Mild cognitive impairment

Long-term course of four clinical subtypes

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Abstract—Objective: To empirically validate the expanded concept of mild cognitive impairment (MCI), which differentiates between four clinical subtypes—amnesic MCI—single domain, amnesic MCI—multiple domains, nonamnesic MCI—single domain, and nonamnesic MCI—multiple domains—and to examine the prevalence, course, and outcome of these four clinical MCI subtypes. **Methods:** We studied a community sample of 980 dementia-free individuals aged 75 years or older who participated in the Leipzig Longitudinal Study of the Aged (LEILA 75+). All participants were examined by neuropsychological testing based on 6 years of observation. The diagnoses of the four clinical MCI subtypes were made according to the original and to slightly modified criteria by Petersen et al. (2001) (both with a cutoff of 1.0 SD and with a cutoff of 1.5 SD). The complete range of outcome types (dementia, death, improvement, stable diagnosis, unstable diagnosis) was described for all subtypes. The relative predictive power of stable MCI for dementia onset was determined. **Results:** MCI—single domain is more frequent than MCI—multiple domains, and the nonamnesic MCI type is as frequent as the amnesic MCI type. The “MCI modified, 1.0 SD” criteria have the highest relative predictive power for the development of dementia (sensitivity = 74%, specificity = 73%). Alzheimer disease (AD) was the most common type of dementia at follow-up in all but one MCI subtype. Participants with nonamnesic MCI—multiple domains were more likely to progress to a non-AD dementia. **Conclusions:** It has been assumed that each MCI subtype is associated with an increased risk for a particular type of dementia. We can only partially agree with this.

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The expanded concept of mild cognitive impairment (MCI) distinguishes four clinical subtypes: amnesic MCI—single domain, amnesic MCI—multiple domains, nonamnesic MCI—single domain, and nonamnesic MCI—multiple domains.^{1,2} These four clinical subtypes assumedly differ in etiology and outcome.^{1,2} Amnesic MCI (single domain as well as multiple domains) is said to have a high likelihood of progressing to Alzheimer disease (AD) dementia. The nonamnesic subtypes are assumed to have a higher likelihood of progressing to a non-AD dementia.^{1,2}

This study addresses several questions. What is the prevalence of the subtypes of MCI? Which types of dementia do the subtypes of MCI commonly relate to? In this study, we also examine the course of and 6-year outcome of MCI in a representative general population sample aged 75 years and older, and describe the complete range of outcome types (dementia, death, improvement, stable diagnosis, unstable diagnosis).

Method. Sample. The data were derived from the Leipzig Longitudinal Study of the Aged (LEILA 75+), a population-based study of the epidemiology of dementia and MCI.³ All subjects gave written informed consent to participate in this study. The local ethics committee approved this study. The total LEILA 75+ sample was comprised of a total of 1,692 community-dwelling individuals aged 75 or older and residing in the Leipzig-South district; 1,500 of these individuals were identified by systematic random sampling from an age-ordered list from the local registry office. Additionally, institutionalized individuals were included in the study by proportion ($n = 192$) by systematic random sampling from an age-ordered list provided by the four institutions in the study area. Thus, the institutionalized individuals included are demographically similar to the rest of the sample. The study design of the LEILA 75+ and recruitment issues with their influence on the outcome of the study are detailed elsewhere.^{3,4}

For this study, we identified subjects using the following inclusion criteria: 1) no dementia diagnosis at baseline and 2) valid cognitive testing at baseline to allow diagnosis of MCI subtypes. Exclusion criteria were Parkinson disease (PD), mental retardation, known brain cancer, and severe weakness or severe sensory impairment leading to invalid cognitive testing. Participants with stroke or depression were not excluded (see Discussion).

