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Trajectories of Relative Performance Across Two Measures of Global Cognitive Function

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Abstract

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Background/Objectives—To examine whether trajectories of global cognitive function over time in studies that change assessment protocols may be modeled based on an individual's performance relative to others in the study cohort.

Design—The Women's Health Initiative Memory Study switched from an in-person interview with the Modified MiniMental State Exam (3MSE) to a telephone-based interview with the Telephone Interview for Cognitive Status (TICSm) for assessing global cognitive function during long term follow-up. Annual cognitive assessments from participants, ranked according to age- and race/ethnicity-adjusted performance levels, were used to identify distinct trajectories. Participants assigned to the resulting trajectories were compared for selected risk factor profiles.

Setting—Extended follow-up of a cohort originally enrolled in a clinical trial of postmenopausal hormone therapy

Participants—Women (N=2,561) aged 75 to 92 years

Results—Our approach grouped participants into five trajectories according to relative cognitive performance over time. These groups differed significantly according to three known risk factors for cognitive decline -- education level, *APOE-ε4* genotype, and type 2 diabetes – and a biomarker based on brain structure that has been linked to increased cognitive decline and Alzheimer's disease. Participants with consistently low relative levels of cognitive function over time and those whose relative performance over time declined to these levels tended to have poorer risk factor profiles.

Conclusion—Longitudinal measures of an individual's relative performance across different assessment protocols for global cognitive function can be used to identify trajectories of change over time that appear to have internal validity with respect to known risk factors.

Keywords

Global cognitive function; Longitudinal trajectories; Assessment modalities; Risk factors

INTRODUCTION

In long-term studies of cognitive aging, assessment protocols may change. An example of this is the Women's Health Initiative Memory Study (WHIMS), which began in 1996 as annual clinic-based assessments for global cognitive function with the Modified Mini-Mental State Examination.[1,2] WHIMS was an ancillary study to the larger Women's Health Initiative (WHI) trials of postmenopausal hormone therapy.[3] In 2008, the WHI ceased clinic visits and shifted to follow-up conducted primarily by mail and telephone. This reorganization led to a change in the instrument used to assess global cognitive function. WHIMS transitioned to the Women's Health Initiative Memory Study of the Epidemiology of Cognitive Health Outcomes (WHIMS-ECHO), in which global cognitive function was assessed with the Telephone Interview for Cognitive Status (TICS-m).[4,5] This change was supported by a validation study that demonstrated 3MSE and TICS-m yielded scores that were highly correlated.[6] TICS-m scores have subsequently been used during WHIMS-ECHO to provide long-term assessments of global cognitive function.[7] Nevertheless, the question remains whether scores from the two measurement protocols can be bridged to

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describe meaningful patterns of cognitive changes over time and across protocols. The focus of this manuscript is to address this practical issue.

One approach to this is calibration of the data from different measurement tools (i.e. 3MSE and TICS-m) onto a common metric.[8,9] Gross, et al.[9] identified four approaches towards this goal: 1) using elements (e.g., items) that are common across protocols; 2) standardizing individual test item scores according to cohort-wide means and standard deviations and summing cross-sectional measures to form a composite with which to assess trajectories; 3) using confirmatory factor analysis to identify common factors among batteries and treating scores as continuous measures; and 4) using confirmatory factor analysis treating scores as discrete measures. These four approaches are focused on ordering participants with respect to their absolute level of cognitive function. We take an alternative approach, instead using the two tests to provide measures of participants' relative levels of cognitive function, i.e. how well they perform on tests compared with other study participants. In doing so, we assume that the two tests are assessing a common domain, i.e., global cognitive function, and that age- and race/ethnicity-adjusted participants' rankings among the cohort provide a relative measure of cognitive functioning. The approach is most analogous to 2) above, but instead of using a z-score to define a participants' performance relative to a cohort mean, we assign percentiles to reflect relative standing within the cohort providing assessments. This avoids the assumption that distributions can be homologized and that standard deviations for the two tests are commensurate.

To assess the this approach's performance, we used trajectory analysis to group participants based on the longitudinal characteristics of their relative cognitive performance over time. We then examined the associations these groups have with known risk factors for cognitive decline. We use risk factors from the domains of socioeconomic status, metabolism, brain structure, and genetics to validate this approach. Our primary goal was to demonstrate that the longitudinal trajectories in relative global cognitive scores can be meaningfully estimated across the two protocols.

