

Dementia Risk and Protective Factors Differ in the Context of Memory Trajectory Groups

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Abstract.

Background: Previous research has identified multiple risk and protective factors for late onset Alzheimer's disease (LOAD). However, it is not known whether these risk and protective factors differ for individuals who are cognitively stable versus those already experiencing declines.

Objective: This study examined how dementia risk factors differ across subgroups of older adults defined by memory trajectory. This line of research may lead to more individualized risk profiles.

Methods: Risk factors for incident LOAD were compared across previously-validated groups of older adults exhibiting different memory trajectories ("Stable-High," "Stable-Low," "Decliner," "Rapid Decliner") using stratified Cox regressions. Participants included 2,593 racially/ethnically diverse older adults (mean age of 76 at study entry) in the Washington Heights-Inwood Columbia Aging Project.

Results: Predictors of incident dementia differed across trajectory groups: older age only incurred independent risk in stable groups, education did not incur independent protection in the rapidly declining group, depression only incurred independent risk in the stable-low group, stroke incurred independent risk in the two extreme groups, and *APOE-ε4* only incurred independent risk in the rapidly declining group.

Conclusion: The finding that different risk factors for LOAD were associated with specific memory trajectories may reflect the existence of resilience or vulnerability factors that modify the individual influences of risk/protective factors. This study highlights the utility of considering interactions between dementia risk factors and a patient's unique cognitive history.

Keywords: Aging, Alzheimer's disease, dementia, memory, neuropsychology

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INTRODUCTION

The trajectory of, or slope of decline in, cognitive performance appears to be a better indicator of incipient late-onset Alzheimer's disease (LOAD) pathology than level of cognitive performance [1]. Previous studies comparing groups of older adults have had limited ability to differentiate between initial level of cognitive function and rate of cognitive decline, as those individuals exhibiting more precipitous trajectories also start out with lower cognitive scores. We recently reported on an empirically-guided approach to subgrouping older adults based on their memory trajectories [2]. Specifically, we identified four distinct memory trajectory phenotypes and validated these phenotypes using rates of incident dementia and patterns of regional brain atrophy: "Stable-High", "Stable-Low", "Decliner", and "Rapid Decliner." These memory trajectory groups allow for comparisons between groups of cognitively stable older adults with different overall levels of memory performance (i.e., "Stable-High" versus "Stable Low"), groups of older adults with similar initial level of memory performance but different rates of subsequent decline (i.e., "Stable Low" versus "Decliner"), and groups of older adults declining at differing rates (i.e., "Decliner" versus "Rapid Decliner").

Investigators have identified numerous antecedent and genetic risk factors in the study of LOAD. While old age is consistently the primary predictor of LOAD, additional modifiable (e.g., education, hypertension, depression) and non-modifiable (e.g., sex, race/ethnicity, *APOE* genotype) factors have also been linked to increased risk [3–6]. Researchers have begun to investigate whether these factors confer differential risk in specific subpopulations. For example, hypertension appears associated with increased dementia risk in mid-life adults, but not very old adults [7, 8]. Possessing at least one *APOE-ε4* allele appears more associated with increased dementia risk among non-Hispanic Whites than among African Americans or Hispanics [9]. It is not known whether LOAD factors such as these confer differential risk in groups of older adults who differ in their memory trajectories. It is possible that targeting certain risk factors may be more or less impactful among older adults who are already on a downward trajectory.

The current study investigated known LOAD risk factors in the context of memory trajectory groups. The specific aims were to (1) identify which risk fac-

tors best predict memory trajectory phenotype in a diverse population of older adults; and (2) identify interactions between risk factors and memory trajectory phenotype in the prediction of incident dementia. Our overarching hypothesis was that LOAD risk factors differ depending on a patient's memory trajectory. This line of research may lead to more individualized risk profiles. Specifically, if different risk factors are found to predict incident disease across the phenotype groups, then the evaluation of LOAD risk for a specific patient may be improved by differently weighting specific risk factors. In addition, it may be possible to identify which modifiable target would be expected have the most substantial impact for a particular patient.

