Stability of Diagnoses of Cognitive Impairment, Not Dementia in a Veterans Affairs Primary Care Population

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OBJECTIVES: To describe the stability of cognitive impairment, not dementia (CIND) in a longitudinal cohort of primary care veterans. To examine the association between baseline brief cognitive screening tests, demographic and clinical characteristics, and cognitive decline.

DESIGN: Follow-up cognitive assessment after an average of 2.5 years of a cohort of veterans in primary care whose baseline status was CIND or normal cognition.

SETTING: Three Department of Veterans Affairs primary care clinics.

PARTICIPANTS: Subjects with CIND at baseline and a sampling of subjects with baseline normal cognition.

MEASUREMENTS: Veterans underwent a standard assessment, including neuropsychological tests and informant interview.

RESULTS: Of 293 potentially eligible individuals, 186 enrolled in the follow-up study. Of the 131 subjects with a baseline diagnosis of CIND, 16 (12%) progressed to dementia, 88 (67%) continued to have a diagnosis of CIND, and 27 (21%) improved to normal cognition. Of the 55 subjects with a baseline diagnosis of normal cognition, one (2%) progressed to dementia, 17 (31%) progressed to CIND, and 37 (67%) remained cognitively normal. In bivariate analyses, poorer performance on baseline cognitive screening tests was associated with cognitive decline, whereas Framingham Stroke Risk Profile (FSRP) and education were not. Similarly, higher scores on cognitive screening tests were associated with return to normal cognition. In multivariable logistic regression models, lower baseline Mini-Cog and Modified Mini–Mental State scores were associated with cognitive decline, whereas Memory Impairment Screen scores, FSRP, and years of education were not.

CONCLUSION: A minority of subjects had worsening of cognitive function sufficient to change diagnostic category. Over an average of 2.5 years, subjects diagnosed with CIND at baseline reverted to normal cognition at a higher rate than progressed to dementia. Cognitive screening tests addressing multiple domains of cognitive impairment were predictive of cognitive decline. **J Am Geriatr Soc 63:1105–1111, 2015.**

Key words: dementia; cognitive impairment; geriatric assessment

Dementia and milder cognitive impairment are prevalent and, as the number of older adults increases, the effect on the healthcare system and on society as a whole is expected to increase dramatically.[1–4] Adults with dementia or cognitive impairment, not dementia (CIND) have higher healthcare costs[5–7] and shorter life spans[8] than those without, and their families have negative psychological,[9] physical,[10] and financial effects.[3,11]

Progression of cognitive decline varies across individuals. A person with a CIND diagnosis is 5 to 23 times as likely to progress to dementia (over a period of 1.5 to almost 6 years) as someone without CIND,[12–15] although not all will progress to dementia, and some may revert to what would be considered normal cognition.[12] Those who revert to normal cognition retain a moderately greater risk of future progression to dementia.[15]

Determining who will progress along a spectrum of worsening cognitive impairment and who might stabilize or improve is not yet possible, but better estimates of the rate of progression and factors associated with progression would inform care. This article reports the cognitive outcomes of primary care veterans who were enrolled initially to examine the performance of brief cognitive screening tests.[16] The cohort for the present study was the subgroup of surviving participants assigned a research diagnosis of CIND or normal cognitive aging based on an assessment in the original study. Participants were reevaluated after 1

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to 4 years (mean 2.5 years). The goals of this study were to describe the stability of baseline diagnoses and examine the association between the baseline brief cognitive screening tests, along with selected demographic and clinical factors, and cognitive decline.

