

Diagnostic Assessment & Prognosis

Better prognostic accuracy in younger mild cognitive impairment patients with more years of education

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Abstract

Introduction: Age and years of education influence the risk of dementia and may impact the prognostic accuracy of mild cognitive impairment subtypes.

Methods: Memory clinic patients without dementia ($N = 358$, age 64.0 ± 7.9) were stratified into four groups based on years of age (≤ 64 and ≥ 65) and education (≤ 12 and ≥ 13), examined with a neuropsychological test battery at baseline and followed up after 2 years.

Results: The prognostic accuracy of amnesic multi-domain mild cognitive impairment for dementia was highest in younger patients with more years of education and lowest in older patients with fewer years of education. Conversely, conversion rates to dementia were lowest in younger patients with more years of education and highest in older patients with fewer years of education.

Discussion: Mild cognitive impairment subtypes and demographic information should be combined to increase the accuracy of prognoses for dementia.

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Keywords:

Memory clinic; Mild cognitive impairment; Dementia; Alzheimer's disease; Neuropsychology; Diagnosis

1. Background

Mild cognitive impairment (MCI) [1] is a clinical syndrome, characterized by a decline in cognitive function greater than what is considered normal and different from mild dementia in that activities of daily life are intact or only minimally disturbed. The risk of future dementia is elevated for persons with MCI [2,3]. However, many memory clinic patients with MCI do not develop dementia, and an MCI classification yields many false positives [2]. To increase the specificity of the MCI classification and account for the heterogeneity inherent in the MCI syndrome, Petersen et al. [4] and Winblad et al. [5] proposed a subtype paradigm, in which MCI is further divided based on whether or not memory is impaired and whether one or several cognitive domains are affected. The resulting categories were amnesic single-domain (aMCI-sd), amnesic

multi-domain (aMCI-md), nonamnesic single-domain (naMCI-sd), and nonamnesic multi-domain (naMCI-md) mild cognitive impairment. We previously reported that aMCI-md results in fewer false positives than non-subtyped MCI and that the other subtypes have little or no prognostic value [6].

Low education is a risk factor for dementia [7,8]. Furthermore, dementia prevalence increases sharply with age, from 1.6% between 60 and 64 years of age, to 4.3% between 70 and 74 years, and 43.1% over the age of 90 [9]. This relationship is also evident in clinical samples [10]. However, there are also indications that both old age and fewer years of formal education attenuate the prognostic accuracy for dementia. Visser et al. [11] reported that the positive predictive value for various definitions of MCI in predicting Alzheimer's disease dementia (ADD) 5 years later was higher in patients older than 65 years, likely because of a higher prevalence of predementia in the older group. However, because both sensitivity and specificity were higher in the younger group, the results can also be interpreted as a better prognostic accuracy among younger

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participants. In another study, Visser et al. [12] reported good prognostic accuracy for subsequent ADD only for amnesic MCI in patients aged 70–85 years, as compared with patients under 69 years of age. Thus, it still remains unclear how patient age influences the prognostic accuracy in MCI. Furthermore, both neuritic plaques and neurofibrillary tangles measured postmortem [13,14] and cerebrospinal fluid Alzheimer's disease biomarkers [15] are more weakly associated with an ADD diagnosis in older people; distinguishing between different states with increasing age is an increasingly difficult task.

In a large population-based study, neuropsychological test results predicted dementia in participants with higher but not lower educational levels [16], possibly because of larger variability in cognitive performance in people with higher educational levels than people with lower educational levels. To the best of our knowledge, there are no clinical studies reporting prognostic accuracy in different education groups or in age and education groups simultaneously.

The aim of the present study was to investigate the influence of years of age and education on the prognostic accuracy of MCI subtypes over a 2-year period.

2. Materials and methods

2.1. Participants

We included 358 consecutive patients from the Gothenburg MCI study [17], a prospective umbrella study conducted at the outpatient memory clinic at the Sahlgrenska University Hospital in Gothenburg, Sweden. First visits took place between 2000 and 2014. All participants were between 40 and 79 years old and experienced cognitive decline (self-reported and/or informant reported) without obvious relation to somatic or psychiatric disorders or traumatic brain injury, with duration of at least 6 months. Cognitive decline was assessed in a clinical interview. In the present study, we included participants who had completed the baseline diagnostic assessment and did not have manifest dementia at baseline (see Section 2.2 for details).

We also included healthy controls, primarily recruited from senior citizen organizations and via information meetings about dementia. Several controls were spouses of patients. All controls were thoroughly interviewed by a research nurse before inclusion. Controls were included if they were physically and mentally healthy and displayed neither self-reported symptoms nor observable signs of cognitive impairment.

In the Gothenburg MCI study, 742 patient participants were included between 2000 and the end of 2014. Of those, 223 participants (57% women, age at baseline 67.4 ± 7.3 , education years 11.1 ± 3.6 , Mini-Mental State Examination [MMSE] 24.8 ± 2.7) had dementia (i.e., global deterioration scale [GDS] ≥ 4) at baseline and were excluded. Sixteen participants (33% women, age at baseline 62.6 ± 8.1 , MMSE 28.7 ± 1.4) had inconclusive data on years of education

and were excluded. One participant (male, age at baseline 30, MMSE 30) was below 40 years of age and was excluded. One hundred three participants (63% women, age at baseline 61.8 ± 9.5 , education years 12.5 ± 3.6 , MMSE 28.4 ± 1.4) lacked follow-up data and were excluded. Of the 399 participants (58% women, age at baseline 64.1 ± 7.9 , education years 12.6 ± 3.6 , MMSE 28.5 ± 1.4) with follow-up data, 41 (49% women, age at baseline 65.7 ± 6.5 , education years 11.7 ± 3.7 , MMSE 28.1 ± 1.5) had an incomplete neuropsychological data set at baseline. This left 358 participants (59% women, age at baseline 64.0 ± 7.9 , education years 12.7 ± 3.6 , MMSE 28.5 ± 1.4) for analysis.

