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Authors

Nettiksimmons, Jasmine
Ayonayon, Hilsa
Harris, Tamara
et al.

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Development and validation of risk index for cognitive decline using blood-derived markers

Jasmine Nettiksimmons, PhD
Hilsa Ayonayon, PhD
Tamara Harris, MD
Caroline Phillips, MS
Caterina Rosano, MD
Suzanne Satterfield, MD, DrPH
Kristine Yaffe, MD
For the Health ABC Study

Correspondence to Dr. Nettiksimmons: jasmine.nettiksimmons@ucsf.edu

ABSTRACT

Objective: We sought to develop and validate a risk index for prospective cognitive decline in older adults based on blood-derived markers.

Methods: The index was based on 8 markers that have been previously associated with cognitive aging: *APOE* genotype, plasma β-amyloid 42/40 ratio, telomere length, cystatin C, glucose, C-reactive protein, interleukin-6, and albumin. The outcome was person-specific cognitive slopes (Modified Mini-Mental State Examination) from 11 years of follow-up. A total of 1,445 older adults comprised the development sample. An index based on dichotomized markers was divided into low-, medium-, and high-risk categories; the risk categories were validated with the remaining sample (n = 739) using linear regression. Amyloid was measured on a subsample (n = 865) and was included only in a secondary index.

Results: The risk categories showed significant differences from each other and were predictive of prospective cognitive decline in the validation sample, even after adjustment for age and baseline cognitive score: the low-risk group (24.8%) declined 0.32 points/y (95% confidence interval [CI]: −0.46, −0.19), the medium-risk group (58.7%) declined 0.55 points/y (95% CI: −0.65, 0.45), and the high-risk group (16.6%) declined 0.69 points/y (95% CI: −0.85, −0.54). Using the secondary index, which included β-amyloid 42/40 (validation n = 279), the low-risk group (26.9%) declined 0.20 points/y (95% CI: −0.42, 0.01), the medium-risk group (61.3%) declined 0.55 points/y (95% CI: −0.72, −0.38), and the high-risk group (11.8%) declined 0.83 points/y (95% CI: −1.14, −0.51).

Conclusions: A risk index based on 8 blood-based markers was modestly able to predict cognitive decline over an 11-year follow-up. Further validation in other cohorts is necessary. *Neurology®* 2015;84:696–702

GLOSSARY

AD = Alzheimer disease; **CI** = confidence interval; **CRP** = C-reactive protein; **Health ABC** = Health, Aging and Body Composition; **IL-6** = interleukin-6; **3MS** = Modified Mini-Mental State Examination.

Cognitive decline is a complex, multifactorial process influenced by other chronic diseases of aging and has been associated with biological markers for conditions such as Alzheimer disease (AD), vascular disease, and inflammation.[1–4] However, cognitive decline is not universally preceded by abnormality in any one of these markers. A combination of biological markers may successfully identify individuals at risk of cognitive decline. Currently, the most useful methods for predicting cognitive decline are expensive or invasive (e.g., MRI, fluorodeoxyglucose-PET, CSF protein levels from lumbar puncture).[5] In contrast, measurements derived from blood are relatively inexpensive and more acceptable to patients and potential research participants. We chose to examine 8 blood-based markers that have been shown to be associated with cognitive decline in participants enrolled in a prospective cohort study with 11 years of cognitive follow-up. The markers were chosen to span a variety of dementia pathways to reflect the fact that most

Supplemental data at Neurology.org

From the Departments of Psychiatry (J.N.) and Epidemiology and Biostatistics (H.A.), University of California–San Francisco; Laboratory of Epidemiology and Population Sciences, Intramural Research Program (T.H.), and Neuroepidemiology Section (C.P.), National Institute on Aging; Center for Aging and Population Health (C.R.), Department of Epidemiology, University of Pittsburgh, PA; Department of Preventive Medicine (S.S.), University of Tennessee Health Science Center; and Departments of Psychiatry, Neurology, and Epidemiology and Biostatistics (K.Y.), University of California–San Francisco, San Francisco Veterans Affairs Medical Center.

