Spectrum of cognition short of dementia

Framingham Heart Study and Mayo Clinic Study of Aging

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ABSTRACT

Objective: To understand the neuropsychological basis of dementia risk among persons in the spectrum including cognitive normality and mild cognitive impairment.

Methods: We quantitated risk of progression to dementia in elderly persons without dementia from 2 population-based studies, the Framingham Heart Study (FHS) and Mayo Clinic Study of Aging (MCSA), aged 70 to 89 years at enrollment. Baseline cognitive status was defined by performance in 4 domains derived from batteries of neuropsychological tests (that were similar but not identical for FHS and MCSA) at cut scores corresponding to SDs of ≤−0.5, −1, −1.5, and −2 from normative means. Participants were characterized as having no cognitive impairment (reference group), or single or multiple amnestic or nonamnestic profiles at each cut score. Incident dementia over the following 6 years was determined by consensus committee at each study separately.

Results: The pattern of hazard ratios for incident dementia, rates of incident dementia and positive predictive values across cognitive test cut scores, and number of affected domains was similar although not identical across the FHS and MCSA. Dementia risks were higher for amnestic profiles than for nonamnestic profiles, and for multidomain compared with single-domain profiles.

Conclusions: Cognitive domain subtypes, defined by neuropsychologically derived cut scores and number of low-performing domains, differ substantially in prognosis in a conceptually logical manner that was consistent between FHS and MCSA. Neuropsychological characterization of elderly persons without dementia provides valuable information about prognosis. The heterogeneity of risk of dementia cannot be captured concisely with one test or a single definition or cutpoint.
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GLOSSARY

AD = Alzheimer disease; **CI** = confidence interval; ***DSM-IV*** = *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition); **FHS** = Framingham Heart Study; **MCI** = mild cognitive impairment; **MCSA** = Mayo Clinic Study of Aging; **PPV** = positive predictive value.

The wide variation in cognitive function in aging, both in levels of performance and rates of change over time, forces clinicians and lay people to focus on categorical descriptions. Labels such as cognitively normal, mild cognitive impairment (MCI), and dementia are applied as if they were discrete entities, but it is accepted that these terms represent demarcations of convenience along the continuum of cognition. MCI occupies a central location in the spectrum of cognitive aging, and its use as a diagnostic term has been criticized because of the heterogeneity of its prognosis.[1–18] There are many reasons for the wide range of dementia risk in persons designated as MCI, but perhaps the most important one is that cognitive functioning that falls between the designations of "typical cognitive aging" and "definitely demented" is remarkably diverse. Changes in memory, attention, executive, language, and visuospatial domains, as well as the magnitude of those changes, have distinct implications for prognosis. The existing studies suggested to us that the diversity of affected domains and cutpoints, rather than a weakness, had

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an underappreciated logic to it for predicting future risk of dementia. We used the Framingham Heart Study (FHS) and Mayo Clinic Study of Aging (MCSA) to address issues of thresholds and subtypes of cognitive impairment based on neuropsychological testing for predicting the subsequent development of dementia. By using 2 large, independent, population-based elderly cohorts with extensive longitudinal observations, we were able to study risk of future dementia across a range of performance that included individuals whose clinical diagnoses ranged from normal to MCI.

METHODS The FHS and MCSA are both longitudinal, population-based studies of cognitive aging including MCI. A detailed description of the participants and study methodologies from the 2 studies is contained in appendix e-1 on the *Neurology*® Web site at Neurology.org. The analyses described here include dementia-free FHS participants who underwent neuropsychological testing between 1999 and 2005 and the initial dementia-free MCSA cohort who underwent neuropsychological testing between 2004 and 2006. The neuropsychological test batteries of the MCSA[19] and the FHS[20] were similar but not identical, and are shown in table 1. To match the MCSA, the FHS cohort was limited to those between the ages of 70 and 89 years at baseline. A Clinical Dementia Rating[21] was also completed at each site. Consensus diagnoses of cognitive normality, MCI, and dementia were determined by the teams at each site. For the current analyses, only those persons dementia-free at baseline were considered for analysis. For both FHS and MCSA, the *DSM-IV* criteria for dementia[22] and the Key Symposium Working Group on Mild Cognitive Impairment criteria for MCI[23,24] were used.