2.2. Procedures

2.2.1. Diagnostic procedures

We used the GDS [18] to determine the cognitive stage of the participants. In the Gothenburg MCI study version, GDS is operationalized using the MMSE [19], the Clinical Dementia Rating [20], the Stepwise Comparative Status Analysis (STEP) [21], and the Investigation of Flexibility, which is a short form of the executive interview [22].

A specialist physician or a registered nurse determined the GDS stage. GDS stage 4 was assigned if STEP was >1 , Investigation of Flexibility was >3 , Clinical Dementia Rating sum of boxes was >1.0 , and MMSE was ≤ 25 . GDS 4 is equivalent to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, dementia criteria [23]. GDS stage 4 or higher at follow-up was considered conversion to dementia and was used as outcome or reference standard [24,25].

2.2.2. Instruments and testing procedure

A licensed psychologist or a psychologist in training, supervised by a licensed psychologist, administered the neuropsychological test battery to patients and controls. Two sessions of approximately 1.5–2 hours were needed to complete the examination. The test sequence was designed to minimize the risk of contamination on the memory tests. We used the Digit Symbol test from either the Wechsler Adult Intelligence Scale-revised [26] or the Wechsler Adult Intelligence Scale–3rd Edition [27] and the Trail-Making Test part B (TMT B) [28] to assess processing speed and attention; the delayed recall trials from the Wechsler Memory Scale Logical Memory subtest [29] and the Rey Auditory Verbal Learning Test [30] to assess verbal episodic memory; the copy condition of the Rey Complex Figure test [31] and the silhouettes subtest of the Visual Object and Space Perception Battery [32] to assess visuospatial function; the Boston Naming Test [33] and the Token test part 5 [34] to assess confrontation naming and comprehension of spoken language, respectively; and the interference part of the Stroop test, Victoria version (Stroop III) [35], and the Parallel Serial Mental Operations test [36] to assess executive functions, parallel distributed processing, automaticity, inhibition, mental control, and tracking. In accordance

with previously published papers from our group [6,36–38], we categorized TMT B as a test of complex attention rather than executive function. The tests in the battery are widely used in clinical settings and research settings and have appropriate reliability and validity [39–42].

2.2.3. Grouping procedures

2.2.3.1. Educational attainment and age at first visit

To investigate the prognostic accuracy of aMCI-md among younger vs. older participants and participants with more vs. less educational attainment, we stratified patients into groups based on years of age (≤ 64 = “Young”; ≥ 65 = “Old”), years of education (≥ 13 = “Edu+”; ≤ 12 = “Edu-”), and their combination (Young Edu+, Young Edu-, Old Edu+, and Old Edu-).

2.2.3.2. MCI subtypes

We used neuropsychological test data from the control group to calculate cutoff scores. In the control group, the younger participants scored significantly better on the Digit Symbol test from Wechsler Adult Intelligence Scale-revised and on Stroop III. Participants with more years of education scored significantly better on the Token test, the TMT B, and Stroop III. Thus, scores from the Digit Symbol test from Wechsler Adult Intelligence Scale-revised were corrected for age, scores from the Token test and TMT B were corrected for education, and Stroop III scores were corrected for both age and education (Table 1). To account for deviations from the standard normal distribution, the test score cutoffs were calculated using percentiles. In this article, we will refer to the 93.3rd percentile as 1.5 standard deviations (SDs).

We used the criteria of Jak et al. [43] to construct the MCI subtype groups. aMCI-sd was operationalized as scoring 1.5 SD or more below the control mean on at least one memory test, with all nonmemory domain test scores above; aMCI-md as scoring 1.5 SD below the control mean on at least one memory test as well as at least one nonmemory test; naMCI-sd as scoring 1.5 SD below the control mean on at least one test in any one nonmemory domain, with both memory test scores and scores in other domains above; naMCI-md as scoring 1.5 SD below the control mean on at least two tests in any two or more nonmemory domains but with both memory scores above. Patients with no test result 1.5 SD or more under the control mean were categorized as “no impairment”. Furthermore, we grouped all patients belonging to any MCI subtype group as “non-subtyped MCI”, that is, the complement group of “no impairment”. The MCI subtypes were then used as predictor variables in the subsequent analyses.

2.3. Statistics

Prognostic accuracy is reported as true positive, false positive, false negative, and true negative observations, sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR-), pretest probability, posttest probability for a positive test, posttest probability for a negative test, and clinical utility index for case finding (CUI+) and screening (CUI-). The clinical utility of the CUI can be interpreted as follows: ≥ 0.81 , excellent; ≥ 0.64 , good; ≥ 0.49 , satisfactory; and < 0.49 , poor [44]. When applicable, we also report receiver operating characteristic curves for

Table 1
Control group neuropsychological data

Group	Neuropsychological test	Cognitive domain	n	M	SD	Mn	1.5 SD cut-off
All controls	Digit Symbol WAIS-r (correct items after 90 seconds)	Speed/attention	72	46.4	9.3	46.5	32.5
	WLM delayed recall (correct items)	Memory	102	22.7	6.7	23	12.0
	RAVLT delayed recall (correct items)	Memory	112	8.9	3.2	9	4.0
	RCF copy (correct items)	Visuospatial function	113	32.9	2.7	34	28.3
	VOSP silhouettes (correct items)	Visuospatial function	112	21.8	3.3	22	17.0
	BNT 30-60 (correct items)	Language	109	24.7	2.7	25	20.0
	PaSMO II (response time in seconds)	Executive function	110	69.5	27.2	60	113.9
Age	≤ 64 (Young)	Digit Symbol WAIS-III (correct items after 120 seconds)	26	66.2	12.4	70.5	41.0
	≥ 65 (Old)	Digit Symbol WAIS-III (correct items after 120 seconds)	15	58.1	12.6	56.0	45.1
Education	≥ 13 (Edu+)	Token test (correct items)	46	21.2	0.9	21.0	20.0
		TMT B (response time in seconds)	46	76.1	19.0	74.0	112.3
	≤ 12 (Edu-)	Token test (correct items)	67	20.7	1.3	21.0	18.5
		TMT B (response time in seconds)	66	88.1	28.9	79.5	141.8
Age and education	Young Edu+	Stroop III (response time in seconds)	22	21.9	4.1	21.0	29.9
	Young Edu-	Stroop III (response time in seconds)	26	25.6	5.8	25.0	36.2
	Old Edu+	Stroop III (response time in seconds)	15	25.9	4.9	27.0	34.7
	Old Edu-	Stroop III (response time in seconds)	33	27.4	6.7	28.0	39.6