MATERIALS AND METHODS

Participants and procedures

Data were included from initially non-demented subjects who participated in at least two visits of the Washington Heights Inwood Columbia Aging Project (WHICAP), a prospective, community-based study of aging and dementia among Medicare recipients 65 years and older residing in Northern Manhattan. Recruitment occurred at two time points, one beginning in 1992 ($n = 1150$) and the other in 1999 ($n = 1443$). Briefly, for both cohorts, a stratified random sample of 50% of individuals aged 65 and older residing in Northern Manhattan was obtained from the Health Care Finance Administration. The sampling strategies and recruitment outcomes of these two cohorts have been described in detail previously [10]. Participants have subsequently been followed at approximately 18–24 month intervals with similar assessments at each interval for up to 25 years. Recruitment, informed consent, and study procedures were approved by the Institutional Review Boards of Columbia Presbyterian Medical Center and Columbia University Health Sciences and the New York State Psychiatric Institute.

Participants were grouped by memory trajectory phenotype, as detailed previously [2]. In brief, growth mixture modeling of age- and education-corrected composite memory scores over an average of 6.0 years ($SD = 3.1$ years; range = 1 to 19 years) was used to obtain the following subject-specific values: intercept (initial level of memory functioning), slope (annualized rate of change in memory functioning), and probability of memory stability versus decline. Participants in the "Stable-High" group

evidenced $\geq 80\%$ probability of stable memory and above-average memory at baseline. Participants in the “Stable-Low” group evidenced $\geq 80\%$ probability of stable memory and below average memory performance at baseline. Participants in the “Decliner” group evidenced $< 80\%$ probability of stable memory and ≥ -1 T-score point of memory decline per year. Participants in the “Rapid Decliner” group evidenced $< 80\%$ probability of stable memory and < -1 T-score point of memory decline per year.

Neuropsychological testing

Participants underwent an in-person evaluation at baseline and each follow-up visit, including full medical and neurological examination and neuropsychological testing in English or Spanish. As described above, participants were grouped based on trajectories of episodic memory performance. Episodic memory was chosen based on previous research demonstrating the sensitivity of episodic memory to LOAD risk and progression [11]. In WHICAP, episodic memory was assessed with the selective reminding test [12]. Based on a previous factor analysis of the WHICAP neuropsychological battery, a memory composite was derived by computing the average z-scores on immediate recall, delayed recall, and delayed recognition trials [13]. In addition to episodic memory, the WHICAP neuropsychological battery includes tests of language, visuo-spatial functioning, and speed/executive functioning.

Consensus diagnosis

Diagnosis of dementia was established by a review of all available clinical information and was based on standard criteria. Following each clinical evaluation, a consensus conference reviewed available data to assign a research diagnosis. First, a diagnosis of dementia was made [14], and then the type was determined based on research criteria for probable or possible AD [15], Lewy body dementia [16], vascular dementia [17], and other dementias.

Demographics and putative risk factors for LOAD

Demographics (i.e., age, sex, education, race, and ethnicity) and putative LOAD risk factors (i.e., depressive symptoms, hypertension, diabetes, heart disease, stroke, apolipoprotein E (*APOE*) genotype) were all measured at baseline.

Depressive symptoms were quantified as a score greater than or equal to 4 on the 10-item Center for Epidemiological Studies Depression Scale [18], which has been shown to be appropriate for use in older adults with and without cognitive impairment in WHICAP and other longitudinal studies of aging [19]. Hypertension, diabetes, heart disease, and stroke were dichotomous variables based on self-report at baseline. Participants were classified as having a particular condition if they responded “yes” when asked about the condition or reported taking medication for the condition. *APOE* genotype was determined as previously described [20], with slight modification [21]. *APOE* status was converted to a dichotomous variable reflecting the presence of at least one epsilon 4 ($\epsilon 4$) allele.