In both studies, regular, periodic follow-up occurred, every 2 to 4 years in FHS and every 15 months in MCSA. At each subsequent visit, participants were examined clinically and neuropsychologically. In the FHS, neurologic and neuropsychological assessments could be triggered at and between visits by history from the informants, including at periodic health status updates and ancillary study visits, through ongoing surveillance of participant medical records or a low score on a screening mental status examination; such "flagged" participants subsequently had annual neurologic and neuropsychological assessments. In the MCSA, all participants underwent clinical and neuropsychological assessments at each follow-up visit. The diagnostic status of each participant was reviewed after each follow-up visit by the consensus committee of each site. Prior diagnoses remain blinded for the MCSA consensus committee, whereas in FHS, the consensus committee members were aware of prior diagnoses. In the MCSA, the date of diagnosis of dementia was the midpoint between the visit at which the dementia diagnosis was made and the prior visit, whereas in FHS, a date of onset of dementia was determined based on all available information and was allowed to be at any time between consecutive FHS assessments. The primary outcome measure in the present analyses was dementia by *DSM-IV* criteria as determined by consensus committee.

The ability to perform the same outcome analyses in FHS and MCSA was not preplanned at the initiation of either study, but rather, was made possible by the generally similar methodologies that the 2 studies had independently adopted. The studies had sufficiently different designs so that combining the data from the 2 studies was deemed less informative than presenting analyses of them in parallel.

Standard protocol approvals and patient consents. Both study protocols were approved by the respective institutional review boards, either Mayo and Olmsted Medical Center for the MCSA, or Boston University Medical Center for the FHS. All participants at both sites provided signed informed consent.

Analyses. The primary analyses of progression to incident dementia were conducted in MCSA and FHS participants who were dementia-free (cognitively normal or MCI) by consensus diagnosis at baseline. The primary predictors in our analyses were the 4 cognitive domain scores generated from the neuropsychological tests (table 1) administered at the baseline visit. The 4 cognitive domains were attention/executive, memory, visuospatial, and language. For each individual test, scores were normalized within each cohort using the baseline dementia-free participants with complete neuropsychological test score data (n = 1,598 for MCSA and n = 773 for FHS). We transformed scores from tests where the distributions were skewed: Trail Making Test, Part B, for both FHS and MCSA, and Boston Naming Test and Hooper Visual Organization in FHS. A *z* score was generated for each test, and that *z* score, or

Table 1 Neuropsychological instruments[a] used in the FHS and MCSA

	FHS	MCSA
Attention/executive domain	Trail-Making Test, Part B	Trail-Making Test, Part B; WAIS-R Digit Symbol Substitution Test
Memory domain	WMS Logical Memory delayed recall; WMS Visual Reproduction delayed recall	WMS-R Logical Memory delayed recall; WMS-R Visual Reproduction delayed recall; Auditory Verbal Learning Test
Language domain	Boston Naming Test	Boston Naming Test; Category Fluency
Visuospatial domain	Hooper Visual Organization Test	WAIS-R Picture Completion Test; WAIS-R Block Design Test
Mental status examination	Mini-Mental State Examination	Short Test of Mental Status

Abbreviations: FHS = Framingham Heart Study; MCSA = Mayo Clinic Study of Aging; WAIS-R = Wechsler Adult Intelligence Scale–Revised; WMS = Wechsler Memory Scale; WMS-R = Wechsler Memory Scale–Revised.
[a] See appendix e-1 for references. For the FHS, the selected tests were chosen from a slightly larger battery to correspond to the tests and domains studied in the MCSA.

the average of the z scores for tests within each cognitive domain (rescaled to a mean of 0 and an SD of 1), represented the domain z score for each participant. A global z score was also constructed for descriptive purposes; it was created in the same manner as the individual domain scores.

Although MCI is the diagnostic term for the starting point of these analyses, our inclusion of persons who were considered cognitively normal meant that our study group was more inclusive. Thus, instead of using "cognitive impairment" to describe a profile of cognitive performance, we will avoid the word "impairment" and instead refer to cognitive profiles. In the current analyses, neuropsychologically defined low cognitive performance was defined in the same manner in both cohorts by the z score in each of the 4 cognitive domains for each participant. Cut scores of ≤ -0.5, -1, -1.5, and -2, corresponding to SDs from the normative mean based on the study-specific baseline values, were evaluated. In addition to evaluating each cognitive domain separately, we also created an amnestic profile group based on scores below cutpoints in the memory domain without (single domain) or with low scores in other domains (multidomain), and a nonamnestic profile of low performance group based on low scores in one (single domain) or more nonmemory domains (multidomain), and without low scores in the memory domain.

We did not examine more severe z score cutpoints because most individuals who were in that range, and indeed some in the <-2.0 cutpoint range, would have been classified with dementia at baseline and therefore excluded from the current analytic datasets.

We defined FHS- or MCSA-specific common reference groups as those individuals whose z scores were >-0.5 for all domains. This reference group corresponded to a cognitively normal group, although it was defined differently than the consensus normal group.