METHODS

Detailed methods and full cohort characteristics for the original study and the baseline assessment have been previously reported.[16] Briefly, a random sample of 630 veterans in primary care was enrolled from the Durham Veterans Affairs (VA) Medical Center between May 2006 and December 2008. Individuals aged 65 and older in primary care were eligible unless they had a diagnosis of dementia, active substance abuse, psychosis, or acute illness requiring urgent care or lived in a nursing home. Enrolled veterans were administered three brief cognitive screening tests (the Modified Mini–Mental State Examination (3MS),[17] the Mini-Cog,[18,19] and the Memory Impairment Screen (MIS)[20]) and a standard assessment that included semi-structured clinical interviews with the participant and an informant, neuropsychological testing, a standardized brief neurological examination, and review of electronic medical records. Research personnel blinded to the results of the screening tests completed the standard assessment. A consensus panel (including authors BP, JB, TH, JWW from neuropsychology and dementia epidemiology, neurology, geriatric psychiatry, and general internal medicine) reviewed all assessment information except the screening test results and assigned a research diagnosis from one of three general categories: normal cognitive function, CIND, and dementia.

All surviving subjects with a diagnosis of CIND (n = 221) and a random sample of surviving subjects with a diagnosis of normal cognition (n = 72) at the baseline assessment were invited to participate in this follow-up study. The random sample of subjects with normal cognition from the original study was needed to ensure unbiased diagnoses in follow-up and to strengthen study design. The follow-up assessment occurred an average of 2.5 years after baseline assessment. Because it was desired to examine the progression of cognitive decline in individuals with CIND, subjects (n = 21) from the original study diagnosed with dementia were excluded. The follow-up assessment battery was the same as the baseline assessment, with the exception that the neurological examination and three brief cognitive screening tests were not repeated. Follow-up interviews with subjects and informants focused on changes since the first examination.

The same consensus panel assigned subjects to the same three general categories (normal cognition, CIND, and dementia) at follow-up based on review of the follow-up standard assessment but not the baseline evaluation or research diagnosis.

Demographic and Clinical Factors

Demographic and medical information was collected at baseline through subject interviews and review of the VA electronic medical record. The Framingham Stroke Risk Profile (FSRP),[21] a standardized, validated measure of vascular burden, was calculated using baseline data. Although originally developed to aid estimates of future risk of stroke, associations between FSRP score and cognitive impairment have been found in multiple cohorts.[22–25] Factors in the FSRP include age, systolic blood pressure, use of antihypertensive therapy, diabetes mellitus, cigarette smoking, prior cardiovascular disease, atrial fibrillation, and left ventricular hypertrophy. For subjects aged 86 and older (the oldest age in the original formulation of FSRP), the highest points from the Framingham age scale were used. Cardiovascular disease was defined as angina pectoris, a history of a myocardial infarction, coronary artery disease, other vascular disease, or a history of congestive heart failure. Left ventricular hypertrophy was considered present if evidence of it was noted in an echocardiogram or electrocardiogram. Systolic blood pressure was an average of all the readings taken in the visits closest in time—before and after—to the original study visit.

Cognitive Screening Tests

A research assistant administered three cognitive screening tests at baseline (3MS,[17] Mini-Cog,[18,19] MIS[20]) in random order before the standard assessment. Neither subjects' informants nor the research nurse administering the neurocognitive testing that was part of the standard assessment observed the administration of the screening tests. The 3MS[17] is a 100-point instrument that assesses several dimensions of cognition and has excellent performance characteristics. It includes the Mini–Mental State Examination (MMSE) and adds items to better assess memory, verbal fluency, similarities, and delayed recall. Scores <83 are considered abnormal. The Mini-Cog[18,19] consists of a three-item recall to assess memory and a clock-drawing test (which also serves as a distraction task) to assess executive function. The clock-drawing task is interpreted as normal (2 points) or impaired (0 points). Scores ranged from 0 to 5, with scores of 2 or less on the overall screening test considered impaired. The MIS[20] consists of free and cued four-word recall. After an interference task (consisting of counting forward and backward, saying the alphabet forward and backward, and counting by threes as necessary to fill 2–3 minutes), 2 points are earned for each word recalled without the cue and 1 point for each word recalled after a cue. Scores range from 0 to 8, with scores <5 indicating impairment.