Health ABC Study coinvestigators are listed on the *Neurology®* Web site at Neurology.org.

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dementias are the result of mixed pathology, potentially accelerated by comorbidities[6]: *APOE* ε4, β-amyloid 42/40 ratio, telomere length, blood glucose, cystatin C, C-reactive protein (CRP), interleukin-6, and albumin.

Previous studies have sought combinations of blood-based markers that differentiated between dementia and control groups.[7,8] We have expanded on this by looking for indicators that *precede* cognitive decline, potentially more useful for research and clinical care. Using a development sample of older adults, we created a risk index using blood-based markers. Then, we evaluated how strongly the index was associated with cognitive decline in a validation sample from the same cohort.

METHODS

Participants. Recruitment for the Health, Aging and Body Composition (Health ABC) Study, a prospective cohort of 3,075 community-dwelling older adults, occurred in 1997–1998. Participants were recruited from a random sample of Medicare-eligible white adults and all black Medicare-eligible residents living within specific zip codes in Pittsburgh, PA, and Memphis, TN. Eligibility required no difficulties performing activities of daily living, walking a quarter mile, or climbing 10 steps without resting and intending to remain in the study area for at least 3 years. Potential participants with life-threatening cancers were excluded.[9] To avoid including participants with prevalent dementia, participants with a baseline Modified Mini-Mental State Examination (3MS) cognitive score <80 were excluded, along with individuals without at least 2 cognitive testing time points. We used a stratified random sample based on race, sex, and age ($<75/75+$) to create two-thirds of the observations as a development sample ($n = 1,632$), reserving the other third for a validation sample ($n = 833$). Missing values for primary markers left us with a final analytic sample of $n = 1,445$ in the development data and $n = 739$ in the validation data.

Standard protocol approvals, registrations, and patient consents. The Health ABC Study protocol was approved by institutional review boards at both clinical sites (University of Pittsburgh, University of Tennessee, Memphis) and the University of California–San Francisco coordinating center. All participants signed informed consent at enrollment.

Outcome. Cognition was assessed with the 3MS, measured at years 1, 3, 5, 8, 10, and 11.[10] The primary outcome for this analysis was changeover time on the 3MS cognitive test. We calculated person-specific slopes (best linear unbiased predictors) from a linear mixed-effects regression model based on the entire available sample.[11]

Markers. The risk index components we examined included *APOE* ε4, β-amyloid 42/40 ratio, telomere length, blood glucose, cystatin C, CRP, interleukin-6 (IL-6), and albumin. *APOE* ε4 is the strongest known genetic risk factor for AD and all-cause dementia, increasing risk of AD by 3-fold.[12,13] However, the ε4 allele is neither necessary nor sufficient for the development of cognitive decline. The ratio of plasma β-amyloid 42 to β-amyloid 40 has been previously found to be predictive of AD and all-cause dementia in meta-analysis.[14] Telomere length (thought to have a role in aging in general) has been associated with cognitive decline and dementia in a number of older populations.[15–17] Diabetes and poor glucose regulation, often marked by elevated fasting blood glucose, have been consistently associated with poor cognitive outcomes.[18] High cystatin C, a marker for poor kidney function, has also been previously associated with cognitive deficit.[19] There is substantial evidence that inflammation has a role in cognitive aging, possibly through a vascular pathway. CRP is a strong risk factor for vascular disease (which is itself a risk factor for dementia) but results linking CRP to cognition conflict with some studies showing a significant association and others failing to find an association.[20,21] High levels of IL-6 have been associated with worse cross-sectional cognitive performance and cognitive decline.[22,23] Low levels of serum albumin have been cross-sectionally associated with cognitive impairment in older adults, and there is evidence that serum albumin may have a role in reducing β-amyloid toxicity.[24,25]

Nearly all of the markers used in this analysis were measured in the entire Health ABC cohort, although plasma β-amyloid was measured in a subset of 998 participants (random sample of race and sex) who had more than one cognitive test measure.