METHODS

Participants were recruited to join WHIMS during 1995–1998. They were 65–80 years old at the time of enrollment and had volunteered and met eligibility criteria for a randomized controlled clinical trial of postmenopausal hormone therapies based on conjugated equine estrogens, as part of the WHI.[1] To join WHIMS, participants consented to annual clinic-based cognitive assessments and adjudication of cognitive impairment (i.e. either mild cognitive impairment or probable dementia). In 2005, after active WHI therapies were discontinued for at least two years, participants were asked to consent to continue clinic-based follow-up. By March of 2008, all clinic-based cognitive assessments were terminated, and participants were asked to consent to telephone-based cognitive assessments in WHIMS-ECHO.

Cognitive measures

In WHIMS, global cognitive function was measured with the Modified Mini Mental State Exam (3MSE),[2] which includes 46 items that contribute to a total score that ranges from 0–

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100, with a higher score reflecting better cognitive functioning. Test items measure abstract reasoning, executive function, verbal recall, naming, praxis, temporal and spatial orientation, verbal fluency, visuo-constructional abilities, and writing.

In WHIMS-ECHO, global cognitive function was assessed with the Telephone Interview for Cognitive Status-modified (TICS-m), a widely-used measure of global cognitive functioning.[5,9] It is a 14-question measure (range of scores 0 to 50; higher scores reflect better performance) with items assessing abstract reasoning, executive function, verbal recall, praxis, verbal fluency, and verbal memory.

We describe trajectories of relative cognitive performance across the change in protocols and use all measures collected during the time span of 5.5 years before and after the transition from WHIMS to WHIMS-ECHO, allocating them to one-year intervals.

Risk Factors for Cognitive Decline

We have selected three known risk factors to represent the domains of socioeconomic status, metabolism, and genetics. We also used a novel brain MRI marker that is predictive of cognitive decline and Alzheimer's disease risk. Each of these four risk factors is separately related to the 3MSE and TICSm scores included in our analyses, with covariate adjustment for current age and race/ethnicity (all $p<0.001$).

Education—At enrollment to WHI, participants reported their educational attainment. We grouped these into four categories: less than 12 years (not high school graduate), high school graduate, some post high school education, and college graduate.

Type 2 Diabetes—At WHI enrollment, participants reported a history of type 2 diabetes, age of onset, and diabetes treatment. Fasting blood glucose was determined on a 5% sample of participants. During WHI follow-up, participants were periodically queried about diabetes treatment.[10] For this report, participants were classified as having type 2 diabetes based on report of diabetes, diabetes treatment or, for those with fasting glucose measurements, if levels exceeded 126 mg/dl. The WHI reported good concordance between laboratory-based and self-reported diabetes.[10] We categorized participants as having diabetes if they met this definition any time prior to the termination of the WHIMS protocol.

Genotype—Apolipoprotein E (*APOE-ε4*) genotypes were assigned based on rs429358 and rs7412 genotype results from imputation and harmonization of genetic data across WHI genome-wide association studies within the WHI Clinical Trials and Observational studies. Imputation was conducted using the 1000 Genomes Project reference panel and the MaCH algorithm as implemented in Minimac ($R^2>0.98$ for each SNP in the study population)[11] and based on the Illumina Omni Express and exome chips for the majority of WHIMS participants.

Structural brain biomarker—The initial WHIMS-MRI study was conducted approximately eight years following WHI randomization and three years, on average, following termination of the WHIMS CEE+MPA or 1.4 years following the CEE-Alone trials.[12] It took place in a subset of 14 clinical sites in a subset of participants.[13] The

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WHIMS-MRI2 study was conducted 12.7 years post-WHI randomization, and 7.7 years, on average, following termination of the CEE+MPA trial or 6.1 years after CEE-Alone trial.[14] WHIMS-MRI2 scanning occurred 4.7 years, on average, following WHIMS-MRI initiation. WHIMS-MRI participants who continued WHI follow-up were invited to join WHIMS-MRI2.