Standard Assessment Measures

The neuropsychological test battery was a subset of one previously used in a number of large epidemiological studies of dementia.[26,27] The tests administered included the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery,[28] which includes assessment of category verbal fluency; confrontational naming (used in an expanded form in this battery); word list learning, recall, and recognition; and praxis copying, recall, and recognition. The Logical Memory Test paragraphs (Wechsler Memory Scale—III),[29] the Controlled Oral Word Association test,[30] and the Trail-Making Test[31] were also administered. A structured neurological examination was also included at baseline.

A semistructured interview based on the Dementia Questionnaire[26,27] was conducted with an informant that the subject named, as was the Dementia Severity Rating Scale.[32] The Clinical Dementia Rating Scale[33] was completed based on all available information from the assessment.

Stability of Cognitive Diagnosis

The association between the baseline brief cognitive screening tests, selected demographic and clinical factors, and cognitive decline was assessed. The main outcome, cognitive decline as a dichotomous variable, was defined as transitioning from a research diagnosis of CIND to dementia or from normal cognition to CIND or dementia. For each subject, a binary variable was coded as 1 if cognitive decline occurred between the baseline and follow-up assessments and 0 if cognitive status remained stable or improved.

Analyses

All analyses were performed using SAS version 9.2 (SAS Institute, Inc., Cary, NC). Age, education, baseline screening test scores, and baseline research diagnosis of participants was compared with that of nonparticipants in the follow-up study using *t*-tests and the chi-square test. The stability of research diagnosis in the entire group is described and stratified according to baseline research diagnosis. For the second aim, examining the association between screening, demographic, and clinical factors and cognitive decline, the predictor variables were constrained to five variables selected a priori: the three brief cognitive screening tests, years of education, and the FSRP. The scores for screening tests in the models were treated as continuous variables. The association between each of the predictors and cognitive decline was examined in bivariate analyses using simple logistic regression models. Separate multiple logistic regression models were then fit to examine the association between cognitive decline and each screener, education, and FSRP at baseline. The association between cognitive decline and each screener was also examined using separate logistic regression models according to baseline diagnosis to explore whether these associations were similar for each baseline diagnostic group. Because of the small number of individuals who progressed in these stratified analyses, only baseline FSRP was included as a covariate in these analyses. Although age is an important predictor of cognitive decline, FSRP was used instead of age in the primary model, because age is a component of the FSRP score calculation. As a sensitivity analysis, models including age instead of FSRP were fit.

The c-statistic is an index of the probability of concordance between the predicted probability from the regression model and the response and is generally reported when logistic regression models are fit. It is an interpretation of understanding how well a model predicts response above random chance; a c-statistic of 0.5 indicates random predictions, and a c-statistic >0.8 has utility in predicting responses of subjects. C-statistics for the models are reported in the footnotes to Table 3.

RESULTS

Sample Characteristics

Of the 293 potentially eligible subjects (Figure 1), 25 could not be contacted, three were not sent a letter, nine were deceased, 34 refused participation at some point in eligibility determination, 19 were no longer eligible, and 17 additional subjects failed to attend their scheduled evaluation appointments. No differences in age or years of education were found between the 186 participants and the 107 nonparticipants. All three cognitive screening scores were lower for the nonparticipants (3MS, 3.2 points lower, $P = .007$; Mini-Cog, 0.7 points lower, $P < .001$; MIS, 0.5 points lower, $P = .03$). There was also an association between baseline diagnosis and participation ($P = .009$); 76% of subjects randomly selected from the normal baseline diagnostic group participated in the