Of the overall sample of 1,692 subjects in LEILA 75+, clinical interviews incorporating neuropsychological assessment were conducted with 1,265 participants (74.8%) at baseline. At baseline, 242 (14.2%) declined to participate, 57 (3.4%) had died, 15 (0.9%) were not traceable, and 113 (6.7%) were shielded by their rela-

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tives, allowing information only by proxy interviews. The 1,265 participants with neuropsychological assessment at baseline did not differ from the remainder of the sample in terms of age ($U = 263553$, $p = 0.455$), sex ($\chi^2 = 0.391$, $df = 1$, $p = 0.532$), or marital status ($\chi^2 = 5.027$, $df = 3$, $p = 0.170$). Of these 1,265 participants, 220 (17.4%) had dementia according to Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria.⁵ Of the remaining 1,045 nondemented participants, 65 individuals met the exclusion criteria of the study. We report on the remaining 980 subjects who met all inclusion criteria.

Instruments. At each assessment, participants were interviewed in their home environment by trained psychologists and physicians. Structured clinical interviews were conducted with the participants. Additionally, short or comprehensive (see below) structured third-party interviews were conducted with proxies. The main instrument used was the SIDAM (Structured Interview for Diagnosis of Dementia of Alzheimer-type, Multi-infarct Dementia and Dementia of Other Etiology according to ICD-10 and DSM-I).⁶ The SIDAM consists of several parts: 1) a neuropsychological test and 2) a section for clinical judgment and third-party information on psychosocial impairment, including a scale for the assessment of activities of daily living with 14 items (SIDAM-ADL Scale).

The test part of the SIDAM consists of 55 items, including all 30 items of the Mini-Mental State Examination (MMSE). The test covers six areas of neuropsychological functioning: 1) orientation, assessing orientation of time and place; 2) memory, measured by delayed verbal recall of a word list and a fictitious name and address, and delayed visual reproduction, questions on biographical knowledge and on historical data unrelated to a person's life; 3) intellectual abilities, assessed by items of abstract thinking (differences, explaining the meaning of idiomatic expressions) and judgment (describing pictures representing actions, and plausibility judgment); 4) verbal abilities and calculation, assessed by calculating serial sevens, spelling backward, and backward digit span; 5) constructional abilities (visual-spatial), assessed by copying figures; and 6) aphasia and apraxia, assessed by naming objects, reading and obeying a sentence, writing a sentence, and performing a three-stage command. For each cognitive domain, age-specific and education-specific norms were used in the evaluation of impairment in cognitive function. The norms for the SIDAM test section were developed on the baseline population (participants without dementia) from which the study sample was recruited.⁷

We assessed complaints of subjective memory impairment in all participants before cognitive testing by asking participants about memory problems (answer "yes" or "no"). Data on sociodemographic variables, medical history, and possible risk factors for dementia and for MCI were collected. Depressive symptoms were assessed with the Center for Epidemiologic Studies Depression scale⁸ and the Structured Clinical Interview for DSM-III-R (SCID).⁹ The capacity to perform activities of daily living was assessed with the SIDAM-ADL Scale and with the ADL/IADL Scale according to Schneekloth and Pothoff.¹⁰ The latter scale¹⁰ consists of 26 items and has been developed according to an internationally used ADL list.¹¹ Using these two scales, the proxy was asked whether the participant was able to perform fundamental and complex activities of daily living. The scale by Schneekloth and Pothoff also assessed whether the activity could be done without help, with aids, or only with help from others. Intact psychosocial functioning was diagnosed if the participant or rather the proxy answered less than two items (of 14 of the SIDAM-ADL Scale) with "yes." If it was not possible to administer the SIDAM test part at any visit (e.g., owing to death or severe weakness, or because relatives refused participation on behalf of the elderly person in their care), a comprehensive structured proxy interview was offered as an option. This included the Clinical Dementia Rating (CDR) scale¹² for assessment of cognitive functioning.

Data collection. Baseline interviews were conducted between January 1997 and June 1998. Study participants were requested to take part in four follow-up assessments conducted in 1.5-year intervals. Study participants were followed up until death or incidence of dementia or for a maximum of 6 years, if the SIDAM could be administered at each follow-up assessment. As long as the SIDAM could be administered to apply diagnostic criteria of MCI and dementia, participants remained in the study. If participants declined further participation, or if insufficient information

prevented applying diagnostic criteria of MCI or dementia, they were excluded from the study. The statistical analysis for those participants was based on the diagnosis established at the last follow-up visit during which the participant underwent cognitive testing.