Casanova, et al.[15] used machine-learning methods to develop novel markers of Alzheimer's disease from structural magnetic resonance imaging database developed by the Alzheimer's Disease Neuroimaging Initiative (ADNI).[16] The Alzheimer's Disease Pattern Similarity (AD-PS) scores provide a high degree of specificity and sensitivity for classifying ADNI participants based on disease status (Alzheimer's disease or normal cognition). AD-PS scores range from 0 to 1 and serve as an index, based on high dimensional structural MRI measures of gray matter volumes, to order individuals according to how closely they conform to patterns seen among images from individuals with Alzheimer's disease in ADNI. AD-PS scores capture the presence of spatial patterns of grey matter tissue atrophy that discriminate between clinical AD cases and cognitively normal controls in the ADNI cohort. In the WHIMS MRI cohort, they identify individuals at increased risk for cognitive decline and cognitive impairment.

Statistical Methods

We analyzed cognitive function data collected within the 5.5 years before and after the transition from the clinic-based to telephone-based assessments (which occurred in 2008). We limited our analysis to participants who had at least two cognitive assessments with both the WHIMS and WHIMS-ECHO protocols during this time span (this includes some participants who died after at least two WHIMS-ECHO assessments). Separately for the 3MSE and TICSm data, we generated residuals for these test scores from linear models with covariate adjustment for participants' age at the time of the cognitive test and race/ethnicity. In addition, to control for any learning effects, we also adjusted for the number of prior assessments of the 3MSE or TICSm. Within each follow-up year, we then ranked participants according to these residuals, calculating their percentile standing relative to others who were assessed during that year.

We used a group-based trajectory modeling approach to identify clusters of longitudinal patterns of percentiles over time. Models were fitted using PROC TRAJ in SAS.[17,18] This approach treats cluster membership as a latent class and, for a specified number of assumed classes, estimates the probability for each participant of their membership in classes, assigning them to the cluster with greatest probability. We chose to model trajectories with cubic splines. In modeling exercises, selection of the number of clusters to include in models can be guided by Bayesian Information Criteria.[17] For our analyses, we pre-specified five clusters and additionally examined the fit of models with additional clusters.

RESULTS

Table 1 provides a description of the 2,561 participants included in our analysis. At the start of WHIMS-ECHO, i.e. mid-way through the span of time we use to assess trajectories, their mean (standard deviation) age was 80.8 (3.5) years, ranging from 75 to 92 years. The initial

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MRI obtained on a subset (N=1,385) of participants occurred an average of 2.6 (0.3) years prior to this time; the second MRI (N=682) was obtained an average of 2.1 (0.4) years after this time. *APOE-ε4* genotype was available for 1,800 participants: 21.3% had one ε4 allele and 1.4% had two ε4 alleles. At enrollment into the WHI trial, 4.9% of the participants met study criteria for type 2 diabetes. At the start of WHIMS-ECHO, type 2 diabetes prevalence had increased to 8.0%.

Table 2 provides raw means for the 3MSE and TICSm scores over time. These declined only slightly within the two timeframes. Note that relatively few 3MSE scores occurred in the year prior to the transition to WHIMS-ECHO. This is attributable to the necessary time to develop subcontracts, obtain IRB approval, and re-consent participants for the new protocol.

Figure 1 portrays the five trajectories fitted by the modeling approach. Participants were distributed fairly evenly among these clusters, with membership rates ranging from 17.5% to 24.8%. Two clusters included participants with fairly constant *relative* performance over time: either consistently high (5: Consistently High), with mean scores ranging between 70–80%ile over time, or consistently low (1: Consistently Low), with mean scores ranging between 20–30%ile over time. Two other clusters included participants whose relative cognitive performance declined over time, either from a relatively high initial level of performance (3: Decline to Median), or from a more moderate initial level of performance (2: Decline to Low). A final cluster of participants was described by a trajectory corresponding to relative improvement from around the 40%ile to the 60%ile (4: Relative Improvement). Note that this may not correspond to absolute improvement in scores, only to relative improvement (i.e. having less decline than other participants).

The Bayesian Information Criteria (BIC) value of fit for our 5–cluster model was 1021.75. A 4-cluster model has BIC=806.51. We examined the fit of models in which greater numbers of clusters were assumed: BIC=1211.71 (6 Groups) and BIC=1291.70 (7 Groups). Given the large sample size, these additional clusters could be treated as distinct given Bayesian Information Criteria. However, we chose to pursue our five-cluster model because it was pre-specified and grouped participants who appeared to be relatively resilient to cognitive decline during follow-up. Our primary aim was to describe the feasibility of our methodological approach.