Abbreviations: BNT, Boston Naming Test; Edu-, ≤ 12 years of education; Edu+, ≥ 13 years of education; M, mean; Mn, median; Old, ≥ 65 years of age; PaSMO, Parallel Serial Mental Operations; RAVLT, Rey Auditory Verbal Learning test; RCF, Rey Complex Figure; s, seconds; SD, standard deviation; TMT, Trail making test; VOSP, Visual Object and Space Perception Battery; WAIS-III, Wechsler Adult Intelligence Scale third edition; WAIS-r, Wechsler Adult Intelligence Scale revised; WLM, Wechsler Logical Memory; Young, ≤ 64 years of age.

graphic comparison of two or more binary diagnostic tests, employing a method described by Biggerstaff [45].

For continuous comparisons, we used t-test and Tukey's test for multiple comparisons. Categorical dichotomous comparisons were done using the chi-square test and multiple comparisons using the Steel-Dwass test. Confidence intervals (CIs) were calculated using a method developed by Wilson [46] with the In Vitro Diagnostics Performance add-in for JMP®, version 13, software (SAS Institute, Cary, NC, 1989–2017), except for posttest probability CIs, where we used the online Diagnostic Test Calculator [47].

3. Results

3.1. Baseline demographics in combined age and education groups and MCI subtypes

MMSE scores were significantly higher in Young Edu+ than those in both Old Edu+ and Old Edu- (Table 2). The aMCI-md group was significantly older than the "no impairment" group and naMCI-sd group, and the naMCI-md group was older than the "no impairment" group. The "no impairment" group had more years of education than both aMCI-md and naMCI-md. MMSE scores were lower in aMCI-md than in the "no impairment" group and naMCI-sd.

The distribution of subtypes in Young Edu+ was significantly different from that in Old Edu+ and Old Edu-, and the subtype distribution in Young Edu- was significantly different from that in Old Edu-. The "no impairment" classification was the most common in the Young Edu+ group (52%), followed by the Young Edu- group (40%); the Old Edu+ group (23%), and the Old Edu- group (16%) (Fig. 1). The aMCI-md classification was the least common in the Young Edu+ group (11%), followed by the Young Edu- group (22%); the Old Edu+ group (23%); and the Old Edu- group (35%).

3.2. Conversion rates

The overall conversion rate or pretest probability of dementia for patients followed for 2 years was 18.9%, which corresponds to 9.5% per year. More Old participants (29%) than Young (11%) converted to dementia ($\chi^2 P < .0001$), and more Edu- participants (26%) converted compared with Edu+ participants (13%; $\chi^2 P$ value = .0023). The conversion rate after 2 years in the Young Edu+ group (6%) was significantly different from the conversion rate in the Old Edu- group (34%, Steel-Dwass P value < .0001) and the Old Edu+ group (22%, Steel-Dwass P = .0036). The difference between Old Edu- and Old Edu+ was nonsignificant. The conversion rate in the Young Edu- group (17%) did not differ significantly from the other groups.

3.3. Prognostic accuracy

Among all patients, only the aMCI-md subtype had significant LR+ (4.6) and LR- (0.4) (Table 3). Non-subtyped MCI also had significant LR+ (1.6) and LR- (0.1).

3.3.1. Age groups and education groups

In both age groups, aMCI-md LR+ and LR- were significant, with higher accuracy in the Young (LR+ 6.1, LR- 0.4) than the Old (LR+ 3.5, LR- 0.5) group (Table 3). aMCI-sd had a significant LR+ (3.6) in the Old group. No other subtypes were significant, but for all tested categories, LR+ was higher, and LR- was lower in the Young group.

For aMCI-md, LR+ and LR- were significant in both education groups, with better accuracy in Edu+ (LR+ 8.1, LR- 0.3) than Edu- (LR+ 3.1, LR- 0.5). No other results were significant, but for all tested categories, LR+ was higher and LR- was lower in Edu+ (Table 3).

Table 2
Descriptive statistics

Group	n	Age (M ± SD)	Sig.	Education (M ± SD)	Sig.	MMSE (M ± SD)	Sig.	Females (%)	Sig.
1 Young Edu+	95	57.7 ± 4.4	3, 4****	15.7 ± 2.1	2, 4****	28.9 ± 1.2	3, 4*	60	
2 Young Edu-	92	57.8 ± 4.6	3, 4****	10.3 ± 1.6	1, 3****, 4**	28.4 ± 1.5		62	
3 Old Edu+	79	70.7 ± 4.1	1, 2****	15.9 ± 2.1	2, 4****	28.3 ± 1.6	1*	54	
4 Old Edu-	92	71.1 ± 3.9	1, 2****	9.3 ± 2.0	1, 3****, 2**	28.3 ± 1.4	1*	59	
A No impairment	119	61.1 ± 7.7	C, X****, E***	13.6 ± 3.3	E, X***, C**	28.9 ± 1.1	C, X****	59	
B aMCI-sd	23	64.9 ± 8.7		13.1 ± 3.5		28.2 ± 1.6		48	
C aMCI-md	81	66.8 ± 7.7	A****	11.9 ± 3.5	A**	27.9 ± 1.5	A****, D**	51	
D naMCI-sd	73	63.6 ± 6.7		13.2 ± 3.8	E**	28.6 ± 1.4	C**	67	
E naMCI-md	62	66.3 ± 7.4	A***	11.2 ± 3.4	A***, D**	28.5 ± 1.5		66	
X Non-subtyped MCI	239	65.5 ± 7.5	A****	12.3 ± 3.6	A***	28.3 ± 1.5	A****	59	
Healthy controls	120	64.1 ± 6.6		12.1 ± 3.0		29.3 ± 0.9		62	

Abbreviations: aMCI-md, amnesic multi-domain mild cognitive impairment; aMCI-sd, amnesic single-domain mild cognitive impairment; Edu-, <12 years of education; Edu+, ≥13 years of education; M, mean; MMSE, Mini-Mental State Examination; naMCI-md, non-amnesic multi-domain mild cognitive impairment; naMCI-sd, non-amnesic single-domain mild cognitive impairment; Old, ≥65 years of age; SD, standard deviation; Young, ≤64 years of age.

