not designed to estimate at what point prior to diagnosis those who develop dementia deviate from normal aging.

In conclusion, our findings suggest that commonly used brief cognitive measures, such as the CASI, could exhibit differences in cognitive functioning at least 10 years prior to clinical diagnosis, with decline accelerating about 3 years prior to clinical diagnosis. Sex, education and *APOE* genotype affect average level of cognitive performance but had little impact on the shape of the cognitive trajectory prior to diagnosis of dementia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The study sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Funding: This study is supported by grants AG033693, AG006781, and AG05136 from the National Institute on Aging and U.S. Department of Veterans Affairs.

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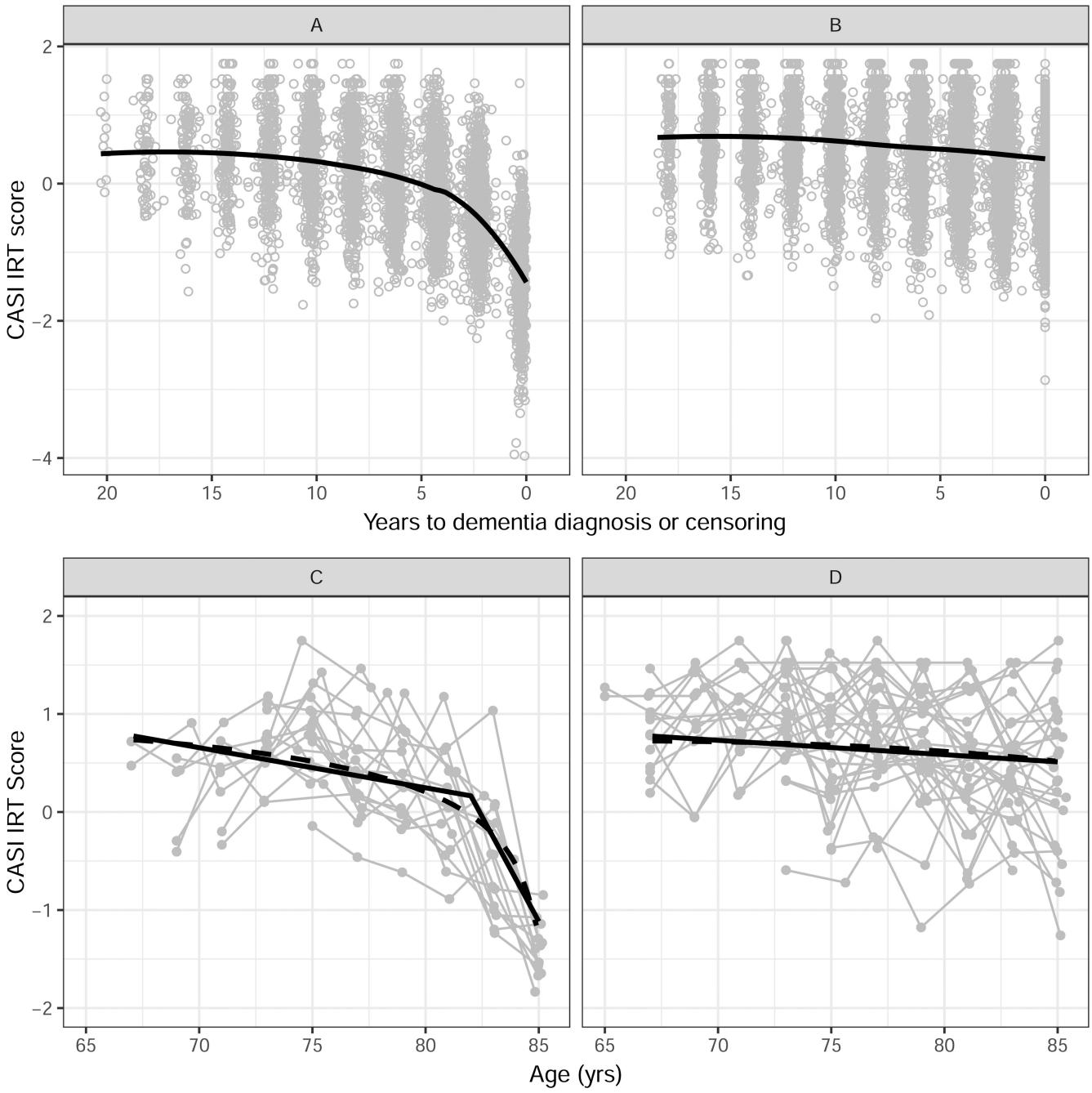

Figure 1. CASI IRT trajectories by dementia status

Upper panels (A, B): CASI IRT scores by time to diagnosis for those diagnosed with dementia (A) or time to censoring† for normal aging (B) for the entire study sample. Solid lines correspond to non-parametric loess smoothed trajectories

†Records for those not diagnosed with dementia were censored at the next to last visit.