Table 3 examines differences in risk factor profiles for the five clusters. For each, significant differences exist among clusters. We did not fit a model in which all four risk factors were included because MRI and genotyping were only included in subsets of participants. However, as noted in a footnote to Table 3, including education and diabetes status (which were available for all participants) as covariates, did not diminish the statistical significance of relationships that AD-PS and *APOE-ε4* had with trajectory clusters.

To portray these graphically and allow comparisons among risk factors, we defined cut-points to connote relatively higher risk for each: lack of college, AD-PS score above the 75th percentile (AD-PS=0.46) for the cohort, presence of an *APOE-ε4* allele, and diabetes at WHI baseline. We then used logistic regression to calculate the odds ratio for these risks defined by these cut-points each trajectory cluster relative to cluster 5 (consistently high

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global cognitive function). Figure 2 portrays the results. For each risk factor cut-point, the confidence interval for the odds ratio of cluster 1 (consistently low global cognitive function) excluded 1. While not fully consistent, there tended to be a rough ordering across the four trajectory clusters relative to the fifth.

DISCUSSION

The work we describe suggests that transforming residual test scores into percentile ranks reflecting study participants' performance relative to that of other study participants may offer a useful strategy for "bridging" pooled longitudinal data on global cognitive function when assessment tools and/or measurement strategies change within and across study protocols. Specifically, our findings suggest: a) the transformation of WHIMS and WHIMS-ECHO 3MSE and TICSm data into relative percentile ranks fit nicely into an a priori planned five-cluster model; b) that the resulting clusters were clinically coherent and distinct; and c) group based trajectories of cognitive performance across the 10+ year observation period conformed to expectations regarding the presence/absence of known risk factors for age-related cognitive decline. An anonymous reviewer has noted that the slopes over the interval spanning the conversion from 3MSE to TICSm scores tend to be steeper (both positively and negatively) than among other intervals, which may reflect a heterogeneity in how individuals responded to the two different assessment modes.

It is noteworthy that the revealed differences in AD-PS scores and *APOE-ε4* frequencies across the identified 5 clusters (Table 3) may offer some insights into the neurobiological underpinnings of these observed cognitive function trajectories. For instance, if we considered both Clusters 4 and 5 as two relatively resilient groups, the observed difference in AD-PS scores suggested these two groups (with an average increase by 0.13) might have the least progression of early neurodegeneration as compared to the other groups (with an average increase by 0.17–0.18). These two groups also carried the lowest genetic risk for AD as determined by *APOE-ε4* alleles,[19] which would predispose older women to less brain reserve at the inception (e.g., Cluster 1) or at a greater risk for cognitive decline (Clusters 2 and 3) due to multiple APOE4-associated changes in brain regions (e.g., continuing hippocampal atrophy; cortical thinning), structural networks (e.g., compromised white matter integrity; altered intrinsic network dynamics) and neural function (e.g., reduced cerebrovascular blood flow; reduced metabolic activities).

While our results are promising, they are not sufficient to determine the validity of the group trajectories described in Figure 1. Specifically, our strategy converted individual performance on assessment instruments to relative scores that reflected individual participants' performance level relative to the group at large. Using this strategy, one's relative percentile standing in the group will change both as a function of variability in individual level performance (i.e., increase or decrease in cognitive functioning) but also as a function of changes in group composition. For example, should proportionally more participants with poor cognitive performance be lost to follow-up in a group, the cognitive trajectories of some remaining participants may appear to "decline" -- as the lower performing members leave the cohort during follow-up. While our approach may benefit

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from the large size of the WHIMS sample, group-based trajectory models have been fitted successfully to much smaller samples[20] and to ordinal data.[21]

Further, confirmatory research is needed to determine the accuracy and clinical validity of the group based trajectories characterized in this paper. Additional limitations include the observational design, which prohibits assumptions about causality in the observed associations between candidate risk factors and cluster membership/cognitive trajectory. While the study cohort was large and diverse, it is not a population-based sample.