NOTE. Number/letter in column Sig. indicates significant difference (* P value < .05; ** P value < .01; *** P value < .001; **** P value < .0001) from the group represented by that number/letter. Categorical multiple comparisons calculated with the Steel-Dwass test, continuous with the Tukey honestly significant difference test. Non-subtyped MCI includes all subtypes and was only compared to No Impairment. Differences between controls and patients were not tested.

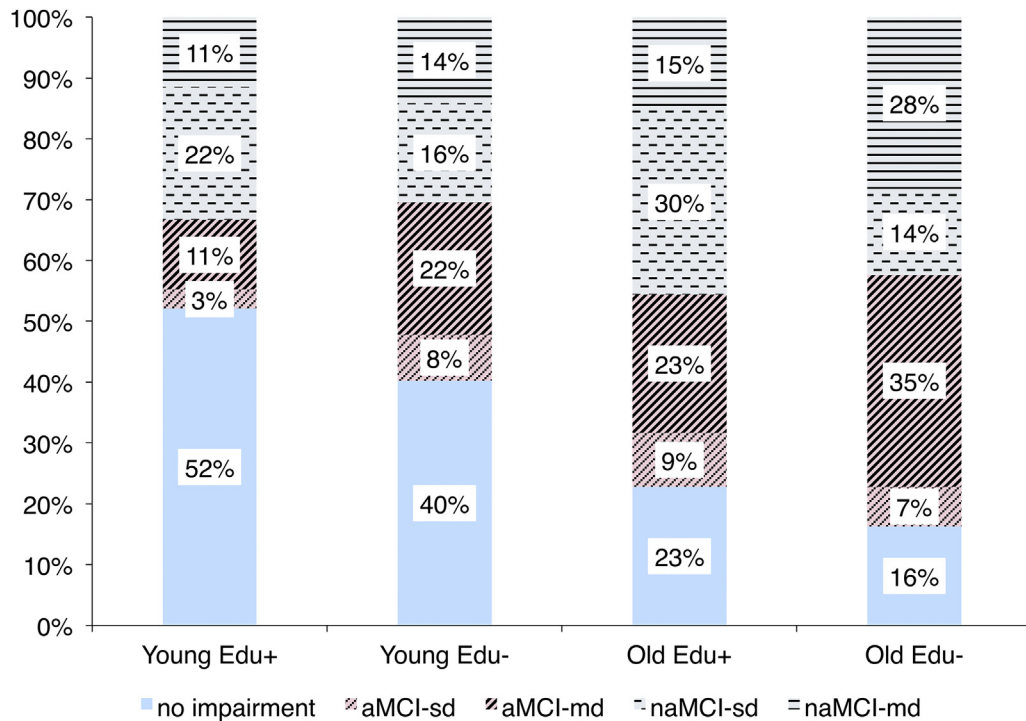


Fig. 1. Prevalence of MCI subtypes in combined age and education groups. Abbreviations: aMCI-md, amnesic multi-domain mild cognitive impairment; aMCI-sd, amnesic single-domain mild cognitive impairment; Edu-, ≤ 12 years of education; Edu+, ≥ 13 years of education; naMCI-md, non-amnesic multi-domain mild cognitive impairment; naMCI-sd, non-amnesic single-domain mild cognitive impairment; Old, ≥ 65 years of age; Young, ≤ 64 years of age. NOTE. Young Edu+ was different from Old Edu- ($P \leq .001$) and Old Edu+ ($P \leq .05$). Young Edu- was different from Old Edu- ($P \leq .01$). Calculated with the Steel-Dwass test.

3.3.2. Combined age and education groups

The subtype aMCI-md was a significant predictor of dementia in all combined age and education groups, with the highest LR+ and the lowest LR- in Young Edu+ (LR+ 15.2, LR- 0.0) (Table 4). In Young Edu+, all subtypes but aMCI-md had LR+ 0.0 and LR- around or above 1.0 and were thus negatively associated with dementia. The subtype naMCI-sd was negatively associated with dementia in both Young Edu+ and Old Edu+ groups.

The receiver operating characteristic curves (Fig. 2) show that aMCI-md was overall better at predicting dementia than all other subtypes and non-subtyped MCI in the Young Edu+ (panel A) and the Old Edu+ (panel C) groups. In the Old Edu+ (panel C) group, aMCI-md was the only significant predictor. In the Young Edu- (panel B) and the Old Edu- (panel D) groups, non-subtyped MCI had a higher sensitivity, and aMCI-md had a higher specificity.

When comparing aMCI-md in the combined age and education groups (Fig. 2, Panel E), it was best at predicting dementia in Young Edu+, followed by Old Edu+. Non-subtyped MCI (Fig. 2, Panel F) was overall better at predicting dementia in Young Edu+ compared with the other groups, and overall worse in Old Edu+.

We also established MCI subtype groups stratified for age alone, education alone, and age and education simulta-

neously for all tests and recalculated all parameters of prognostic accuracy. The results were similar to those presented here (results not shown).

4. Discussion

To our knowledge, no previous study has reported prognostic accuracy in a clinical sample as influenced by years of education, years of age, or years of age and education simultaneously. In the present study, we show that both age and years of education influence the prognostic accuracy of MCI and MCI subtypes.