Lower panels (C,D): Individual observed and estimated mean age trajectories for those diagnosed with dementia at age 85 (C) or normal aging censored at age 85 (D). For college educated females in the 75 and under baseline age cohort.

Solid black line: fitted (piece-wise) linear primary models
Dashed black line: fitted fractional polynomial (FP) models
The components of the fitted FP model for normal aging are of the form $((age + 10.1)/10)^2$ and $((age + 10.1)/10)^3$, where age was centered at 75 years, and for time to dementia diagnosis (t) are of the form: $((t + 0.1)/10)^{-0.5}$ and $((t + 0.1)/10)^{-0.5} * \log(((t + 0.1)/10))$.

Table 1
Characteristics of ACT study participants in the analysis

	Normal aging (n=3275)	Diagnosed with dementia (n=1040)
	Mean, SD (range)	
Age at enrollment (years)	73.5, 6.1 (65-101)	76.7, 6.3 (65-96)
Age at diagnosis of dementia/last visit (years)	81.6, 7.3 (67-107)	85.3, 6.0 (68-103)
Follow-up time to last visit (years)	8.0, 5.3 (1-20)	8.6, 4.7 (1-20)
Baseline standard CASI score	94.3, 4.2 (65-100)	91.5, 5.4 (62-100)
Standard CASI score at time of dementia diagnosis/censoring *†	93.9, 4.5 (59-100)	77.8, 9.9 (14-99)
Baseline CASI IRT score	0.42, 0.67 (-2.12, 1.75)	-0.02, 0.73 (-1.98, 1.75)
CASI IRT score at time of dementia diagnosis/censoring *‡	0.35, 0.68 (-2.86, 1.75)	-1.32, 0.63 (-3.97, 1.46)
	Frequency (%)	
Female	1891 (58)	645 (62)
With college degree	2388 (73)	610 (59)
≥1 *APOE* ε4 allele ††	669 (24)	306 (34)

CASI: Cognitive Abilities Screening Instrument (score 0-100); IRT: Item Response Theory. CASI IRT score were scaled to have approximately mean 0 and standard deviation 1 at the 5th biennial visit.

*Censored at next to last visit.

†163 participants who were diagnosed with dementia did not have valid CASI scores at diagnosis and 20 subjects who were not diagnosed with dementia were missing CASI scores at last visit;

‡166 participants who were diagnosed with dementia did not have valid CASI IRT scores at diagnosis and 31 subjects who were not diagnosed with dementia were missing CASI IRT scores at last visit;

††Not available for 466 participants with no dementia and 138 participants who were diagnosed with dementia.

Table 2

Estimated CASI IRT trajectory coefficients (95% CI) from the primary model

	Intercept*	Slope per year increase in age†	Additional Pre-CP Slope per year closer to diagnosis	CP years prior to diagnosis	Additional Post-CP Slope per year closer to diagnosis
Normal aging	0.66 (0.63, 0.68)	-0.015 (-0.017, -0.012)			
Diagnosed with dementia	0.45 (0.41, 0.49)		-0.026 (-0.032, -0.021)	3.1 (3.0, 3.2)	-0.41 (-0.43, -0.39)

CASI IRT score: Cognitive Abilities Screening Instrument Item Response Theory score were scaled to have approximately mean 0 and standard deviation 1 at the 5th biennial visit; CI: confidence interval; CP: Change-point.

*Intercepts correspond to college educated females in the 75 years and under baseline age cohort and, for the dementia group who are 10 years from diagnosis;

†By model definition there is a common age slope for participants with and without dementia diagnosis.

Table 3

Estimated mean differences[†] (95% CI) in CASI IRT comparing normal aging to those diagnosed with dementia, at selected years from diagnosis

Years from diagnosis	Mean difference (95% CI)[*]
15 years	0.08 (0.02, 0.13)
10 years	0.21 (0.17, 0.25)
5 years	0.34 (0.30, 0.38)
2 years	0.85 (0.81, 0.89)

CASI IRT score: Cognitive Abilities Screening Instrument Item Response Theory score were scaled to have approximately mean 0 and standard deviation 1 at the 5th biennial visit; CI: confidence interval.

[†]For subjects of the same sex, age, age cohort and education level;

[*]Estimated from the primary trajectory model.