It is unclear how our approach may be influenced by missing data (i.e. irregular patters of observation over time that may be affected by missed visit, lost follow-up, or death). All longitudinal analytical methods may be compromised by differential missingness. It is important to note that by ranking individuals with respect to others at the same stage of follow-up (i.e. not lost or deceased), we are capturing relative, not absolute cognitive function. Thus, an individual's ranking may be influenced by missing data. Haviland, et al., report results from a simulation experiment to assess the impact of group-based trajectory modeling and found that while group membership was sensitive to missing data, the overall shape of modeled trajectories was not materially influenced by the missing data mechanisms they modeled. To assess the sensitivity of our findings to missing data, we restricted our analyses to the subset of individuals who had at least three cognitive assessments for both 3MSE and TICSm. This reduced the total sample size from 2,561 to 2,015 (82%). When this subset was analyzed in the same manner, there was very little difference between the fitted trajectories and group memberships, and all risk factor relationships remained significant ($p<0.001$). This provides some reassurance that, whatever the missing data mechanisms that defined the composition of this subset compared with our analysis cohort, these did not materially affect our results.[22]

In conclusion, the strategy of transforming residual cognitive performance scores to percentile ranks to reflect relative performance may be useful for bridging data across changes in assessment protocols.

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Impact Statement

We certify that this work is novel. This research demonstrates that longitudinal trajectories of cognitive function can be developed in studies during which assessment protocols are changed over time. The internal validity of these trajectories is assessed by examining the risk factor profiles of individuals grouped into clusters aligned with these trajectories. Four risk factor relationships are examined, using representatives from the domains of demography, genetics, clinical assays, and brain structure.

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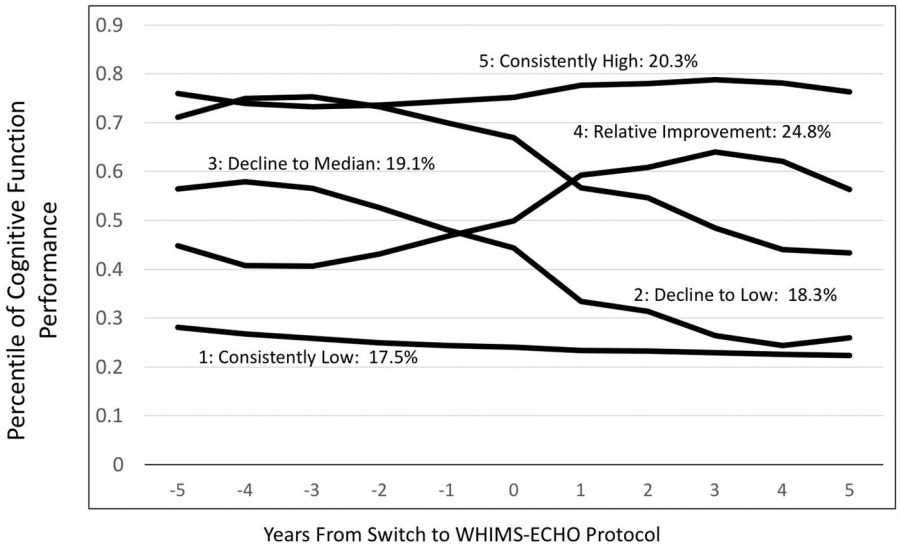

Figure 1.

Characteristic patterns of changes in cognitive function over time spanning the MRI, as identified through trajectory analyses.

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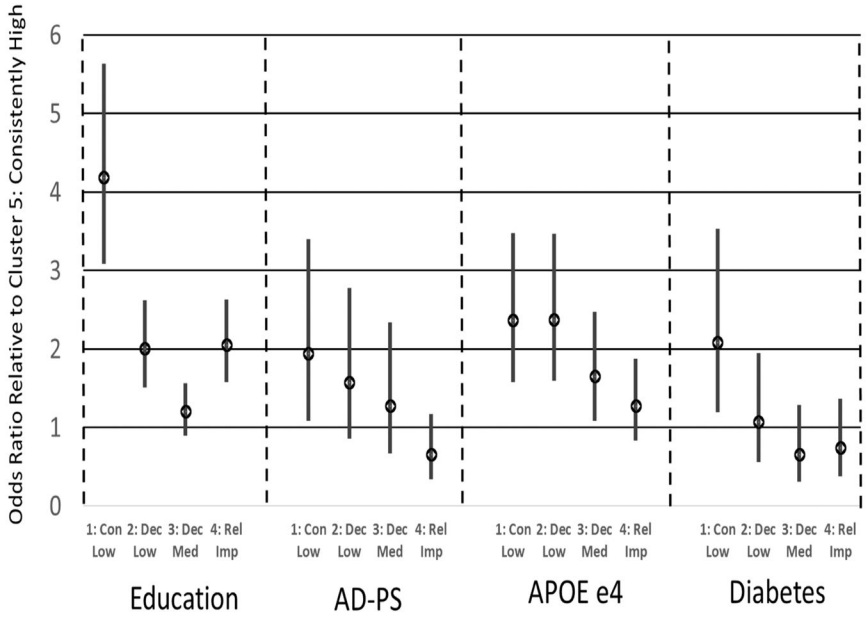

Figure 2.