Statistical analysis

Descriptive statistics and group comparisons were conducted in SPSS 22. Trajectory groups were characterized based on sociodemographics and putative LOAD risk factors using analyses of variance with Bonferroni-corrected *post-hoc* tests for continuous variables and chi square tests for categorical variables. The grouping variable in these analyses was memory trajectory group. Multinomial logistic regression models were used to identify independent predictors of group membership. Specifically, the dependent variable was memory trajectory group (i.e., “Stable-High”, “Stable-Low”, “Decline”, “Rapid Decline”). Continuous independent variables were age and education. Categorical independent variables were female sex, African American race, Hispanic ethnicity, a score of four or higher on the CESD, and the presence of hypertension, diabetes, heart disease, stroke, or at least one *APOE*- $\epsilon 4$ allele. Models were built to allow for comparisons between adjacent trajectory groups. Specifically, the “Stable-Low” group was the initial reference category. Thus, comparisons with “Stable-High” reflect differences in initial memory level (as groups did not differ in rate of memory change), and comparisons with “Decline” reflect differences in rate of memory change (as groups did not differ in initial memory level). In a separate multinomial logistic regression model, the reference category for the dependent variable was changed to the “Rapid Decline” group to obtain parameter estimates comparing “Rapid Decline” and “Decline” groups. Independent variables and overall model fit for this second model were identical. Our hypothesis was that the risk/protective factors

would differentiate trajectory groups, with the general pattern showing that declining groups would have more risk factors (e.g., age, depression, hypertension, diabetes, heart disease, stroke, *APOE-ε4*) and fewer protective factors (e.g., higher education).

We also examined putative risk and protective factors within each trajectory group using Cox regression analyses in Mplus 7. In all models, the time to event variable was age of dementia diagnosis or age at last follow-up for participants who remained non-demented over the course of follow-up. In an initial model using the entire sample, we examined predictors of incident dementia independent of trajectory group. Independent variables were baseline age, female sex, African American race, Hispanic ethnicity, education, presence of depression, hypertension, heart disease, diabetes and stroke, *APOE-ε4* status, and three dummy variables reflecting membership in the “Stable-High”, “Stable-Low”, or “Decline” groups. We hypothesized that memory trajectory group membership would be associated with incident dementia, independent of the included risk/protective factors. Next, interactions between the three dummy variables reflecting trajectory group and each of the other predictors were added to this model. We hypothesized that at least some of the risk/protective factors would be differently related to incident dementia across the groups. Finally, four separate models examined predictors of incident dementia within each of the four memory trajectory groups. Independent variables in each of these stratified models included baseline age, female sex, African American race, Hispanic ethnicity, education, presence of depression, hypertension, heart disease, diabetes and stroke, and *APOE-ε4* status.

We hypothesized that different risk/protective factors would predict incident dementia in the different memory trajectory groups.

RESULTS

Characterizing memory trajectory groups based on putative risk factors

Table 1 presents characteristics of the four trajectory groups: “Stable-High” ($n = 1,129$), “Stable-Low” ($n = 444$), “Decline” ($n = 696$), and “Rapid Decline” ($n = 324$). All groups were, on average, in their 8th decade of life at study entry, predominantly female, with 9-10 years of education. Each group comprised approximately 30% African Americans and approximately 40% Hispanics. A history of diabetes and stroke were each significantly more frequent in the two groups of decliners, compared to one or both of the stable groups. Within the two stable groups, hypertension was more prevalent in the group that started out with lower memory scores. More members of the “Decliner” group had at least one *APOE-ε4* allele, as compared to the “Stable-Low” group. There were no significant group differences in the frequency of depression.

A multinomial regression model including the first eleven variables listed in Table 1 was significant ($\chi^2(33) = 242.51$; $p < 0.001$). Compared to the “Stable-Low” group, individuals in the “Stable-High” group were more likely to be female ($B = 0.66$; $SE = 0.14$; $p < 0.001$) and less likely to be African American ($B = -0.59$; $SE = 0.18$; $p = 0.001$) or Hispanic ($B = -0.891$; $SE = 0.20$; $p < 0.001$). Compared