Baseline fasting blood samples were obtained in the morning via standard venipuncture; after processing, the specimens were aliquoted, frozen at −70°C, and shipped to the Health ABC Core Laboratory at the University of Vermont (Burlington). Serum cystatin C was measured using a BNI nephelometer (Dade Behring, Deerfield, IL) that used a particle-enhanced immunonephelometric assay (N Latex cystatin C). The assay range is 0.195 to 7.33 mg/L. Plasma IL-6 level was measured in duplicate using ELISA kits (R&D Systems, Minneapolis, MN), with detectable limit of 0.10 pg/mL. Serum CRP level was measured in duplicate using ELISA based on purified protein and polyclonal anti-CRP antibodies (Calbiochem, EMD Biosciences Inc., Darmstadt, Germany). The CRP assay was standardized according to the World Health Organization First International Reference Standard with a sensitivity of 0.08 μg/mL. Albumin was measured with a colormetric technique on a Johnson & Johnson Vitros 950 analyzer (New Brunswick, NJ). Plasma glucose was measured by an automated glucose oxidase reaction (YSI 2300 Glucose Analyzer; Yellow Springs Instruments, Yellow Springs, OH).

Telomere length was measured at the University of Utah using DNA extracted from blood leukocytes; average telomere lengths were measured by quantitative PCR. Relative average telomere lengths were determined by comparing each DNA sample with a reference DNA sample using the standard curve method with coefficient of variation of 5.8%.[26] β-Amyloid 40 and β-amyloid 42 were measured from stored plasma obtained at the first follow-up visit (year 2) at the laboratory of Dr. Steven G. Younkin at the Mayo Clinic, Jacksonville, FL, using Innogenetics (Ghent, Belgium) INNO-BIA assays. Detection limits for this assay are 12 pg/mL for β-amyloid 40 (interassay coefficient of variation = 9.9%, mean within-assay coefficient of variation = 3.5%) and 5 pg/mL for β-amyloid 42 (interassay coefficient of variation = 9.3%, mean interassay coefficient of variation = 2.3%).

Statistical analysis. The development and validation datasets were compared for differences in demographics and blood marker distributions. Frequencies and percentages are reported for demographics; reported p values were obtained from χ^2 tests. We reported medians, ranges, and p values from nonparametric tests for blood markers, because many were substantially skewed.

Index development methods. Before constructing the index, we dichotomized each continuous marker using bootstrapped area under the curve analysis at a cutoff predictive of substantial

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cognitive decline, which we defined as having a 3MS slope in the lowest quartile for the entire analytic sample; this corresponded to approximately 0.8 points lost annually. Although accepted clinical cutoffs exist for some of the markers, none were designed to target preclinical decline. To evaluate the strength of association between the dichotomized markers and cognitive decline before constructing the index, we used individual linear regression models with robust standard errors using person-specific slopes as the outcome.

We created a weighted risk score based on logistic regression coefficients using the same weighting methodology as in the late-life dementia index of Barnes et al.[27] where markers with β coefficients >0.75 were given a weight of 2 and all other markers were given a weight of 1. Preliminary analysis suggested that plasma amyloid 42/40 ratio was the strongest predictor for cognitive decline, but it was measured on a smaller subset of subjects. We chose to exclude amyloid from the primary index to avoid a substantial sample size reduction; however, we created a secondary index that includes amyloid. Both the primary and secondary risk indexes were divided into low-, medium-, and high-risk ranges based on the cognitive slope distribution at each level of the index in the development data.

Index validation methods. We evaluated the association between the low-, medium-, and high-risk categories and cognitive decline (person-specific 3MS slope) using linear regression models, with and without adjustment for age and baseline 3MS, to evaluate whether the indexes were determining clinically apparent baseline differences or actually predictive of prospective cognitive decline.

Analysis was performed using all available complete cases with SAS version 9.3 (SAS Institute, Cary, NC) and R version 3.0.0.

RESULTS

Table 1 describes the participants in the development and validation samples. The 2 samples do not significantly differ on demographic characteristics, markers, or number of cognitive assessments.

Development results. Cutpoints for the dichotomized blood markers ranged from the 38th to the 87th percentile in the development data (table 2). All of the dichotomized markers were significantly associated with cognitive decline in the development data.