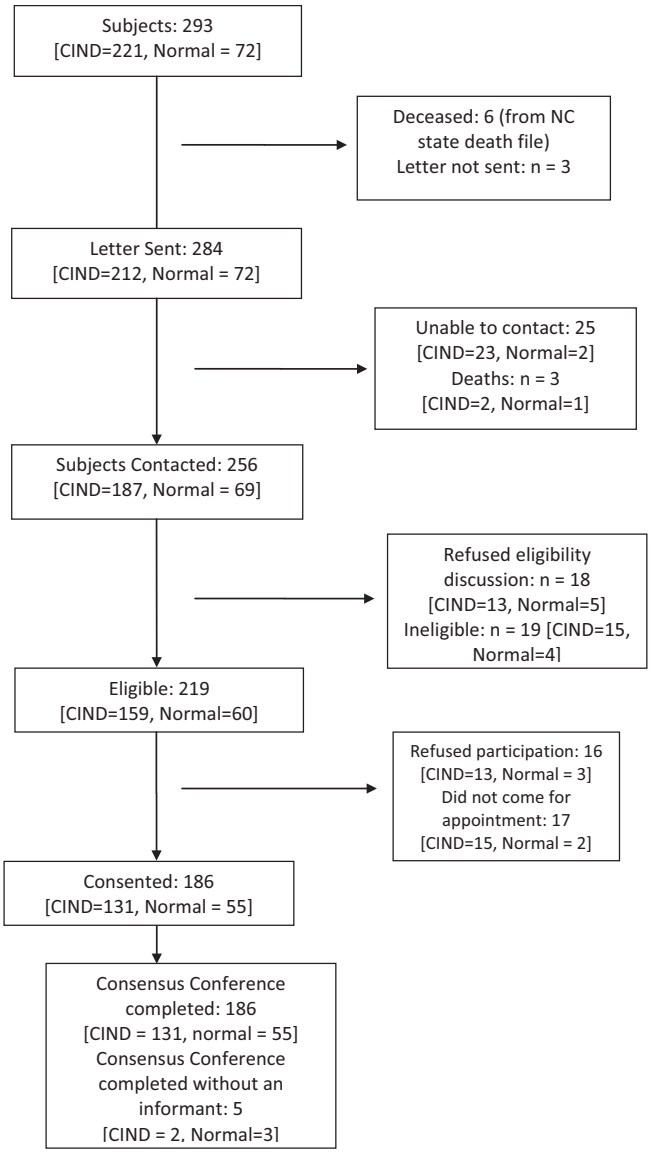

Figure 1. Subject flow. CIND, cognitive impairment, not dementia; NC = North Carolina.

follow-up study, compared with 59% of subjects with a baseline CIND diagnosis.

Of the 186 subjects who participated in the follow-up study, 131 had a baseline diagnosis of CIND, and 55 had a baseline diagnosis of normal cognition. The mean time ± standard deviation between baseline and follow-up assessments was 2.5 ± 0.8 years. As indicated in Table 1, the cohort was predominantly male, as is typical for veterans in this age group. Prevalence of presumptive risk factors for cognitive impairment was high (hypertension, 82.3%; diabetes mellitus, 44.6%; depression, 22.6%; history of stroke, 10.2%).

Stability of Cognitive Diagnosis

Of the 131 subjects with a baseline diagnosis of CIND, 16 (12%) progressed to dementia, 88 (67%) remained stable with a diagnosis of CIND, and 27 (21%) improved to a diagnosis of normal cognition. Of the 55 subjects with a baseline diagnosis of normal cognition, one (2%) progressed to dementia, 17 (31%) progressed to CIND, and 37 (67%) had normal cognition at both assessment times.

The 27 subjects who moved from a CIND diagnosis to normal cognition had higher scores at baseline on all three cognitive measures than the 88 subjects who retained a CIND diagnosis or the 16 who moved from CIND to a dementia diagnosis. The 3MS means were 89.8 ± 4.8 for subjects moving from CIND to normal cognition, 85.7 ± 8.4 for those with staying in CIND, and 76.6 ± 13.5 for those moving from CIND to dementia. Similar patterns were seen for the Mini-Cog and MIS.