Table 1
Characteristics of the four trajectory groups

	Stable-High (SH)	Stable-Low (SL)	Decline (D)	Rapid Decline (RD)	Group differences
<i>n</i>	1129	444	696	324	–
Age	74.9 ± 5.8	74.6 ± 5.1	77.4 ± 6.5	78.6 ± 6.4	SH = SL < D < RD
<i>n</i> , % Female	834 (73.9)	287 (64.6)	443 (63.6)	217 (67.0)	SH > SL = D = RD
Education	10.4 ± 4.8	9.8 ± 5.9	9.4 ± 4.6	9.3 ± 4.8	SL = SH > D = RD
<i>n</i> , % African American	318 (28.6)	134 (30.4)	260 (37.8)	124 (39.0)	SH = SL < D = RD
<i>n</i> , % Hispanic	407 (36.0)	212 (47.7)	265 (38.1)	133 (41.0)	SH < SL > D = RD
<i>n</i> , % Depression	181 (19.9)	73 (19.5)	92 (19.0)	48 (20.8)	SH = SL = D = RD
<i>n</i> , % Hypertension	674 (61.0)	298 (67.7)	421 (61.6)	200 (62.3)	SH < SL > D = RD
<i>n</i> , % Diabetes	165 (14.9)	84 (19.1)	119 (17.4)	76 (23.5)	SH < SL = D < RD
<i>n</i> , % Heart disease	229 (20.7)	89 (20.2)	172 (25.2)	79 (24.5)	SH = SL = D = RD
<i>n</i> , % Stroke	76 (8.4)	27 (7.2)	54 (11.2)	27 (11.5)	SH = SL < D = RD
<i>n</i> , % <i>APOE-ε4</i>	279 (26.1)	99 (22.8)	189 (30.6)	92 (31.8)	SH = SL < D = RD
Number of study visits	3.9 ± 1.2	4.0 ± 1.0	3.1 ± 1.1	3.3 ± 1.1	SH = SL > D = RD
<i>n</i> , % incident dementia	74 (6.6)	80 (18.0)	210 (30.2)	231 (71.3)	SH < SL < D < RD

Percentages reflect valid percentages.

to the “Stable-Low” group, individuals in the “Decliner” group were older ($B = 0.06$; $SE = 0.01$; $p < 0.001$), more likely to have an *APOE-ε4* allele ($B = 0.44$; $SE = 0.17$; $p = 0.008$), and more likely to report having heart disease ($B = 0.37$; $SE = 0.18$; $p = 0.037$). In a separate multinomial regression with the “Decliner” group as the reference category, membership in the “Rapid Decliner” group was only independently associated with older age ($B = 0.05$; $SE = 0.01$; $p < 0.001$). There was also a trend for higher diabetes prevalence in the “Rapid Decliner” group, compared to the “Decliner” group ($B = 0.42$; $SE = 0.22$; $p = 0.057$).

Incident dementia risk within memory trajectory groups

As shown in Table 1, a subset of participants in each of the four groups developed dementia over the course of follow-up, with the “Stable-High” group exhibiting the lowest incidence rate, followed by “Stable-Low”, “Decliner”, and “Rapid Decliner”. Among cases of dementia, 93% met criteria for LOAD. As shown in Table 2, trajectory group was a strong predictor of dementia conversion. Independent of trajectory group, older age, female sex, lower education, depression, ethnicity, absence of hypertension, presence of stroke, and presence of an *APOE-ε4* allele were uniquely associated with incident dementia. When interactions involving trajectory group were added to this model, there was evidence that age, education, depression, and heart disease (all p 's < 0.05) each related to dementia conversion differently across trajectory groups.

Table 2 also presents results from models stratified by memory trajectory group. Incident dementia in the “Rapid Decliner” group was significantly associated with the presence of stroke and the presence of an *APOE-ε4* allele. Lower education and the absence of hypertension were significantly associated with incident dementia in the “Decliner” group. Significant predictors of incident dementia in the “Stable-Low” group included older age, lower educational attainment, the presence of depression, and the absence of heart disease. Significant predictors of incident dementia in the “Stable-High” group included older age, lower educational attainment, Hispanic ethnicity, the absence of hypertension, and the presence of stroke. It should be noted that there were fewer Hispanics in the “Stable-High” group than in the other three groups.

DISCUSSION

This study explored risk and protective factors for dementia in four groups of initially cognitively healthy older adults based on memory trajectories. The main finding was that different risk and protective factors were associated with incident dementia within each of the four memory trajectory groups. This observation underscores the importance of considering interactions between LOAD risk factors and a patient's unique cognitive history when evaluating dementia risk.