Odds ratios and 95% confidence intervals for markers of increased risk for cognitive decline for each cluster relative to cluster 5 (Consistently High). The following categorizations were used: lack of college, ADPS score above the 75th percentile (ADPS=0.46) for the cohort, presence of an *APOE-ε4* allele, and diabetes at WHI baseline.

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Table 1

Distribution of risk factors for cognitive deficits and dementia for participants contributing to the analysis.

Risk Factor for Cognitive Impairment	Mean (standard deviation) or N (Percent) N=2,561
Age at WHIMS-ECHO start	80.8 (3.5)
Age at MRI	
MRI1 (N=1365)	78.5 (3.7)
MRI2 (N=682)	82.8 (3.5)
Timing of MRI relative to WHIMS-ECHO	
MRI1	−2.6 (0.3)
MRI2	2.1 (0.4)
Race/Ethnicity, N (%)	
American Indian	5 (0.2%)
Asian	10 (1.9%)
African-American	161 (6.3%)
Hispanic/Latina	37 (1.4%)
White	2289 (89.4%)
Other/Multiple	34 (1.3%)
Education	
< High school	112 (4.4%)
High school graduate	561 (21.9%)
Some post-HS education	976 (38.1%)
College graduate	912 (35.6%)
AD-PS Score	
MRI-1 (N=817)	0.33 (0.23)
MRI-2 (N=567)	0.44 (0.26)
APOE-ε4, (N=1800)	
None	1390 (77.2%)
1 allele	384 (21.3%)
2 alleles	26 (1.4%)
Type 2 Diabetes	
At WHI enrollment	125 (4.9%)
Prior to WHIMS-ECHO	205 (8.0%)

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Table 2

Raw 3MSE and TICSm scores by year.

Year	3MSE		TICSm	
	N	Score (SD)	N	Score (SD)
−5	2498	97.4 (2.9)	0	
−4	2495	97.4 (2.8)	0	
−3	2080	97.3 (3.0)	0	
−2	2155	97.0 (3.2)	0	
−1	2423	97.0 (3.2)	0	
0	273	96.7 (4.3)	0	
1	0		1846	34.9 (5.1)
2	0		2194	34.9 (5.1)
3	0		2222	34.6 (5.3)
4	0		2025	34.7 (5.3)
5	0		1782	34.7 (5.4)

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Table 3

Differences among trajectory groups according to risk factors.

Risk Factor	Cognitive Trajectory Group					p-value
	1. Consistently Low	2. Decline to Low	3. Decline to Median	4. Relative Improvement	5. Consistently High	
Education						
< High school	12.2%	4.1%	1.2%	4.2%	1.0%	
High school graduate	34.5%	22.0%	17.0%	23.3%	13.8%	<0.001
Some post-HS education	34.5%	41.4%	37.2%	40.5%	36.2%	
College graduate	18.7%	32.5%	44.6%	32.0%	49.0%	
AD-PS Score *						
Initial MRI (N=817)	0.35 (0.02)	0.33 (0.02)	0.30 (0.02)	0.23 (0.01)	0.28 (0.02)	<0.001
Follow-up MRI (N=567)	0.52 (0.03)	0.50 (0.03)	0.42 (0.03)	0.36 (0.02)	0.41 (0.02)	<0.001
APOE-ε4 Alleles (1 or 2) (N=1800)	29.2%	30.1%	22.8%	18.7%	15.1%	<0.001
Type 2 Diabetes						
At WHI enrollment	9.1%	4.9%	3.1%	3.5%	4.6%	<0.001
Prior to midpoint	11.9%	6.8%	8.0%	9.0%	6.0%	0.03

*Higher AD-PS scores reflect greater similarity to Alzheimer's disease

**Differences related to AD-PS score and *APOE-ε4* alleles remained significant (p<0.001) after covariate adjustment for education and diabetes.