We calculated incidence rates for dementia based on baseline cognitive performance groupings. We also calculated hazard ratios (HRs) and 95% confidence intervals (CIs) using Cox proportional hazards models with age as the time scale. We report HRs that were not adjusted for sex or education. Additional analyses showed that sex and education adjustment had a negligible effect on the results; equating the number of tests per domain between FHS and MCSA also had little effect. Positive predictive values (PPVs) were also calculated using data obtained up to 45 months after baseline evaluations for both cohorts. We selected the 45 months point to maximize the number of participants available for analysis.

RESULTS The 2 cohorts are described in table 2. By design, the age range of both was 70 to 89 years. The MCSA cohort included 1,969 initially dementia-free individuals, of whom 1,598 were in the analytic cohort because they had at least one follow-up assessment as well as information on all 4 domain scores. The FHS cohort included 915 participants, of whom 142 were excluded because of incomplete follow-up or missing neuropsychological data, leaving

Table 2 Demographic and cognitive features of participants at baseline, grouped by dementia status: Mayo Clinic Study of Aging and Framingham Heart Study

	Framingham Heart Study		Mayo Clinic Study of Aging	
	Incident dementia (n = 113)	Remained dementia-free (n = 660)	Incident dementia (n = 162)	Remained dementia-free (n = 1,436)
Age at visit date, y, median (IQR)	81.2 (76.8, 85.1)	77.6 (72.9, 82.1)	82.7 (79.6, 86.0)	79.1 (74.8, 83.2)
Sex, male, n (%)	29 (38)	323 (46)	84 (52)	733 (51)
Duration of follow-up, y, median (IQR)	3.2 (1.9, 4.7)	5.3 (5.8, 6.0)	2.9 (1.9, 4.5)	5.7 (3.1, 6.6)
Educational attainment, n (%)				
<High school degree	18 (23)	69 (10)	28 (17)	148 (10)
High school degree	30 (39)	274 (39)	55 (34)	494 (34)
Some college	18 (23)	173 (25)	39 (24)	345 (24)
College degree	11 (14)	180 (26)	40 (25)	449 (31)
Short Test of Mental Status,[a] median score (IQR) (max 38 points)	—	—	31 (29, 33)	34 (32, 36)
Mini-Mental State Examination,[b] median score (IQR) (max 30 points)	28 (26, 29)	29 (28, 30)	—	—
Clinical Dementia Rating, global median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0.5)	0 (0, 0)
Functional Activities Questionnaire,[a] total (IQR)	—	—	1 (0, 3)	0 (0, 1)
Baseline cognitive domain, z scores, median (IQR)				
Memory	−0.91 (−1.67, 0.27)	0.10 (−0.62, 0.77)	−0.96 (−1.56, −0.31)	0.11 (−0.55, 0.75)
Language	−0.63 (−1.26, −0.19)	0.07 (−0.65, 0.50)	−0.80 (−1.42, −0.27)	0.14 (−0.44, 0.67)
Attention/executive	−0.87 (−1.69, −0.09)	0.10 (−0.36, 0.71)	−1.01 (−1.61, −0.28)	0.06 (−0.61, 0.64)
Visuospatial	−0.43 (−1.02, 0.19)	0.05 (−0.69, 0.65)	−0.60 (−1.29, 0.03)	0.13 (−0.55, 0.68)

Abbreviation: IQR = interquartile range.
[a] Performed only in the Mayo Clinic Study of Aging.
[b] Performed only in Framingham Heart Study.

773 in the analytic cohort. To match to the MCSA, the duration of follow-up in FHS was truncated to 6 years. Both cohorts demonstrated a narrow range of the Clinical Dementia Rating and brief mental status examination scores (Mini-Mental State Examination in FHS and the Short Test of Mental Status in MCSA). The overall rate of incident dementia was slightly higher in the FHS (19.7, 95% CI 15.3–24.1, per 1,000 person-years) compared with the MCSA (15.9, 95% CI 12.9–19.5, per 1,000 person-years).

The percentages of participants who were within the different scoring ranges using a global *z* score were very similar across the cut scores for FHS and MCSA: ≤−0.5 (59% and 54%), −1.0 (35% and 35%), −1.5 (18% and 19%), and −2.0 (9% and 8%). Table e-1 shows the composition of different subtypes at the −1.5 cut score.