Table 1. Baseline Subject Characteristics

Characteristic	Overall, N = 186	Baseline Diagnosis	
		CIND, n = 131	Normal Cognition, n = 55
Age, mean ± SD	74.5 ± 6.5	74.8 ± 6.5	73.6 ± 6.3
Sex, n (%)[a]			
Male	179 (96.2)		
Female	7 (3.8)		
Race, n (%)			
Black	53 (28.5)	39 (29.8)	14 (25.5)
White	133 (71.5)	92 (70.2)	41 (74.5)
Education, years, mean ± SD[b]	12.9 ± 3.6	12.9 ± 3.7	13.1 ± 3.3
Diabetes mellitus, n (%)	83 (44.6)	66 (50.4)	17 (30.9)
High blood pressure, n (%)	153 (82.3)	110 (84.0)	43 (78.2)
Stroke, n (%)	19 (10.2)	17 (13.0)	2 (3.6)
Depression, n (%)	42 (22.6)	36 (27.5)	6 (10.9)
Framingham Stroke Risk Profile score, mean ± SD	17.3 ± 5.4	17.9 ± 5.6	16.0 ± 4.8
Modified Mini–Mental State Examination score, mean ± SD	86.7 ± 9.0	85.3 ± 9.4	89.9 ± 6.9
Mini-Cog score, mean ± SD[b]	3.4 ± 1.4	3.3 ± 1.4	3.6 ± 1.4
Memory Impairment Screen score, mean ± SD	6.7 ± 1.5	6.4 ± 1.5	7.3 ± 1.2

[a] To avoid potential identification of subjects, baseline diagnoses are not broken down according to sex.

[b] One subject had missing data for years of education, and three had missing data for Mini-Cog scores (all three subjects with a baseline diagnosis of cognitive impairment, not dementia (CIND)).

SD = standard deviation.

Cognitive Decline

Overall, 34 of 186 veterans (18%) had cognitive decline.

In bivariate analyses (Table 2), scores of all three cognitive screening tests at baseline were significantly associated with cognitive decline, whereas FSRP and years of education were not. Higher scores on the cognitive screening tests were associated with lower odds of cognitive decline from baseline to follow-up assessment. For example, the odds of cognitive decline were 0.94 times lower with a 1-point increase on the 3MS. In subgroup analyses according to baseline diagnoses (CIND or normal aging), lower scores at baseline on each of the three cognitive screening tests were associated with greater cognitive decline at the follow-up assessment.

In multivariable logistic regression models (Table 3), higher baseline scores on the 3MS and Mini-Cog were independently associated with lower odds of cognitive decline after adjusting for FSRP and years of education. In the overall cohort, baseline MIS, FSRP, and years of education were not associated with cognitive decline. In the CIND subgroup analyses, higher scores at baseline on each of the three screening tests were independently associated with lower odds of cognitive decline after adjusting for FSRP, although for the normal cognition subgroup, only MIS was associated with cognitive decline (Table 3).

In sensitivity analyses including age instead of FSRP in the multivariable logistic regression models (not shown), the associations between the cognitive screening tests and cognitive decline were similar.

DISCUSSION

The trajectory of cognitive impairment that leads to dementia is not linear. CIND or MCI often precede dementia but not always. The diagnosis of CIND in this clinical sample of veterans was more likely to presage a return to normal cognition than a progression to dementia. After an average 2.5 years of follow-up, approximately 20% of those with a baseline CIND diagnosis improved to a diagnosis of cognitively normal, 12% progressed to dementia, and 67% received the same CIND diagnosis. Other cohorts have found similar fluidity.[13,34–36]

One study[37] found that approximately 16% of those initially diagnosed with mild cognitive impairment (MCI) at an Alzheimer's disease center had reverted to normal after a year. In a longer community study,[15] 38% of those with incident MCI converted to normal over the course of 5.1 years. In the longer than 10-year follow up of subjects in the Cardiovascular Health Study, an "unstable" course of MCI was reported in which 20% of subjects moved from MCI to normal at some point.[38] The similarities in these transition rates are somewhat surprising because it is likely that the current cohort, formed from veterans in primary care, would include veterans who are more ill than cohorts formed from community-based samples and, as