Weights for the primary and secondary indexes were derived with 2 separate logistic regression models using membership in the lowest slope quartile as the outcome (table 2). The primary index resulted in equal weights for all markers. The secondary index (amyloid) resulted in a weight of 2 for amyloid and a weight of 1 for all other markers. Linear trend tests for both indexes were highly significant ($p < 0.0001$). Low-, medium-, and high-risk categories were created based on the person-specific cognitive slope distribution in the development data. For the primary index (potential range 0–7), a score of 0–1 was considered low risk, 2–3 was medium risk, and 4–7 was high risk. For the secondary index (potential range 0–9), a score of 0–2 was low risk, 3–5 was medium risk, and 6–9 was high risk.

Table 1 Description and comparison of the development and validation samples

	Development (n = 1,445)	Validation (n = 739)	p Value
Female, n (%)	766 (53.0)	399 (54.0)	0.66
Black, n (%)	504 (34.9)	250 (33.8)	0.63
Age, y, n (%)			
Age ≤72	589 (40.8)	319 (43.2)	0.56
72 < age ≤ 76	582 (40.3)	285 (38.6)	
Age >76	274 (19.0)	135 (18.3)	
Education < high school, n (%)	267 (18.5)	141 (19.2)	0.71
***APOE* ε4 (present), n (%)**	396 (27.4)	217 (29.4)	0.34
Cognitive assessments, mean (SD)	4.9 (2.0)	4.9 (1.9)	0.71
Continuous blood markers, median (range)			
Telomere length, bp	4,750 (350, 15,700)	4,750 (1,780, 10,680)	0.30
Cystatin C, mg/L	0.99 (0.38, 4.21)	0.99 (0.51, 6.10)	0.89
Fasting glucose, mg/dL	94 (47, 305)	94 (71, 328)	0.37
C-reactive protein, μg/mL	1.66 (0.16, 85.18)	1.61 (0.15, 62.85)	0.69
Albumin, g/dL	4.0 (3.0, 5.5)	4.0 (3.1, 4.8)	0.13
Interleukin-6, pg/mL	1.73 (0.21, 14.13)	1.81 (0.30, 15.96)	0.18
β-Amyloid 42/40 ratio	0.18 (0.05, 1.82)	0.17 (0.06, 0.81)	0.12
Outcome, median (range)			
Estimated 3MS slope	−0.30 (−7.83, 0.82)	−0.27 (−5.45, 0.84)	0.23

Abbreviations: bp = base pairs; 3MS = Modified Mini-Mental State Examination.
The p values for frequencies were derived from χ^2 tests. The p values for medians derive from large sample approximations of Wilcoxon rank sum tests.

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Table 2 Risk index components						
Blood markers	Direction associated with cognitive decline	Cutoff	Percentile	*p* Value	Primary index β (weight)	Secondary index β (weight)
Telomere length, bp	Low	6,230	86th	0.001	0.22 (1)	−0.04 (1)
Cystatin C, mg/L	High	1.235	87th	0.002	0.41 (1)	0.36 (1)
Serum glucose, mg/dL	High	107.5	78th	0.01	0.36 (1)	0.65 (1)
C-reactive protein, μg/mL	High	4.24	86th	0.01	0.33 (1)	0.15 (1)
Albumin, g/dL	Low	3.90	44th	0.01	0.25 (1)	0.33 (1)
Interleukin-6, pg/mL	High	2.40	70th	<0.001	0.31 (1)	0.38 (1)
APOE ε4 (present/absent)	—	—	—	<0.001	0.59 (1)	0.81 (1)
β-Amyloid 42/40 ratio	Low	0.177	50th	<0.001	—	0.22 (2)

Abbreviation: bp = base pairs.
Cutoffs were derived in the development data using bootstrapped receiver operating characteristic curves based on the binary outcome defined as having a Modified Mini-Mental State Examination (3MS) slope in the lowest quartile. The *p* values are provided for how well the dichotomized marker predicts 3MS decline (slope) in linear regression models with robust standard errors. All values derived from development data.