Table 3 gives the HRs for incident dementia from Cox proportional hazards modeling for each cohort. The pattern of HRs across domain-specific subtypes and across different cut scores was similar but not identical between the 2 studies. HRs in the MCSA were systematically higher than those of the FHS, which corresponds to the difference in dementia incidence rates (per 1,000 person-years) in the reference groups of the FHS (6.4, 95% CI 2.2–10.5) vs MCSA (2.8, 95% CI 1.5–5.3). HRs at the most stringent cutpoint should be viewed with caution because

Table 3 HRs for incident dementia: Framingham Heart Study and Mayo Clinic Study of Aging

		Framingham Heart Study				Mayo Clinic Study of Aging			
			95% CI				95% CI		
	Cut score	HR	Lower	Upper	*p* Value	HR	Lower	Upper	*p* Value
SD aMCI	≤−0.5	2.8	0.9	8.9	0.09	7.9	3.6	17.3	<0.0001
MD aMCI		6.9	3.4	14.2	<0.0001	17.6	9.6	32.3	<0.0001
SD naMCI (all)		1.2	0.4	3.4	0.72	3.3	1.6	7.2	0.002
SD language		2.2	0.6	8.0	0.25	6.0	2.3	16.0	0.0003
SD attn/exec		2.1	0.6	8.0	0.26	3.8	1.5	9.6	0.006
SD vis-spatial		—	—	—	—	1.2	0.3	5.5	0.79
MD naMCI		2.7	1.1	6.9	0.04	6.4	3.1	13.2	<0.0001
SD aMCI	≤−1.0	5.5	2.0	14.7	0.0008	14.9	7.2	30.8	<0.0001
MD aMCI		12.7	5.9	27.2	<0.0001	29.5	15.6	55.6	<0.0001
SD naMCI (all)		1.8	0.7	4.8	0.25	6.8	3.3	13.7	<0.001
SD language		2.5	0.7	9.4	0.18	8.5	3.3	21.8	<0.0001
SD attn/exec		3.6	0.9	13.9	0.06	9.5	4.2	21.3	<0.0001
SD vis-spatial		0.9	0.2	4.3	0.89	3.0	1.0	9.5	0.06
MD naMCI		3.7	1.4	10.1	0.01	16.5	8.3	33.0	<0.0001
SD aMCI	≤−1.5	17.5	7.6	40.1	<0.0001	25.9	12.3	54.6	<0.0001
MD aMCI		13.1	4.7	36.4	<0.0001	57.4	27.8	118.6	<0.0001
SD naMCI (all)		4.5	1.7	11.6	0.002	14.0	7.0	28.0	<0.0001
SD language		3.6	0.4	30.9	0.24	13.5	4.7	38.8	<0.0001
SD attn/exec		9.8	3.7	25.7	<0.0001	24.1	11.4	51.2	<0.0001
SD vis-spatial		—	—	—	—	5.9	2.1	17.0	0.0009
MD naMCI		6.8	2.0	23.2	0.002	26.6	12.8	55.4	<0.0001
SD aMCI	≤−2.0	19.6	7.8	49.3	<0.0001	29.3	10.4	82.9	<0.0001
MD aMCI		39.3	8.7	176.9	<0.0001	154.9	58.9	407.4	<0.0001
SD naMCI (all)		8.4	3.2	22.0	<0.0001	31.3	15.1	64.5	<0.0001
SD language		—	—	—	—	40.5	17.3	95.1	<0.0001
SD attn/exec		8.8	3.4	23.1	<0.0001	49.6	18.5	132.6	<0.0001
SD vis-spatial		—	—	—	—	16.4	5.7	47.1	<0.0001
MD naMCI		2.6	0.2	30.1	0.57	26.7	10.6	67.1	<0.0001

Abbreviations: aMCI = amnestic mild cognitive impairment; attn/exec = attention/executive domain; CI = confidence interval; HR = hazard ratio; MD = multidomain; naMCI = nonamnestic mild cognitive impairment; SD = single domain; vis-spatial = visuospatial domain.
Missing values reflect cells with too few cases to calculate a hazard ratio.

many individuals with scores worse than that cut score were considered to have prevalent dementia at baseline.

The pattern of dementia incidence rates was also similar between FHS and MCSA (table 4). For example, at a cut score of −1.0 or −1.5, the highest incidence rates occurred with the amnestic multidomain profile (between 50.4 and 148.6 per 1,000 person-years) while much lower rates were seen with a single-domain nonamnestic (visuospatial and language) profile (between 3.4 and 32.2 per 1,000 person-years). The multidomain, nonamnestic profile of domain scores showed values in between. PPVs for incident dementia at 45 months post baseline (figure) were also similar across the 2 cohorts. Numbers of participants in each diagnostic group and numbers of participants with incident dementia are given in table e-2. The numbers of persons with some definitions of low cognition at baseline or incident dementia were very small, even with the overall large sample sizes of FHS and MCSA, thus accounting for wide CIs of some estimates.