This study used a novel approach to provide support for the potential of cognitive and health behaviors to keep one on a stable memory trajectory in late

Table 2
Predictors of incident dementia, expressed as odds ratios (95% confidence interval)

	Entire sample (<i>n</i> = 2593)	Stable-High (<i>n</i> = 1129)	Stable-Low (<i>n</i> = 444)	Decline (<i>n</i> = 696)	Rapid Decline (<i>n</i> = 324)
Stable-High [†]	0.12 (0.09–0.16)**	–	–	–	–
Stable-Low [†]	0.28 (0.23–0.36)**	–	–	–	–
Decliner [†]	0.46 (0.39–0.55)**	–	–	–	–
Age	1.02 (1.00–1.03)*	1.05 (1.01–1.09)*	1.05 (1.01–1.10)*	1.01 (0.99–1.03)	1.00 (0.98–1.01)
Female	1.28 (1.08–1.52)*	1.62 (0.85–3.10)	1.31 (0.78–2.22)	1.19 (0.88–1.61)	1.18 (0.95–1.46)
Education	0.93 (0.91–0.95)**	0.94 (0.87–1.00)*	0.87 (0.82–0.92)**	0.90 (0.86–0.93)**	0.98 (0.96–1.00)
African American	1.23 (0.92–1.63)	1.89 (0.66–5.43)	1.07 (0.34–3.43)	1.00 (0.60–1.66)	1.17 (0.83–1.65)
Hispanic	1.78 (1.33–2.34)**	5.75 (2.16–15.30)**	2.31 (0.84–6.34)	1.14 (0.67–1.93)	1.40 (0.98–1.99)
Depression	1.24 (1.05–1.47)*	0.80 (0.46–1.38)	1.85 (1.26–2.72)*	1.35 (0.98–1.85)	1.13 (0.94–1.37)
Hypertension	0.78 (0.67–0.92)*	0.60 (0.36–1.01)*	0.89 (0.60–1.33)	0.73 (0.54–0.99)*	0.96 (0.79–1.16)
Diabetes	0.95 (0.79–1.16)	1.29 (0.72–2.31)	0.83 (0.45–1.53)	0.84 (0.59–1.21)	1.15 (0.96–1.39)
Heart disease	0.90 (0.90–0.75)	0.64 (0.32–1.30)	0.49 (0.25–0.98)*	0.96 (0.69–1.32)	1.01 (0.83–1.23)
Stroke	1.37 (1.10–1.71)*	2.11 (1.10–4.07)*	1.13 (0.58–2.17)	1.14 (0.76–1.73)	1.39 (1.13–1.72)*
<i>APOE-ε4</i>	1.19 (1.02–1.40)*	1.27 (0.76–2.11)	1.10 (0.69–1.76)	1.26 (0.93–1.71)	1.19 (1.00–1.43)*

* $p < 0.05$, ** $p < 0.001$, [†]Reference group = Rapid Decliner.

life. In bivariate analyses, membership in the “Stable-High” or “Stable-Low” groups (i.e., resistance to memory decline) was associated with: younger age [22], race [23], higher educational attainment [24], and the absence of diabetes [25] or stroke [26]. Aside from age and race, these factors are all modifiable. It should also be noted that these factors are not perfectly associated with trajectory. For example, 7.2% of individuals in the “Stable-Low” group reported having had a stroke, but having higher education and being free from depression were more strongly related to dementia conversion within this group than was stroke. These observations support the existence of resilience factors that buffer against the negative effects of risk factors on memory trajectories and AD risk.

In multivariate analyses, differences in initial level of memory performance across the two stable groups were only related to demographic factors (i.e., sex, race/ethnicity). Older individuals and those with an *APOE-ε4* allele or heart disease were more likely to show memory decline than individuals with similar initial memory performance but stable memory trajectories (i.e., “Stable-Low” versus “Decliner” groups). Finally, individuals with rapid memory decline were older and had higher diabetes prevalence than individuals with less rapid memory decline (i.e., “Decliner” versus “Rapid Decliner”). These findings highlight the importance of measuring rates of cognitive decline, not just cognitive level, to determine risk and protective factors in aging research.

Variables that predicted dementia conversion within at least one of the trajectory groups are consistent with previous studies: older age, Hispanic ethnicity [3], lower educational attainment [4], depression [5], stroke [6], and the presence of an *APOE-ε4* allele [7]. A novel finding in the current study was that different risk and protective factors were associated with incident dementia within each of the four trajectory groups. Specifically, older age was only a significant risk factor for incident dementia in the two stable groups, higher education was not a significant protective factor in the “Rapid Decliner” group, heart disease or hypertension only appeared to be protective against incident dementia in one or two groups, and the presence of an *APOE-ε4* allele was only associated with incident dementia in the “Rapid Decliner” group.