Validation results. Both the primary and secondary risk indexes were significantly associated with cognitive decline in the validation data. Using the primary index, 24.8% of the validation sample subjects were considered low risk, 58.7% were considered medium risk, and 16.6% were considered high risk for cognitive decline (table 3). All 3 risk levels (low, medium, high) differed significantly from each other with and without adjustment for age. Effect sizes for the risk levels actually increased slightly in age-adjusted analysis, with participants in the medium- and high-risk categories on the primary index showing annual decline of 0.56 and 0.80 points per year (medium: −0.56, 95% confidence interval [CI]: −0.67, −0.46; high: −0.80, 95% CI: −0.96, −0.63), compared with the low-risk group, which showed an average decline of 0.34 points per year (95% CI: −0.48, −0.19). Controlling for baseline cognitive score resulted in only minor attenuation of the effect, mainly in the high-risk group. This is evident in the figure, showing age-adjusted estimates for 3MS trajectories in each group; while the low and medium groups have a similar baseline (low-risk group: 92.8, 95% CI: 91.9, 93.7; medium-risk group: 92.7, 95% CI: 92.0, 93.4), the high-risk group starts the study at a substantially lower baseline (91.0, 95% CI: 89.9, 92.0). Results were largely similar for the secondary (amyloid-based) index, with only minor differences between unadjusted and age-adjusted estimates and significant differences at each risk level. On the secondary index, 26.9% of participants were considered low risk, and lost 0.29 points/y after adjustment for age (95% CI: −0.52, −0.06). Medium-risk participants (61.3%) lost 0.64 points/y (95% CI: −0.81, −0.46) and high-risk participants (11.8%) lost 1.02 points/y (−1.35, −0.70). Again, adjustment for baseline cognitive score attenuated these effects slightly, but the risk levels remained significantly different from each other.

Table 3 Estimated annual decline on 3MS by risk category (points per year)							
		Unadjusted		Age-adjusted		Age/baseline 3MS adjusted	
	No. (%)	Annual decline (95% CI)	*p*	Annual decline (95% CI)	*p*	Annual decline (95% CI)	*p*
Primary index							
Low (0–1)	167 (24.8)	−0.29 (−0.42, −0.17)	—	−0.34 (−0.48, −0.19)	—	−0.32 (−0.46, −0.19)	—
Medium (2–3)	395 (58.7)	−0.51 (−0.57, −0.43)	0.003	−0.56 (−0.67, −0.46)	0.002	−0.55 (−0.65, −0.45)	0.001
High (4–7)	112 (16.6)	−0.74 (−0.89, −0.59)	<0.001	−0.80 (−0.96, −0.63)	<0.001	−0.69 (−0.85, −0.54)	<0.001
Secondary index (including amyloid)							
Low (0–2)	75 (26.9)	−0.33 (−0.52, −0.13)	—	−0.29 (−0.52, −0.06)	—	−0.20 (−0.42, 0.01)	—
Medium (3–5)	171 (61.3)	−0.69 (−0.82, −0.56)	0.002	−0.64 (−0.81, −0.46)	0.004	−0.55 (−0.72, −0.38)	0.002
High (6–9)	33 (11.8)	−1.09 (−1.39, −0.80)	<0.001	−1.02 (−1.35, −0.70)	<0.001	−0.83 (−1.14, −0.51)	<0.001

Abbreviations: CI = confidence interval; 3MS = Modified Mini-Mental State Examination.
The *p* values were derived from a linear regression model with the lowest risk group as the reference. Age-adjusted estimates presented are based on the middle age group.