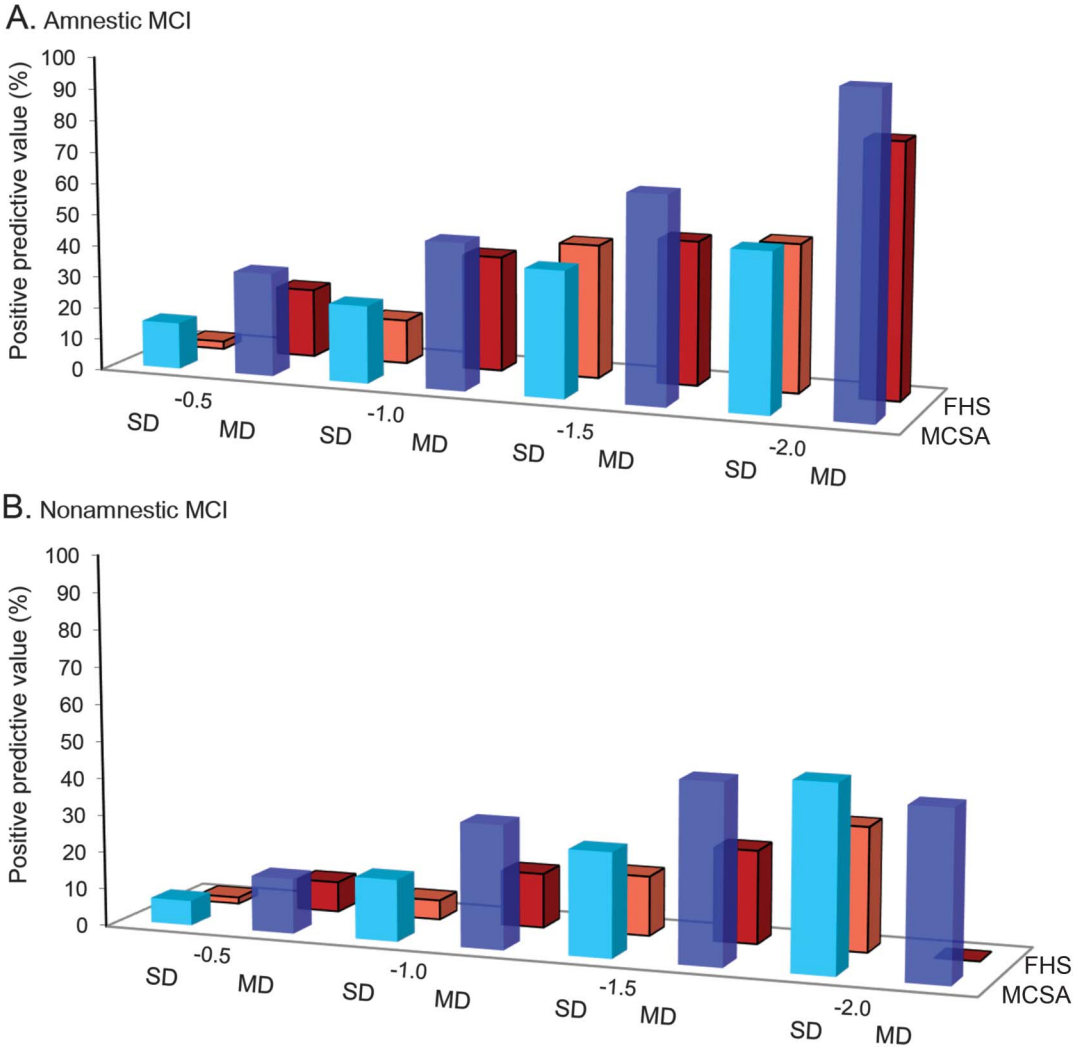
There are several generalizations that can be made based on common patterns of dementia risk in FHS and MCSA participants. HRs and rates of incident dementia generally increased with more stringent cut scores. Amnestic profiles had higher HRs than nonamnestic. Multidomain low score profiles had

Table 4 Rates of incident dementia (per 1,000 person-years): Framingham Heart Study and Mayo Clinic Study of Aging