The prognostic accuracy, or criterion validity, for both aMCI-md and non-subtyped MCI was the highest in the Young Edu+ group and the lowest in the Old Edu- group. Conversely, annual conversion rates to dementia from aMCI-md were the lowest in the Young Edu+ group and the highest in the Old Edu- group. Thus, with older age and fewer years of education at baseline, the rate of conversion to dementia increased, and the prognostic accuracy of aMCI-md and non-subtyped MCI decreased. The remaining subtypes provided no basis for prognosis. Furthermore, in older patients and in patients with fewer years of education, multi-impairment MCI was more common, and in younger patients and patients with more years of education, absence of cognitive impairments was commonplace. Differences in

Table 3
Prognostic accuracy 1

Age or education group	Category	TP/FP/FN/TN	Sensitivity, % (CI)	Specificity, % (CI)	LR+ (CI)	LR- (CI)	Pre-test probability, % (CI)	Post-test probability test +, % (CI)	Post-test probability test -, % (CI)	AUC	CUI+	CUI-
All patients	Non-subtyped MCI	64/175/4/115	94 (86–98)	40 (34–45)	1.6 (1.4–1.7)*	0.2 (0.1–0.4)*	19 (15–23)	27 (25–29)	3 (1–8)	67.0	0.25	0.38
	aMCI-sd	7/16/61/274	10 (5–20)	95 (91–97)	1.9 (0.8–4.4)	1.0 (0.9–1.0)ns		30 (16–51)	18 (17–19)	52.4	0.03	0.77
	aMCI-md	42/39/26/251	62 (50–72)	87 (82–90)	4.6 (3.3–6.5)*	0.4 (0.3–0.6)*		52 (43–60)	9 (7–12)	74.2	0.32	0.78
	naMCI-sd	4/69/64/221	6 (2–14)	76 (71–81)	0.3 (0.1–0.7)*	1.2 (1.1–1.3)*		6 (2–13)	23 (21–24)	59.0	0.00	0.59
	naMCI-md	11/51/57/239	16 (9–27)	82 (78–86)	0.9 (0.5–1.7)	1.0 (0.9–1.1)		18 (11–28)	19 (17–21)	50.7	0.03	0.67
Young	Non-subtyped MCI	19/82/1/85	95 (76–99)	51 (43–58)	1.9 (1.6–2.3)*	0.1 (0.0–0.7)*	11 (7–16)	19 (16–22)	1 (0–7)	72.9	0.18	0.50
	aMCI-sd	3/7/17/160	15 (5–36)	96 (92–98)	3.6 (1.0–12.8)*	0.9 (0.7–1.1)		30 (11–61)	10 (8–11)	55.4	0.05	0.87
	aMCI-md	13/18/7/149	65 (43–82)	89 (84–93)	6.0 (3.5–10.4)*	0.4 (0.2–0.7)*		42 (30–54)	4 (3–8)	77.1	0.27	0.85
	naMCI-sd	1/35/19/132	5 (1–24)	79 (72–85)	0.2 (0.0–1.7)	1.2 (1.1–1.4)*		3 (0–17)	13 (11–14)	58.0	0.00	0.69
	naMCI-md	2/22/18/145	10 (3–30)	87 (81–91)	0.8 (0.2–3.0)	1.0 (0.9–1.2)		8 (2–26)	11 (10–13)	51.6	0.01	0.77
Old	Non-subtyped MCI	45/93/3/30	94 (83–98)	24 (18–33)	1.2 (1.1–1.4)*	0.3 (0.1–0.8)*	28 (22–35)	33 (30–35)	9 (3–24)	61.6	0.31	0.22
	aMCI-sd	4/9/44/114	8 (3–20)	93 (87–96)	1.1 (0.4–3.5)	1.0 (0.9–1.1)		31 (13–58)	28 (26–30)	50.5	0.03	0.67
	aMCI-md	29/21/19/102	60 (46–73)	83 (75–89)	3.5 (2.3–5.6)*	0.5 (0.3–0.7)*		58 (47–68)	16 (11–21)	71.7	0.35	0.70
	naMCI-sd	3/34/45/89	6 (2–17)	72 (64–80)	0.2 (0.1–0.7)*	1.3 (1.1–1.5)*		8 (3–21)	34 (31–37)	60.7	0.01	0.48
	naMCI-md	9/29/39/94	19 (10–32)	76 (68–83)	0.8 (0.4–1.6)	1.1 (0.9–1.3)		24 (14–38)	29 (26–33)	52.4	0.04	0.54
Edu+	Non-subtyped MCI	20/87/3/64	87 (68–96)	42 (35–50)	1.5 (1.2–1.9)*	0.3 (0.1–0.9)*	13 (9–19)	19 (16–22)	5 (2–12)	64.7	0.16	0.40
	aMCI-sd	2/8/21/143	9 (2–27)	95 (90–97)	1.6 (0.4–7.3)	1.0 (0.9–1.1)		20 (5–52)	13 (11–14)	51.7	0.02	0.83
	aMCI-md	16/13/7/138	70 (49–84)	91 (86–95)	8.1 (4.5–14.5)*	0.3 (0.2–0.6)*		55 (41–70)	5 (3–9)	80.5	0.38	0.87
	naMCI-sd	0/45/23/106	0 (0–14)	70 (63–77)	0.0 (–)	1.4 (1.3–1.6)*		0 (0–14)	18 (16–19)	64.9	0.00	0.58
	naMCI-md	2/21/21/130	9 (2–27)	86 (80–91)	0.6 (0.2–2.5)	1.1 (0.9–1.2)		9 (2–27)	14 (12–16)	52.6	0.01	0.74
Edu–	Non-subtyped MCI	44/88/1/51	98 (88–100)	37 (28–45)	1.5 (1.4–1.8)*	0.1 (0.0–0.4)*	25 (19–31)	33 (30–36)	2 (0–12)	67.8	0.33	0.36
	aMCI-sd	5/8/40/131	11 (5–24)	94 (89–97)	1.9 (0.7–5.6)	0.9 (0.8–1.1)		39 (18–64)	23 (21–25)	52.7	0.04	0.72
	aMCI-md	26/26/19/113	58 (43–71)	81 (74–87)	3.1 (2.0–4.7)*	0.5 (0.4–0.7)*		50 (39–61)	14 (11–19)	69.5	0.29	0.70
	naMCI-sd	4/24/41/115	9 (4–21)	83 (76–88)	0.5 (0.2–1.4)	1.1 (1.0–1.2)†		14 (6–31)	26 (24–29)	54.2	0.01	0.61
	naMCI-md	9/30/36/109	20 (11–34)	78 (71–84)	0.9 (0.5–1.8)	1.0 (0.9–1.2)		23 (13–37)	25 (22–28)	50.8	0.05	0.59