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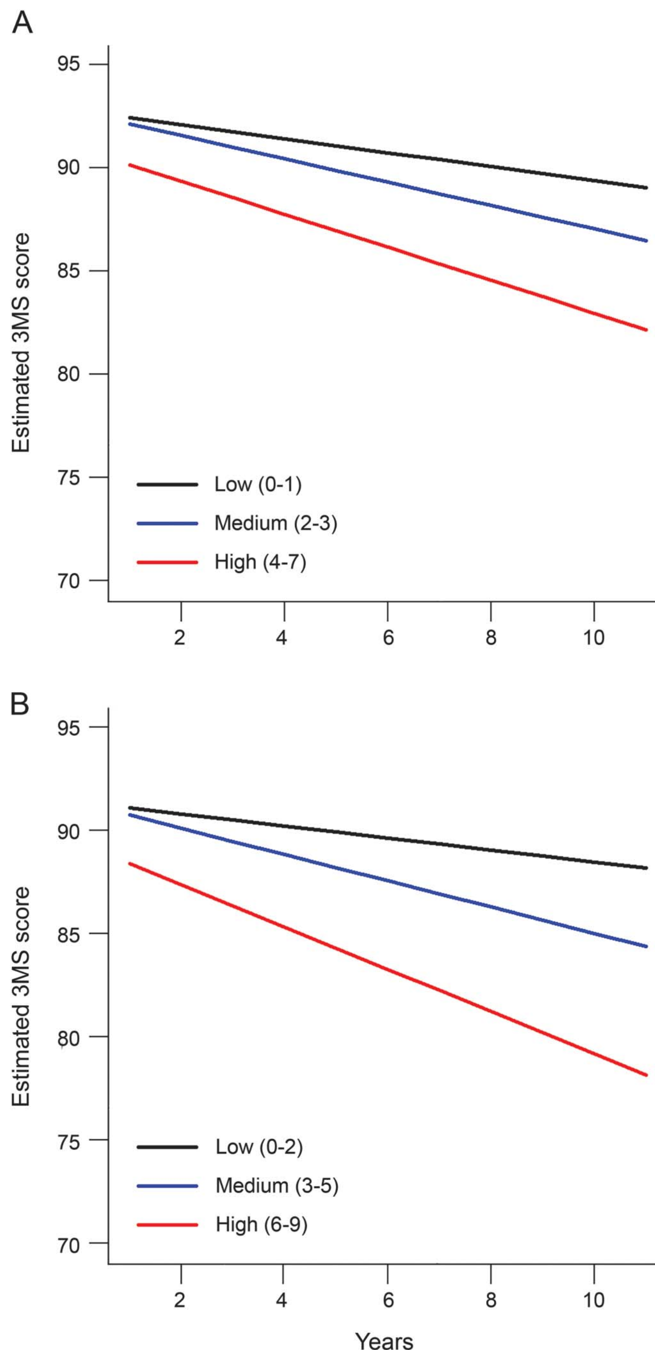
Figure Age-adjusted estimates of 3MS by risk group



Estimated 3MS trajectories by risk group after adjusting for age (estimates shown correspond to the middle age group). Separate figures are presented for the primary (A) and secondary (B) indexes; the secondary index additionally contained amyloid and was based on a smaller sample. 3MS = Modified Mini-Mental State Examination.

DISCUSSION We found that the low-, medium-, and high-risk categories in both our primary and secondary indexes were significantly associated with longitudinal cognitive decline independent of age. The risk indexes were predictive with modest effect sizes (approximately 0.4 3MS points per year difference between high- and low-risk groups) even when controlling for baseline 3MS, which suggests that the indexes can provide valuable predictive information about future cognitive trajectories in addition to what could be inferred using baseline cognitive status. Although there is not a universally agreed on definition of meaningful clinical change on the 3MS, a 5-point change has been suggested and used in previous studies.[3,28–30] Based on the average annual change in age-adjusted analysis, the low-risk group would reach a 5-point change after more than 14 years and the high-risk group would reach such a point in less than 7 years.