Diagnosis. Consensus conferences of physicians and psychologists were held for each subject. The clinical diagnosis of dementia was made according to DSM-IV criteria. The cognitive criteria for a dementia diagnosis were based either on cognitive testing or on CDR data (if only proxy interviews had been conducted). To differentiate between dementia of AD, vascular dementia (VD), or dementia not further specified (other dementias), the SIDAM diagnostic algorithms⁶ based on DSM-IV diagnostic guidelines were used. This includes the Hachinski and Rosen scores, which were used to aid in the diagnosis of VD. The diagnosis of dementia types was not supported by neurologic investigation, imaging, or autopsy.

The validity of dementia diagnosis was investigated in a subsample of the study participants ($n = 74$). The 74 individuals have been thoroughly investigated in the memory clinic of the University of Leipzig with physical and neurologic status, cognitive testing, EEG, brain imaging, and blood testing, with very good agreement ($\kappa = 0.85$).

The diagnosis of MCI subtypes was made according to Petersen.² MCI diagnoses were always based on SIDAM cognitive testing. The CDR was never used for MCI diagnosis. Four MCI subtypes were examined: 1) amnesic MCI—single domain—isolated memory impairment of more than 1.0 SD compared with the age- and education-specific norms and no difficulty in other area of cognitive functioning; 2) amnesic MCI—multiple domain—two or more cognitive domains are impaired, one of which is memory impairment (impairment of more than 1.0 SD below the mean of the respective age- and education-matched population); 3) nonamnesic MCI—single domain—impairment in a single domain other than memory of more than 1.0 SD; and 4) nonamnesic MCI—multiple domain—impairments on two or more domains of more than 1.0 SD but no memory impairment. In addition to the cutoff of 1.0 SD to define cognitive impairment, a cutoff of 1.5 SD was also analyzed. The two cutoffs were analyzed because various cutoffs are used in the literature.

All four MCI subtypes also had to meet the following criteria: 1) the presence of a subjective cognitive complaint—participants or informants (or both) reported cognitive impairment; 2) intact ability to perform activities of daily living—forgetfulness did not compromise overall functional ability; impairment due to physical disease was not sufficient for exclusion; and 3) absence of dementia—assessed by DSM-IV criteria.

We also introduced slightly modified criteria for the MCI subtypes by excluding Criterion 1 from the necessary diagnostic criteria (the presence of a subjective cognitive complaint). The importance of subjective memory impairment in the prediction of dementia is questionable, and it may not be of additional predictive value.¹³

Analysis. All statistical computations were performed using SPSS for Windows (version 12.0.1). To analyze possible nonresponse bias, χ^2 analysis and the Mann-Whitney U test were applied. For all analyses, the significance level was set at $\alpha = 0.01$. The frequencies of MCI subtypes at baseline were calculated as percentage prevalences. The frequencies of different outcomes (death, dementia, improvement, stable diagnosis, unstable diagnosis) according to the diagnosis at baseline were calculated. The conversion rates to dementia were computed for the four clinical MCI subtypes separately as well as for the combined MCI group (all subtypes together). The prognostic power of the different sets of diagnostic MCI criteria for the prediction of future dementia was quantified in terms of the area under the curve derived from receiver operating characteristic analysis.