		Framingham Heart Study			Mayo Clinic Study of Aging		
			95% CI			95% CI	
	Cut score	Adjusted incidence rate	Lower	Upper	Adjusted incidence rate	Lower	Upper
SD aMCI	<−0.5	18.1	0.4	35.9	26.3	13.8	49.9
MD aMCI		51.5	35.2	67.9	67.1	51.1	88.2
SD naMCI (all)		8.0	1.5	114.4	5.2	1.5	18.9
SD language		20.8	0.0	50.9	7.7	0.6	106.6
SD attn/exec		14.2	0.0	30.6	13.7	5.3	35.4
SD vis-spatial		—	—	—	2.2	0.1	50.3
MD naMCI		19.3	7.3	31.2	17.3	10.1	46.3
SD aMCI	<−1.0	34.8	8.7	60.8	63.0	37.1	106.9
MD aMCI		96.8	57.5	136.2	105.6	72.2	154.3
SD naMCI (all)		13.2	3.3	23.1	16.5	7.8	35.0
SD language		17.0	0.0	36.5	32.2	13.5	77.2
SD attn/exec		19.4	0.0	42.7	11.0	0.1	—
SD vis-spatial		5.5	0.0	13.2	3.4	0.0	—
MD naMCI		24.1	9.0	39.3	55.5	32.1	95.7
SD aMCI	<−1.5	121.6	55.0	188.2	106.3	49.5	228.4
MD aMCI		148.6	20.1	277.2	50.4	0.1	—
SD naMCI (all)		37.9	7.4	68.4	43.8	26.6	72.0
SD language		28.7	0.0	85.0	13.5	0.0	—
SD attn/exec		69.1	15.8	122.5	103.9	55.7	193.8
SD vis-spatial		—	—	—	8.9	0.2	328.8
MD naMCI		50.4	9.7	91.1	77.6	34.6	174.0
SD aMCI	<−2.0	145.0	37.6	252.4	29.1	0.0	—
MD aMCI		216.9	0.0	442.9	143.2	0.0	—
SD naMCI (all)		80.9	15.5	146.4	103.7	57.9	185.9
SD language		—	—	—	190.0	76.2	474.0
SD attn/exec		83.1	17.1	149.0	378.1	145.9	980.0
SD vis-spatial		—	—	—	22.7	0.3	—
MD naMCI		29.9	0.0	88.5	24.1	0.0	—

Abbreviations: aMCI = amnestic mild cognitive impairment; attn/exec = attention/executive domain; CI = confidence interval; MD = multidomain; naMCI = nonamnestic mild cognitive impairment; SD = single domain; vis-spatial = visuospatial domain.
Missing values reflect cells with too few cases to calculate an incidence rate.

Figure PPVs for incident dementia at 45 months post baseline



PPVs (in percent) for incident dementia at 45 months post baseline for FHS (red bars) and MCSA (blue bars). PPVs are shown for amnestic MCI (A) and nonamnestic MCI (B) SD (lighter color) and MD (darker color) at the cutpoints of −0.5, −1.0, −1.5, and −2.0. FHS = Framingham Heart Study; MCI = mild cognitive impairment; MCSA = Mayo Clinic Study of Aging; MD = multidomain; PPV = positive predictive value; SD = single domain.

higher HRs than single domain. Within any cut score level, the lowest rates of incident dementia occurred with the single-domain nonamnestic profile in the visuospatial domain. The single-domain nonamnestic profile in the executive domain generally had a comparable prognosis to the single-domain amnestic profile. The highest HRs, incidence rates, and PPVs occurred with multidomain amnestic profiles. For example, the multidomain amnestic pattern at a cut score of <-1.5 had a PPV for incident dementia by 45 months of 65% in the MCSA and 46% in the FHS. In contrast, a single-domain amnestic profile at a cut score of <-1.0 had a PPV of only 25% for the MCSA and 14% for the FHS. The single-domain nonamnestic profile at a cut score of <-1.0 had even lower PPVs of 5% in FHS and 17% in MCSA (see the figure).

DISCUSSION Our evaluation of different formulations of cognitive profiles among individuals without dementia in 2 independent cohorts demonstrated the same heterogeneity of prevalences and dementia outcomes as observed in prior studies of more narrowly defined MCI.[1–9,14,18,25] We eliminated 2 other common sources of variation in MCI outcomes[26] by utilizing elderly cohorts that had been recruited randomly from defined geographical regions. We assert that the breadth and depth of low cognitive performance across different neuropsychologically defined domains ordered the risk for future dementia in a rational and biologically meaningful way. Involvement of multiple cognitive domains implies more widespread cerebral abnormalities, which in turn would be expected to more often produce progression of cognitive decline over time. Single-domain involvement, in general,

represents more circumscribed dysfunction, and should have a more favorable prognosis. Amnestic involvement, reflecting the dominant role of Alzheimer disease (AD) and its typical anatomical predilection for the medial temporal lobe,[27] carried a worse prognosis than nonamnestic involvement. Nevertheless, among those with particularly low performance in nonamnestic domains, future dementia was a considerable risk. These clinical-anatomical-prognostic associations are not novel, but they are obscured when overly simplistic definitions of MCI are used.