Table 2. Bivariate Analyses of Predictors of Cognitive Decline in Overall Sample and According to Baseline Diagnosis

Predictor	Progression	No Progression	Unadjusted Odds Ratio (95% Confidence Interval)	*P*-Value
	Mean ± Standard Deviation			
Overall (N = 186)	n = 34	n = 152		
3MS	81.6 ± 12.3	87.8 ± 7.7	0.94 (0.90–0.97)	.001
Mini-Cog	2.7 ± 1.7	3.5 ± 1.3	0.67 (0.51–0.87)	.003
MIS	6.1 ± 1.9	6.8 ± 1.3	0.76 (0.61–0.96)	.02
FSRP	18.4 ± 5.4	17.1 ± 5.4	1.05 (0.98–1.12)	.19
Years of education	11.9 ± 3.2	13.1 ± 3.7	0.91 (0.82–1.01)	.08
Subgroup with baseline diagnosis of CIND (n = 131)	n = 16	n = 115		
3MS	75.6 ± 13.5	86.6 ± 7.9	0.90 (0.86–0.96)	<.001
Mini-Cog	2.3 ± 1.8	3.4 ± 1.3	0.59 (0.40–0.87)	.008
MIS	5.6 ± 2.0	6.5 ± 1.4	0.71 (0.52–0.97)	.03
FSRP	19.3 ± 5.5	17.7 ± 5.6	1.05 (0.96–1.16)	.30
Years of education	11.5 ± 3.5	13.1 ± 3.8	0.90 (0.78–1.04)	.14
Subgroup with baseline diagnosis of normal cognition (n = 55)	n = 18	n = 37		
3MS	87.1 ± 8.0	91.3 ± 5.9	0.92 (0.84–0.996)	.04
Mini-Cog	3.±1.5	3.9 ± 1.3	0.63 (0.41–0.96)	.03
MIS	6.6 ± 1.7	7.7 ± 0.6	0.43 (0.23–0.81)	.01
FSRP	17.7 ± 5.4	15.2 ± 4.4	1.12 (0.99–1.28)	.08
Years of education	12.3 ± 3.0	13.4 ± 3.4	0.90 (0.75–1.07)	.23

Three subjects did not have Mini-Cog baseline scores, two of whom had a baseline diagnosis of cognitive impairment, not dementia (CIND) and did not progress and one of whom had a baseline diagnosis of CIND and progressed.
FSRP = Framingham Stroke Risk Profile; 3MS = Modified Mini–Mental State Examination; MIS = Memory Impairment Screen.

Table 3. Logistic Regression Models for the Outcome of Cognitive Decline for Each of the Brief Dementia Screening Tests Adjusted for Framingham Stroke Risk Profile (FSRP) Score and Education

Model	Overall	CIND Only	Normal Cognition Only
	Adjusted Odds Ratio (95% Confidence Interval) *P*-Value		
Model 1			
3MS	0.94 (0.90–0.99) .01	0.91 (0.86–0.96) <.001	0.93 (0.85–1.02) .12
FSRP	1.02 (0.95–1.10) .61	1.04 (0.94–1.15) .47	1.09 (0.95–1.24) .24
Years of education	0.996 (0.88–1.13) .95		
Model 2			
Mini-Cog	0.70 (0.53–0.92) .01	0.60 (0.40–0.89) .01	0.66 (0.43–1.02) .06
FSRP	1.03 (0.95–1.11) .47	1.06 (0.96–1.18) .26	1.10 (0.96–1.26) .17
Years of education	0.95 (0.85–1.07) .40		
Model 3			
MIS	0.83 (0.64–1.06) .13	0.72 (0.53–0.98) .04	0.45 (0.23–0.86) .02
FSRP	1.02 (0.95–1.10) .53	1.04 (0.95–1.14) .43	1.09 (0.95–1.25) .20
Years of education	0.94 (0.84–1.05) .25		