Results. Table 1 summarizes the baseline characteristics of the sample. As in the total LEILA 75+ cohort, females outnumber males in this study. The mean age was 81.5 years. According to the structured interviews, a total of 164 participants had strokes either before the study's beginning or over the course of the study, 59 of these before baseline. A total of 47 participants fulfilled DSM criteria for major depression according to the SCID inter-

Table 1 Characteristics of the baseline population (*n* = 980)

Baseline sample	Participants		
	All	At least one follow-up completed	No follow-up completed
No. of cases	980	863	117
Age, years			
Range	75–99	75–99	75–96
Mean (SD)	81.5 (4.8)	81.5 (4.9)	82.0 (4.6)
MMSE, mean (SD)	27.1 (2.1)	27.7 (2.1)	26.4 (2.2)
Sex, <i>n</i> (%)			
Male	246 (25)	227 (26.3)	19 (16.2)
Female	734 (75)	636 (73.7)	98 (83.8)
Level of education, <i>n</i> (%)			
Low	220 (22.4)	188 (21.8)	32 (27.4)
Middle	624 (63.7)	550 (63.7)	74 (63.2)
High	135 (13.8)	124 (14.4)	11 (9.4)
Missing	1 (0.1)	1 (0.1)	

MMSE = Mini-Mental State Examination.

view at one (or more) visits during the study (14 of these were at baseline).

Prevalence of MCI subtypes at baseline. Prevalence rates at baseline for all four MCI subtypes are shown in table 2. If original criteria were applied with a cutoff of 1.0 SD, 4.5% of the sample then had amnesic MCI–single domain, 5.5% had amnesic MCI–multiple domains, 2.1% had nonamnesic MCI–multiple domains, and 7.1% had nonamnesic MCI–single domain. As one might expect, the prevalence rates were lower in all four MCI subtypes (original criteria) if the cutoff was set at 1.5 SD instead of 1.0 SD, i.e., if the MCI was more severe. If modified criteria were applied by dropping the criterion of subjective memory impairment, the prevalence rates were considerably higher. Modified criteria with a cutoff of 1.0 SD identified amnesic MCI–single domain in 9.3%, amnesic MCI–multiple domains in 10.9%, nonamnesic MCI–multiple domains in 3.9%, and nonamnesic MCI–single domain in 17.4%. Again, if the severity level was increased by setting the cutoff at 1.5 SD instead of 1.0 SD, the prevalence rates of all four MCI types (modified criteria) decreased.

We investigated whether the prevalence rates were different for the four MCI types. The prevalence was lowest for nonamnesic MCI–multiple domains and highest for nonamnesic MCI–single domain. χ^2 analyses show that, irrespective of the diagnostic criteria used (modified or original criteria, 1 SD or 1.5 SD), prevalence rates were higher for MCI–single domain than for MCI–multiple domains (χ^2 between 8.048 and 83.793 depending on diagnostic criteria, *df* = 1, *p* = 0.000). There were no significant differences between prevalence rates of the amnesic MCI type and the nonamnesic MCI type.

Examination at follow-up. Out of 980 participants at baseline, 117 participants (11.9%) had to be excluded from analysis at the first follow-up because they declined further participation, or there was insufficient information to apply diagnostic criteria of MCI or dementia (table 1).

These 117 participants did not differ from the remainder of the sample (*n* = 863, 88.1%) with regard to age (*U* = 46491, *p* = 0.164), sex (χ^2 = 5.551, *df* = 1, *p* = 0.058), education (χ^2 = 3.268, *df* = 2, *p* = 0.195), or complaints of impaired memory expressed by the individual or significant others at the baseline assessment (χ^2 = 4.781, *df* = 3, *p* = 0.189). However, they had a lower MMSE score at baseline (*U* = 41597, *p* = 0.002). The remaining 863 participants had at least one followed-up assessment after baseline and could therefore be analyzed in relation to their diagnostic outcome. Participants were followed up for an average of 4.3 years (SD = 1.94). Table E-1 on the *Neurology* Web site at www.neurology.org shows the number of investigated participants and the applied methods for each of the six assessments. At each visit, the majority of participants were clinically investigated, also including cognitive testing.

Of the 863 participants for whom at least one follow-up examination was available, 171 participants (19.8%) developed dementia, and 195 (22.6%) died without a diagnosis of dementia during the entire observation period. Of the 171 participants developing dementia during the study, 89 received a diagnosis of AD, 42 received a diagnosis of VD, and 40 received a diagnosis of dementia not further specified. Of the 171 subjects who developed dementia, 128 (75%) were diagnosed based on cognitive testing, 24 (14%) were diagnosed based on proxy interview for shielded participants, and 19 (11%) were diagnosed based on proxy interview for deceased participants.