The similarity of the pattern of HRs, rates of incident dementia, and PPV at 45 months between MCSA and FHS across amnestic and nonamnestic MCI and across different cut scores suggests that the estimates and ordering of risk may be generalizable to elderly, middle-class North American populations with average educational attainment. The similar results are particularly gratifying since the FHS and MCSA neuropsychological test batteries were not identical and there were other differences in how participants were diagnosed and followed, and how time to onset of dementia was calculated between the 2 studies as described in the methods section.

Neuropsychological characterization by the use of multiple tests in different domains is superior to a single brief instrument that allows MCI to be diagnosed only as "present vs absent." However, traditional pencil and paper neuropsychological assessments are impractical for many reasons, including cost and lack of access to neuropsychological assessment skills in many settings. Moreover, some cautions are needed in using neuropsychological profiles. The use of deviation from normative means as a way of defining cognitive performance guarantees that a certain fraction of the population being studied will be classified as abnormal. Our data show that the approach provides meaningful assessment of risk when applied to an elderly population. However, in individuals younger than 65 years who have a 10-fold-lower rate of incident dementia than individuals aged 80 years,[28,29] a cut score of $z < -1.0$ or $z < -1.5$ would have a far lower PPV. Second, because of the emphasis on amnestic domain deficits, nonamnestic domains are sometimes grouped together. Because there may be multiple nonamnestic domains (3 in the current analyses), the number of individuals labeled as having nonamnestic cognitive impairment will invariably be larger than those labeled amnestic. Nonamnestic MCI involving the executive domain was the most informative nonamnestic type, emphasizing that impairments in the nonamnestic domains themselves have divergent outcomes.

Our domain-based approach utilizes a widely accepted model of cognitive function in the dementia spectrum that is used in recent diagnostic criteria.[30,31] The domains of memory, attention/executive, language, and visuospatial cognition also have established clinical–anatomical correlations that are widely accepted and understood.[32] However, while some form of a continuous function involving neuropsychological test scores avoids assumptions about relationships between tests and domains, results of latent profile[33] or cluster[34,35] analyses identify similar cognitive constructs to the ones we used. We acknowledge that alternative ways of defining cognitive domains might be able to demonstrate the same wide variation in risk of future dementia in a more efficient manner, but the point of this exercise was to demonstrate that the risk of future dementia is logically related to the depth and breadth of cognitive functioning in individuals without dementia.

The popularly used cutoff score for MCI of −1.5 SD below the mean represents a reasonable compromise for making the categorical diagnosis of MCI clinically meaningful. There will never be a perfect set of cut scores; the heterogeneity of the range between cognitive normality and dementia ensures that any cut score, including this one, will have imperfect precision.

Our analyses differ from most prior reports on MCI because we included individuals who were diagnosed clinically as cognitively normal, in order to explore the full range of cognitive performance in the nondementia spectrum. Our results should also make clear that there is an equal amount of heterogeneity in outcomes within the categorical diagnosis of cognitive normality. This reality is embodied in the criteria for preclinical AD that acknowledges there are persons considered cognitively normal who score lower than their peers and therefore are at higher risk of experiencing cognitive decline.[36] Consistent with that view, even when a neuropsychological domain cut score of <-0.5 was used, there was increased risk of incident dementia. To be sure, the incidence rates at cut scores of <-0.5 were very low, but at least for amnestic multidomain patterns, the HRs were significant.

Neuropsychological test score cutpoints are important and central to identifying dementia-free persons who are at risk of cognitive decline. There are other features that are also relevant that we were not able to consider in our analyses. The role of biomarkers in determining risk of progression in MCI is being actively explored,[37,38] but biomarkers relate to etiology, and our focus here was on the cognitive spectrum. Because cognitive performance is an intrinsic component of dementia, and because biomarkers share variance with cognitive performance, it is not surprising that cognitive outcomes are often more powerful than biomarkers when they are entered into the same prediction models.[39] We could have

explored the interaction between cognition and functional impairment,[17] but it was not feasible for several reasons. We lacked a common instrument between FHS and MCSA, and furthermore, our focus was on the role of domain-specific cognitive impairment. We also could have included the role of subjective cognitive complaints,[40] but all of these additional features would have detracted from our focus on neuropsychological characterization.