We chose to combine 8 markers representing a variety of pathways associated with cognitive decline ranging from markers of general aging (telomere length) to AD-specific markers (*APOE*, amyloid). We also emphasized markers for inflammation (CRP, IL-6) and vascular pathways (glucose, cystatin C) because previous studies have demonstrated a strong role for both in AD and all-cause dementia.[7,31,32] Albumin performs a number of functions that may influence cognitive decline on multiple pathways including antioxidant defense, inhibition of β-amyloid–peptide fibrils, and transport of metals, fatty acids, cholesterol, and drugs.[33,34] We were interested to find that the cutoff percentile for what qualified as the at-risk level of the blood markers varied widely between markers, encompassing less than 15% to as much as 85% of the development sample. Our cutoff results may be useful to other researchers examining the relationship between these markers and cognitive decline or dementia; often such markers are categorized based on simple percentiles because of a lack of a priori information on informative groupings. We were interested to find that, in many cases, our cutoffs were similar to clinical cutoffs used; our blood glucose cutoff was 107.5 mg/dL and the 2012 International Diabetes Federation guidelines list 126 mg/dL as a cutoff of concern.[35] Similarly, our cystatin-C cutoff of 1.235 mg/L was near the cutoff used for preclinical kidney disease (>1.0 mg/L).[36]

Our analysis had a number of limitations. Our primary outcome, person-specific 3MS slope, was derived using best linear unbiased predictors from a longitudinal regression model across more than 10 years of follow-up, which has many advantages over a simpler change score model. However, slope estimates in individuals with fewer cognitive observations were shrunk in magnitude toward the overall average, relative to individuals with more observations.[11] This is a conservative approach but risks the possibility that individuals lost to follow-up earlier, potentially because of cognitive decline, were assigned a slope that did not reflect the full degree of their impairment. Although the β-amyloid 42/40 ratio was one of the most predictive markers, it was only available on a subset of the participants, reducing the precision

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of our estimates. We chose a fairly straightforward weighting scheme for the construction of the index to make the index easy to use, but a sensitivity analysis using an alternate approach with exact logistic regression coefficients for each marker resulted in similar performance in the development data. We used separate development and validation samples, but both were from the same cohort; further validation will be necessary in other populations.

One unambiguous benefit of the primary index is that all of the components could be measured inexpensively from a single blood draw and do not require research staff with specialized training for components such as neuropsychological testing or additional procedures such as imaging. Therefore, this risk index could be used affordably in large cohort studies. This could be especially useful for studies that are designed to closely monitor participants as they undergo biological and clinical changes associated with cognitive decline. Likewise, the risk index could be used in a research setting to seed a prevention trial with individuals who are more likely to exhibit decline, thereby providing a greater opportunity to observe the effect of the intervention. The risk index could be used in a clinical setting, combined with patient/informant report, family history, and the Barnes et al.[27] late-life dementia risk index (which focuses on demographics, health history, medical imaging, and cognitive testing), to provide a more comprehensive risk profile for cognitive decline. This would allow clinical practitioners to closely monitor high-risk patients for cognitive change, initiate treatment at an earlier stage, and encourage tighter control of conditions that are risk factors for dementia, such as hypertension and diabetes. A risk profile could help inform patients' medical and financial planning and potentially provide motivation for lifestyle changes associated with cognitive resilience, such as more exercise and social engagement.

Our results have demonstrated internal validity of the risk indexes in this cohort and have shown promise in identifying prospective cognitive change independent of baseline cognitive status. Further study in other populations is necessary to determine whether these indexes have robust external validity. Nearly all of the components of our indexes are time-varying, thereby allowing an individual's risk category to vary over time. Future studies with repeated laboratory measures will be needed to evaluate whether changes in the index track with cognitive performance over time. If so, the risk index could have even greater value as a clinical monitoring device.

AUTHOR CONTRIBUTIONS

Dr. Nettiksimmons designed and conceptualized the study, conducted data analysis, interpreted data, and drafted and revised the manuscript. Dr. Yaffe designed and conceptualized the study, interpreted data, reviewed and revised the manuscript, and supervised the study. Drs. Ayonayon, Harris, Satterfield, Rosano, and Ms. Phillips reviewed and revised the manuscript.

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DISCLOSURE

J. Nettiksimmons, H. Ayonayon, T. Harris, C. Phillips, C. Rosano, and S. Satterfield report no disclosures relevant to the manuscript. K. Yaffe serves on data safety monitoring boards for Takeda, Inc., and a study sponsored by the NIH, and has served as a consultant for Novartis and Pfizer. Go to Neurology.org for full disclosures.

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