Outcome. We investigated the outcome of the participants with the baseline diagnosis MCI in two ways. First, all four clinical MCI subtypes were combined in one group (MCI), i.e., the four clinical subtypes were analyzed together (table E-2 and table 3). Second, the four clinical subtypes were analyzed separately (table 4) (see below).

All clinical subtypes combined. Table E-2 shows different outcomes at each follow-up, and table 3 shows the outcome over the whole study. There were no significant differences between MCI and cognitively unimpaired participants at baseline regarding age, sex, and education. Cognitively unimpaired participants developed dementia at a rate of 13% to 17% over 4.3 years of average observation time (table 3). Participants with a diagnosis of MCI progressed to dementia at a rate of 31% to 44%, depending on the diagnostic criteria used (modified vs original, 1 SD vs 1.5 SD). The conversion rate to dementia over 4.3 years was higher if the original MCI criteria were applied in contrast with the modified criteria. Also, the conversion rate to dementia increased if a severity degree of cognitive impairment of 1.5 SD instead of 1.0 SD was chosen.

There was no significant difference between the MCI group and cognitively unimpaired participants regarding the proportion of participants who died without having a diagnosis of dementia during their lifetime.

Approximately one-fifth of the participants with a diagnosis of MCI at baseline improved their cognitive status, i.e., they no longer met the diagnostic criteria of MCI during the course of follow-up. Between 5% and 11% of participants with MCI remained stable; they met diagnostic criteria of MCI for the length of observation. Between 4% and 13% of participants with MCI had an unstable course (participants improved to non-MCI and later received a diagnosis of MCI again).

Table 2 Prevalence rates of original and modified* MCI subtypes (*n* = 980)

Original and modified subtypes for MCI	Severity level of MCI	Baseline prevalence, age 75+		
	SD†	n	%	95% CI
Amnesic MCI—single domain				
Original criteria	1.0	44	4.5	3.2–5.8
	1.5	29	3.0	1.9–4.1
Modified criteria	1.0	91	9.3	7.5–11.1
	1.5	56	5.7	4.2–7.2
Amnesic MCI—multiple domains				
Original criteria	1.0	54	5.5	4.1–6.9
	1.5	9	0.9	0.3–1.5
Modified criteria	1.0	107	10.9	9.0–12.9
	1.5	18	1.8	1.0–2.6
Nonamnesic MCI—multiple domains				
Original criteria	1.0	21	2.1	1.2–3.0
	1.5	4	0.4	0.0–0.8
Modified criteria	1.0	38	3.9	2.7–5.1
	1.5	7	0.7	0.2–1.2
Nonamnesic MCI—single domain				
Original criteria	1.0	70	7.1	5.5–8.7
	1.5	49	5.0	3.6–6.4
Modified criteria	1.0	171	17.4	15.0–19.8
	1.5	88	9.0	7.2–10.8
MCI (all subtypes)				
Original criteria	1.0	189	19.3	16.8–21.8
	1.5	91	9.3	7.5–11.1
Modified criteria	1.0	407	41.5	38.4–44.6
	1.5	169	17.2	14.8–19.6
Non-MCI (no impairment in cognitive domains)				
Original criteria	1.0	791	80.7	78.2–83.2
	1.5	889	90.7	88.9–92.5
Modified criteria	1.0	573	58.5	55.4–61.6
	1.5	811	82.8	80.4–85.2

* Original mild cognitive impairment (MCI) subtypes according to Petersen²; modified MCI subtypes exclude the criterion of subjective memory impairment.

† The different MCI subtypes were determined according to different severity levels: cognitive performance 1.0 SD and 1.5 SD below the mean of age- and education-matched control subjects.