Abbreviations: aMCI-md, amnesic multi-domain MCI; aMCI-sd, amnesic single-domain MCI; AUC, area under the curve; CI, confidence interval; CUI–, clinical utility index; CUI+, clinical utility index; Edu–, ≤12 years of education; Edu+, ≥13 years of education; LR–, negative likelihood ratio; LR+, positive likelihood ratio; MCI, Mild Cognitive Impairment; naMCI-md, non-amnesic multi-domain MCI; naMCI-sd, non-amnesic single-domain MCI; Old, ≥65 years of age; TP/FP/FN/TN, true positive/false positive/false negative/true negative; Young, ≤64 years of age.

NOTE. LRs are significant if the CI does not cover 1. Post-test probabilities are significant if the CI does not cover the pre-test probability for the category, marked with asterisk for LRs. CUI+ is the product of sensitivity and positive predictive value; CUI– is the product of specificity and negative predictive value. The clinical utility of the CUI can be interpreted as: ≥ 0.81, excellent; ≥ 0.64, good; ≥ 0.49, satisfactory; and <0.49, poor [45].

*P value < .05.

†Not significant.

Table 4
Prognostic accuracy 2

Combined age and education group	Category	TP/FP/FN/TN	Sensitivity, % (CI)	Specificity, % (CI)	LR+ (CI)	LR- (CI)	Pre-test probability, % (CI)	Post-test probability test +, % (CI)	Post-test probability test -, % (CI)	AUC	CUI+	CUI-
Young Edu+	Non-subtyped MCI	5/41/0/49	100 (57–100)	54 (44–64)	2.2 (1.8–2.8)*	0.0 (-)	5 (2–12)	11 (7–13)	0 (0–11)	77.2	0.11	0.54
	aMCI-sd	0/3/5/87	0 (0–43)	97 (91–99)	0.0 (-)	1.0 (1.0–1.1)		0 (0–67)	5 (4–6)	51.7	0.00	0.91
	aMCI-md	5/6/0/85	100 (57–100)	93 (86–97)	15.0 (6.9–32.5)*	0.0 (-)		45 (25–61)	0 (0–7)	96.7	0.45	0.93
	naMCI-sd	0/21/5/69	0 (0–43)	77 (67–84)	0.0 (-)	1.3 (1.2–1.5)*		0 (0–22)	7 (5–8)	61.7	0.00	0.71
	naMCI-md	0/11/5/79	0 (0–43)	88 (79–93)	0.0 (-)	1.1 (1.1–1.2)*		0 (0–35)	6 (4–7)	56.1	0.00	0.83
Young Edu–	Non-subtyped MCI	14/41/1/36	93 (70–99)	47 (36–58)	1.8 (1.4–2.2)*	0.1 (0.0–1.0)*	16 (10–25)	25 (21–30)	3 (0–16)	69.4	0.24	0.45
	aMCI-sd	3/4/12/73	20 (7–45)	95 (87–98)	3.9 (1.0–15.5) [†]	0.8 (0.7–1.1)		43 (16–75)	14 (11–18)	57.4	0.09	0.81
	aMCI-md	8/12/7/65	53 (30–75)	84 (75–91)	3.4 (1.7–6.9)*	0.6 (0.3–1.0)*		40 (25–57)	10 (6–16)	68.9	0.21	0.76
	naMCI-sd	1/14/14/63	7 (0–30)	82 (72–89)	0.4 (0.1–2.6)	1.1 (1.0–1.4)		7 (1–33)	18 (16–21)	55.8	0.00	0.67
	naMCI-md	2/11/13/66	13 (4–38)	86 (76–92)	0.9 (0.2–3.8)	1.0 (0.8–1.3)		15 (4–42)	16 (14–20)	50.5	0.02	0.72
Old Edu+	Non-subtyped MCI	15/46/3/15	83 (61–94)	25 (16–37)	1.1 (0.9–1.4)	0.7 (0.2–2.1)	23 (15–33)	25 (20–30)	17 (6–38)	57.1	0.20	0.20
	aMCI-sd	2/5/16/56	11 (3–33)	92 (82–96)	1.4 (0.3–6.4)	1.0 (0.8–1.2)		29 (8–65)	22 (19–26)	51.5	0.03	0.71
	aMCI-md	11/7/7/54	61 (39–80)	89 (78–94)	5.3 (2.4–11.7)*	0.4 (0.2–0.8)*		61 (42–78)	11 (7–19)	74.8	0.37	0.78
	naMCI-sd	0/24/18/37	0 (0–18)	61 (48–72)	0.0 (-)	1.6 (1.3–2.0)*		0 (0–23)	33 (28–37)	69.7	0.00	0.41
	naMCI-md	2/10/16/51	11 (3–33)	84 (72–91)	0.7 (0.2–2.8)	1.1 (0.9–1.3)		17 (5–45)	24 (20–28)	52.6	0.02	0.64
Old Edu–	Non-subtyped MCI	30/47/0/15	100 (89–100)	24 (15–36)	1.3 (1.1–1.5)*	0.0 (-)	33 (24–43)	39 (35–42)	0 (0–34)	63.6	0.39	0.24
	aMCI-sd	2/4/28/58	7 (2–21)	94 (85–98)	1.0 (0.2–5.3)	1.0 (0.9–1.1)		33 (9–72)	33 (30–35)	50.1	0.02	0.63
	aMCI-md	18/14/12/48	60 (42–75)	77 (66–86)	2.7 (1.5–4.6)*	0.5 (0.3–0.8)*		56 (43–69)	20 (14–28)	68.7	0.34	0.62
	naMCI-sd	3/10/27/52	10 (4–26)	84 (73–91)	0.6 (0.2–2.1)	1.1 (0.9–1.3)		23 (8–50)	34 (31–38)	53.1	0.02	0.55
	naMCI-md	7/19/23/43	23 (12–41)	69 (57–79)	0.8 (0.4–1.6)	1.1 (0.9–1.4)		27 (15–44)	35 (29–41)	53.7	0.06	0.45