This pattern of results may be related to differences in the prevalence, and therefore the statistical variability, of the risk factors within each of the trajectory groups, as summarized above. Indeed, several risk factors were associated with membership in one of

the declining groups, and membership in the declining groups itself was an indicator of preclinical AD. It is also possible that some unmeasured genetic or biological vulnerability modifies the individual influences of other potential risk/protective factors (e.g., age) in the declining groups. The finding that having an *APOE-ε4* allele was only associated with incident dementia in the “Rapid Decliner” group suggests that dementia may be more strongly genetically pre-determined in this highest-risk group. In contrast, the presence of protective factors in the more stable groups may have buffered against the deleterious impact of having an *APOE-ε4* allele. Indeed, a reduction in the association between *APOE-ε4* and dementia has also been reported in older adults who reach their 10th decade of life cognitively intact, consistent with a survivor effect model [27].

The finding that hypertension appeared to be protective against incident dementia is consistent with a recent study of “the oldest old” [9]. While mid-life hypertension is associated with increased risk of later dementia [8], later-life hypertension may protect against dementia, perhaps through enhanced cerebral perfusion. This finding may also reflect the higher likelihood of identifying paradoxical protective factors in subgroups of the healthiest older adults (e.g., those with Stable-High memory trajectories or those that reach the 10th decade of life dementia free). The survivor effect model states that such groups comprise a higher proportion of individuals who are resilient against certain risk factors, as evidenced by their maintenance of physical or cognitive health in the face of these risk factors [28]. Thus, the presence of risk factors in subgroups of the healthiest older adults may reflect a correlate of successful cognitive aging rather than a protective factor.

The different pattern of predictors across the four memory trajectory groups is unlikely to be the result of different sample sizes. For example, twice as many variables were associated with incident dementia in the “Stable-Low” group than in the “Decliner” group even though the latter group comprised approximately 250 more members, as well as 130 more incident dementia cases. In addition, the presence of an *APOE-ε4* allele was only significantly associated with dementia incidence in the “Rapid Decliner” group, which was the smallest of the four groups.

This study focused on a limited set of LOAD risk/protective factors that have consistently emerged in prior work. Future research should examine additional factors in the context of cognitive trajectory groups. For example, cholesterol, current and past

alcohol use, and genetic polymorphisms other than *APOE-ε4* could be considered. It should also be noted that in the current study, risk/protective factors were only considered at study entry. Future research may reveal how changes in modifiable factors interact with cognitive trajectory to influence dementia risk. Another limitation of this study is that the presence of health conditions (e.g., hypertension, diabetes, heart disease) was determined via self-report. While all participants were non-demented at the time these health conditions were ascertained, it is possible that some reports were inaccurate. Strengths of this study include the large, diverse, population-based sample followed over time, as well as the sophisticated statistical approach to identifying memory trajectory phenotypes based not only on overall level of memory functioning, but also rate of memory decline.

The results of this study demonstrate that the maintenance of memory function in late life is related to modifiable cognitive and health factors. The finding that different LOAD risk factors predict incident dementia among individuals following different memory trajectories highlights the utility of considering interactions between LOAD risk factors and a patient's unique cognitive history when evaluating dementia risk. Because a growth mixture modeling approach requires a large longitudinal sample, it is unlikely that patients can be placed into statistically-defined groups in the clinical setting. However, memory scores obtained from repeat clinical neuropsychological evaluations can be used to approximate a patient's memory trajectory (e.g., high and stable versus rapidly declining). Given that this study is the first of its kind, it would be important to replicate its specific findings before applying them to a clinical context. However, the general approach of considering interactions between a patient's memory trajectory and his/her specific set of risk and protective factors has the potential to allow clinicians to refine prognosis and/or identify high-priority intervention targets. For example, our study suggests that reducing stroke risk in a patient with rapid memory decline should take priority, while treatment of underlying causes of depression would take priority in a patient with low baseline memory, but a stable memory trajectory.

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