A limitation of our analyses was the censoring of individuals diagnosed with prevalent dementia at baseline. The impact of the censoring by dementia was reflected in the smaller than expected number of participants with scores at the $z < -2.0$ level. The distinction between MCI and dementia is based on degree of impairment in activities of daily living,[30,41] but our observation of the high risk of incident dementia in persons with multidomain amnestic MCI at cut scores of <-1.5 demonstrates the inevitable continuity with dementia.

MCI as a segment of the spectrum of cognitive impairment short of dementia is a powerful construct permitting risk stratification in a variety of research contexts in individuals without dementia. Similar to the concept of "hypertension," it is useful as a categorical label, but it should not obscure the continuous nature of the risk function. Risk of dementia does not begin and end at one cutpoint, and low cognitive performance has domain-specific risks that are logically related to the complex biology of AD and the other major diseases that cause late-life dementia.

AUTHOR CONTRIBUTIONS

David S. Knopman: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data. Alexa Beiser: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, statistical analysis. Mary M. Machulda: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, acquisition of data. Julie Fields: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval. Rosebud O. Roberts: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, acquisition of data, obtaining funding. V. Shane Pankratz: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, statistical analysis. Jeremiah Aakre: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, statistical analysis. Ruth H. Cha: analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, statistical analysis. Walter A. Rocca: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, statistical analysis. Michelle M. Mielke: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval. Bradley F. Boeve: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval. Sherral Devine: study concept or design, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision. Robert J. Ivnik: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision. Rhoda Au: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision, obtaining funding. Sanford Auerbach: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, acquisition of data. Philip A. Wolf: study concept or design, accepts responsibility for conduct of research and will give final approval, study supervision, obtaining funding. Sudha Seshadri: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision, obtaining funding. Ronald C. Petersen: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, obtaining funding.

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D. Knopman served as deputy editor for *Neurology*®; serves on a data safety monitoring board for Lundbeck Pharmaceuticals and for the DIAN study; is an investigator in clinical trials sponsored by TauRx Pharmaceuticals, Lilly Pharmaceuticals, and the Alzheimer's Disease Cooperative Study; serves as a consultant to the Bluefield Project to Cure Frontotemporal Dementia; and receives research support from the NIH. A. Beiser receives research support from the NIH. M. Machulda receives research support from the NIH. J. Fields receives research support from the NIH. R. Roberts receives research support from the NIH, AbbVie Health Economics and Outcomes Research, and from the Driskill Foundation. V. Pankratz receives research support from the NIH. Jeremiah Aakre receives research support from the NIH. R. Cha reports no disclosures relevant to the manuscript. W. Rocca receives research support from the NIH. M. Mielke receives research support from the NIH and the Driskill Foundation. B. Boeve receives publishing royalties for *The Behavioral Neurology of Dementia* (Cambridge University Press, 2009) and research support from Cephalon, Inc., Allon Therapeutics, Inc., GE Healthcare, the NIH, and the Mangurian Foundation. S. Devine receives research support from the NIH. R. Ivnik serves on the editorial boards of *The Clinical Neuropsychologist and Aging*, *Neuropsychology*, and *Cognition*; receives publishing royalties for *Clinical Interpretation of the WAIS-III and WMS-III* (Academic Press, 2003); and research support from the NIH. R. Au receives research support from the NIH, Alzheimer's Association, and the National Parkinson Foundation. S. Auerbach receives research support from the NIH. P. Wolf receives research support from the NIH. S. Seshadri receives research support from the NIH. R. Petersen serves on data monitoring committees for Pfizer, Inc. and Janssen Alzheimer Immunotherapy, is a consultant for Roche, Inc., Merck, Inc., and Genentech, Inc., receives publishing royalties from *Mild Cognitive Impairment* (Oxford University Press, 2003), and receives research support from the NIH. Go to Neurology.org for full disclosures.

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This Week's *Neurology*® Podcast

Spectrum of cognition short of dementia: Framingham Heart Study and Mayo Clinic Study of Aging (see p. 1712)

This podcast begins and closes with Dr. Robert Gross, Editor-in-Chief, briefly discussing highlighted articles from the November 10, 2015, issue of *Neurology*. In the second segment, Dr. Jeff Burns talks with Dr. David Knopman about his paper on the spectrum of cognition short of dementia. In our "What's Trending" feature of the week, Dr. Ted Burns interviews Dr. Terrence Cascino about what the AAN is doing to combat the trend of physician burnout. In the next part of the podcast, Dr. Stacey Clardy focuses her interview with Dr. Sean Pittock on the topic of neuromyelitis optica assay development, treatments, and mimics, including MOG antibodies.

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