Abbreviations: aMCI-md, amnesic multi-domain MCI; aMCI-sd, amnesic single-domain MCI; AUC, area under the curve; CI, confidence interval; CUI–, clinical utility index; CUI+, clinical utility index; Edu–, ≤12 years of education; Edu+, ≥13 years of education; LR–, negative likelihood ratio; LR+, positive likelihood ratio; MCI, Mild Cognitive Impairment; naMCI-md, non-amnesic multi-domain MCI; naMCI-sd, non-amnesic single-domain MCI; Old, ≥65 years of age; TP/FP/FN/TN, true positive/false positive/false negative/true negative; Young, ≤64 years of age.

NOTE. LR+ are significant if the CI does not cover 1. Post-test probabilities are significant if the CI does not cover the pre-test probability for the category, marked with asterisk for LR+. CUI+ is the product of sensitivity and positive predictive value; CUI– is the product of specificity and negative predictive value. The clinical utility of the CUI can be interpreted as: ≥ 0.81, excellent; ≥ 0.64, good; ≥ 0.49, satisfactory; and <0.49, poor [45].

*P value < .05.

[†]Not significant.

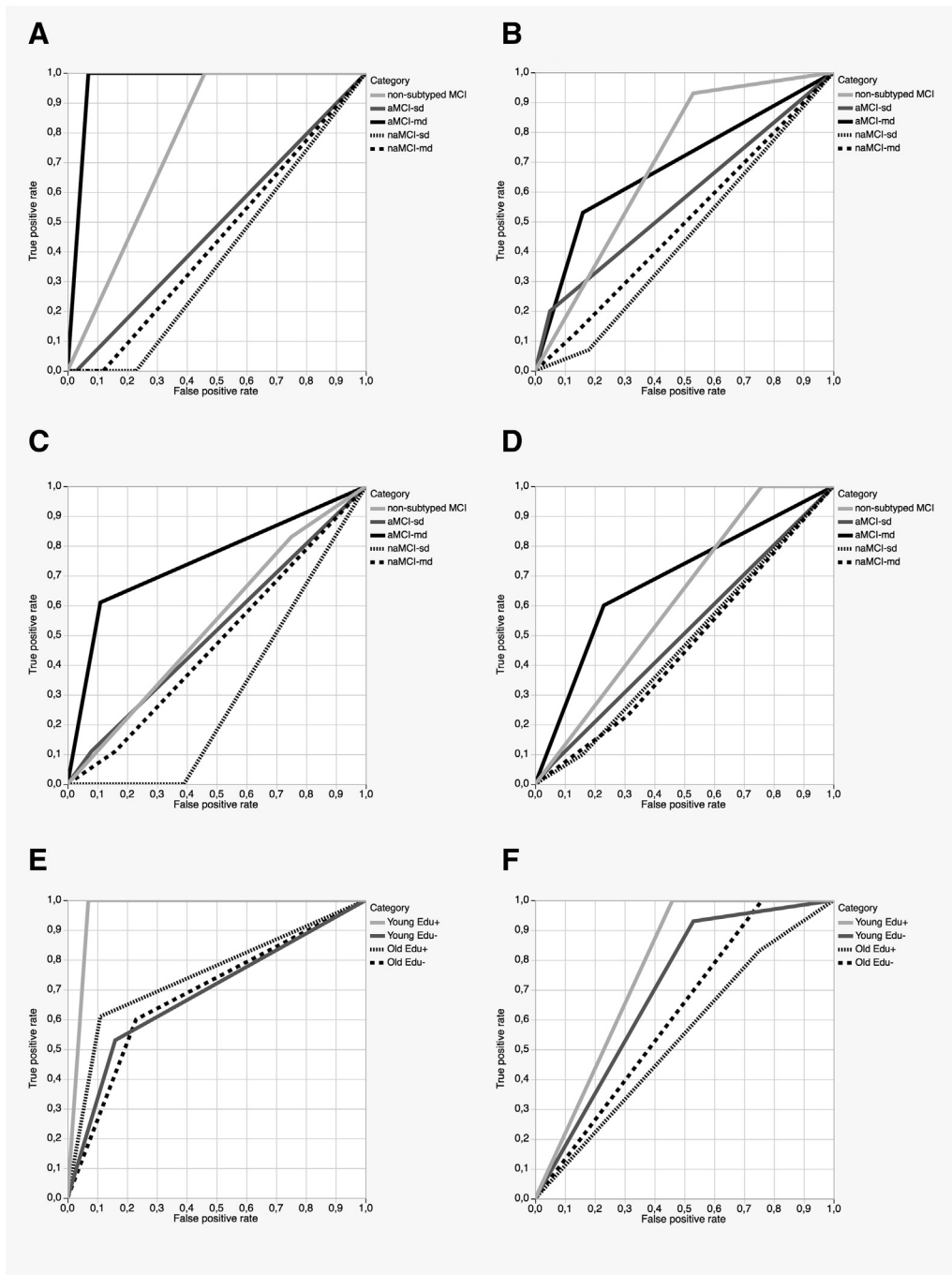


Fig. 2. Panel A–H. ROC curves. Abbreviations: aMCI-md, amnescticmulti-domain MCI; aMCI-sd, amnesctic single-domain MCI; Edu–, ≤ 12 years of education; Edu+, ≥ 13 years of education; naMCI-md, non-amnesctic multi-domain MCI; naMCI-sd, non-amnesctic single-domain MCI; Old, ≥ 65 years of age; Young, ≤ 64 years of age. NOTE. ROC curves plotting true positive rate over false positive rate for the MCI subtypes in (A) Young Edu+, (B) Young Edu–, (C) Old Edu+, and (D) Old Edu–, and for (E) aMCI-md, and (F) non-subtyped MCI in the combined age and education groups. ROC, receiver operator characteristics; MCI, non-subtyped mild cognitive impairment.

subtype prevalence likely also partly explain the differences in conversion rates between the combined age and education groups.