Modified Mini–Mental State Examination (3MS) models: c-statistic (number of observations in model): overall, 0.65 (185); cognitive impairment, not dementia (CIND) only, 0.79 (131); normal cognition only, 0.69 (55).
Mini-Cog models: c-statistic (number of observations in model): overall, 0.66 (182); CIND only, 0.70 (128); normal only, 0.69 (55).
Memory Impairment Screen (MIS) models: c-statistic (number of observations in model): overall, 0.63 (185); CIND only, 0.64 (131), normal cognition only 0.75 (55).

discussed below, had a higher vascular disease burden than those samples.

Vascular disease burden is of interest because, if the vascular factors that constitute the FSRP were strongly associated with progression of cognitive impairment, hope could be had that incident dementia could be lessened by modifying potential risk factors. For example, systolic blood pressure, use of antihypertensives, control of diabetes mellitus, cigarette smoking, left ventricular hypertrophy, and cardiovascular disease—all contributors to the FSRP—might all be amenable to modification. Nevertheless, no evidence was found in this cohort of an association between baseline FSRP and cognitive decline. There are significant methodological differences between studies that found an association between cognition and the FSRP and the current study. The Framingham Offspring Study,[24] the English Longitudinal Study of Ageing (ELSA),[23] and a community study of the southeastern

stroke belt (REGARDS)[22] all used a cross-sectional design and found an association between the FSRP and cognitive performance. The Whitehall II Study used a longitudinal approach and found an association between midlife FSRP and development of cognitive impairment 10 years later.[25]

In addition to the methodological differences, it is also possible that the overall high prevalence of vascular risk factors (and thus higher FSRP scores) in the current cohort is indicative of a different population than those in the other studies. The mean FSRP of 17.3 ± 5.4 observed in this study was considerably higher than the mean FSRP reported in the Whitehall Study (4.5 ± 3.6), REGARDS (9.6 ± 10.0), ELSA (10–11), and Framingham Offspring Study (~7). The last two studies' means are extrapolated from reported percentages of stroke risk based on FSRP scores. Of these cohorts, the current one is the only clinical population and would be expected to have higher vascular disease burden than a community population. Perhaps the higher vascular disease burden that this cohort's FSRP suggests resulted in too little variation between the VA subjects for there to be differentiation based on the bluntness of only three broad diagnostic possibilities.

There was an association in the cohort between baseline 3MS and Mini-Cog scores and cognitive decline over the time of this study. Both of these screening tests assess more than one cognitive domain. No association was found between MIS score and cognitive decline over this period in subjects with CIND at baseline. In a study of the Whitehall II cohort, higher FSRP scores were associated with more cognitive decline in all domains except for memory.[25] In the Mayo Clinic Study of Aging,[15] subjects with CIND and deficits in multiple domains were more likely to progress than those with deficits in a single domain. The MIS score reflects memory only. It is possible that any domain alone is less predictive of future cognitive functioning than inclusion of more domains. It is possible that only memory is a weaker predictor.

Limitations of the current study include that the authors drew from the primary care clinics associated with one VA medical center and that the sample was largely male with high rates of chronic medical illness; results may not generalize to older women or less medically ill populations. Strengths include the study design, which allowed for repeated assessment, including informant interviews of subjects, and the richness of information available in the VA electronic medical record, which has imaging results and medication refill histories.

In conclusion, this cohort of community-dwelling veterans in primary care found an association between the 3MS and Mini-Cog and progression of cognitive decline but not between the 3MS and Mini-Cog and education and vascular burden as measured using the FSRP. Primary care providers can consider using cognitive screening instruments that assess more than one cognitive domain to better gauge current cognitive functioning and potential for future improvement or decline. Because subjects in the cohort diagnosed with CIND were more likely to revert to normal cognition than to develop dementia, encouragement can be offered to those affected, although the higher risk of dementia once a CIND diagnosis is made could be used to prod individuals and families to make decisions about future care while they are still able.

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