In the separate comparisons of age and education, there were differences in prognostic accuracy, but they were

smaller than when age and education were combined. For aMCI-md, both more years of education and a lower age increased the likelihood of an accurate prognosis. For non-subtyped MCI, the prognostic accuracy was better among the younger patients.

In one study, Visser et al. [12] reported a better prognostic accuracy in patients aged between 70 and 85 years than in patients aged between 40 and 69 years. In another study, Visser et al. [11] reported a better prognostic accuracy in patients aged between 55 and 64 years than between 65 and 85 years of age. These results are contradictory. Our results are in agreement with the latter study. The differences between Visser (2008) on the one hand and Visser (2005) and our results (better prognostic accuracy in younger patients) on the other could be explained in part by the choice of different cut-points between the age groups (65 vs. 70 years of age) but could also stem from differences in MCI criteria and outcome measures. We applied dementia as an outcome, regardless of etiology, whereas Visser et al. reported ADD only [11,12].

Furthermore, our results are in congruence with Chary et al. [16], who concluded that prognostic accuracy was higher for dementia among cognitively normal participants with higher education than participants with lower education. Their data originated from a population-based study, and only a fraction (<10%) of the participants had MCI. Our study is, to our knowledge, the first to report similar results in memory clinic patients with MCI.

A better prognostic accuracy in younger people may have several explanations. For instance, Wisdom et al. [48] showed that variability in Wechsler Adult Intelligence Scale-IV subtest performance increased with age. This implies a reduced performance of any attempt to predict dementia based on neuropsychological test scores, as the error would grow larger with increasing age. That is, in younger patients, test performance may be more likely to reflect an actual pathological process, as opposed to natural variation and normal age-related functional changes. The intraindividual variability in cognitive function also increases with age [49], which may result in lower reliability of classifications based on cognitive tests [43]. Furthermore, the occurrence of plaques and tangles in the brains of ADD patients decreases with increasing age but increases in healthy individuals [13,14], that is, the purported hallmarks of Alzheimer's disease become less disease-specific with increasing age. Deckers et al. [50] reported that known midlife risk factors and protective factors for dementia fail to predict dementia in persons aged more than 85 years. These factors may lead to a further blurring of the border between disease and health with increasing age, making any prognostic assessment increasingly difficult.

There are no universally applicable guidelines for desirable levels of sensitivity and specificity [51], although some have called for sensitivities and specificities around 85% [52]. In our results, only aMCI-md in Young Edu+ patients reached those levels. In a clinical setting, a test that can reliably establish the presence or absence of disease as a basis for treatment decisions would be ideal. To achieve this, the positive clinical utility index (the product of sensitivity and post test probability if the test is positive)

should be above 0.8 [44]. Our results indicate that no MCI subtype achieves this in memory clinic patients.

A strength of the present study is that it reports novel results, namely that age and education together and in combination impact the accuracy of a dementia prognosis based on MCI subtypes. The results are of clinical interest and may be used to infer clinical utility of MCI subtyping.

The study also has a few limitations. We used our own normative data for neuropsychological test variables, which might affect the generalizability of our results. Furthermore, both the index test (MCI subtype based on neuropsychological test results) and the reference standard ($GDS \geq 4$, mild dementia) were based on cognitive tests, creating a slight risk of incorporation bias. Data collection was part of a large umbrella study and was undertaken without regard for statistical power to detect differences in prognostic accuracy. A larger sample size would likely result in smaller CIs and more precise parameter estimates. Furthermore, our results are derived from patients seeking care at a secondary-care memory clinic and might not be representative of the general population, thus conclusions should not be generalized outside of this specific setting. Also, with a larger sample, other independent predictor variables such as sex and biomarker status as well as specific dementia etiologies, for example, ADD and subcortical vascular dementia, could be incorporated into analyses of prognostic accuracy.

5. Conclusion

In all clinical contexts, care needs to be taken not to over-interpret cognitive deviations, particularly in older individuals with low education. Any risk assessment based on MCI subtype should take the age and educational attainment of the patient into account. If not, the risk of dementia may be overestimated in older patients with lower education and underestimated in patients who are young and highly educated. Overall, aMCI-md is the most appropriate subtype for detecting future dementia. The influence of years of age and years of education on the prognostic accuracy of biomarker-based MCI classifications needs further attention, as well as potential sex differences in influence of years of age and education on prognostic accuracy.

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Authors' contributions: All authors have made substantial contributions to the conception and design of the work, contributed to the acquisition and interpretation of data, the critical revision of the article, and approved of the version to be published. M.G. performed all analyses and drafted the work. Statement of Ethics: The study was carried out in accordance with the Helsinki Declaration of 1975 and was approved by the local ethics committee (Registration Number: L091-99, 15 March 1999/T479-11, 8 June 2011). Written informed consent was obtained from all participants.

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using traditional (e.g., PubMed) sources. Publications reporting measures of prognostic accuracy of mild cognitive impairment (MCI) subtypes for future dementia in polychotomized age and/or education groups are cited.
2. Interpretation: Our findings suggest that both years of age and years of education of a patient influence the prognostic accuracy of MCI subtypes.
3. Future directions: The influence of years of age and years of education on the prognostic accuracy of other predictors of dementia, that is, biomarker based MCI classifications, needs further attention.

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