Table E-3 shows the proportion of participants with stroke or depression within the different diagnostic groups. Between 5% and 7% of the participants with MCI (all subtypes) at baseline fulfilled the criteria of a major depression during the study. Between 18% and 23% had experienced stroke. We investigated whether MCI participants with improved cognitive function or an unstable course could have had depression account for their clinical phenotype (table 3). Only 0% to 6% of those with improvement fulfilled criteria for depression during the study. Of participants with an unstable course, 0% to 10%, had depression. The outcome groups did not differ significantly in the proportion of participants with depression. In contrast, stroke had a significant influence on the outcome. Approximately 40% of participants who progressed to dementia

had a stroke during or before the study. The outcome groups did differ (with one exception) in the proportion of participants with stroke irrespective of the applied MCI criteria (modified or original, 1 SD or 1.5 SD) (always $p < 0.02$). If the modified MCI criteria (1.5 SD) were applied, the outcome groups did not differ significantly in the proportion of strokes.

Separate analysis of four clinical subtypes. In all but one MCI subtype (nonamnesic, multiple domains impaired), the most common type of dementia at follow-up was AD (table 4). Of those subjects who had had a diagnosis of amnesic MCI—multiple domains (MCI severity = 1.5 SD) at baseline and developed dementia at follow-up, 100% of the participants with dementia had AD. However, the number of participants with amnesic MCI—multiple do-

Table 3 Outcome of cognitively unimpaired participants and participants with MCI at baseline (*n* = 863)*

Outcome	Diagnostic criteria	Non-MCI at baseline				MCI at baseline		
		SD	All, n (%)	Participants with depression, n (%)	With stroke, n (%)	All, n (%)	Participants with depression, n (%)	With stroke, n (%)
Diagnosis of dementia	Original	1.0	105 (15.0) [16 dc]†	6 (5.7)	42 (40.0)	66 (40.2)‡ [3 dc]	5 (7.6)	26 (39.4)
		1.5	136 (17.4) [17 dc]	11 (8.1)	55 (40.4)	35 (43.8)§ [2 dc]	0 (0)	13 (37.1)
	Modified	1.0	65 (12.6) [13 dc]	6 (9.2)	27 (41.5)	106 (30.6) [6 dc]	5 (4.7)	41 (38.7)
		1.5	115 (16.0) [15 dc]	11 (9.6)	51 (44.3)	56 (38.9)¶ [4 dc]	0 (0)	17 (30.4)
Deceased, no diagnosis of dementia	Original	1.0	159 (22.7)	6 (3.8)	32 (20.1)	36 (22.0)	2 (5.6)	7 (19.4)
		1.5	175 (22.3)	6 (3.4)	36 (20.6)	20 (25.0)	2 (10.0)	3 (15.0)
	Modified	1.0	111 (21.5)	4 (3.6)	22 (19.8)	84 (24.3)	4 (4.8)	17 (20.2)
		1.5	153 (21.3)	5 (3.3)	33 (21.6)	42 (29.2)	3 (7.1)	6 (14.3)
Stable diagnosis	Original	1.0	315 (45.1)	14 (4.4)	34 (10.8)	8 (4.9)	2 (25.0)	3 (37.5)
		1.5	415 (53.0)	20 (4.8)	40 (9.6)	6 (7.5)	2 (33.3)	2 (33.3)
	Modified	1.0	195 (37.7)	9 (4.6)	24 (12.3)	37 (10.7)	3 (8.1)	6 (16.2)
		1.5	368 (51.2)	19 (5.2)	36 (9.8)	9 (6.3)	2 (22.2)	2 (22.2)
MCI incidence	Original	1.0	58 (8.3)	5 (8.6)	7 (12.1)	—	—	—
		1.5	26 (3.3)	2 (7.7)	4 (15.4)	—	—	—
	Modified	1.0	68 (13.2)	5 (7.4)	7 (10.3)	—	—	—
		1.5	39 (5.4)	2 (5.1)	5 (12.8)	—	—	—
Improvers (MCI to non-MCI)	Original	1.0	—	—	—	36 (22.0)	2 (5.6)	2 (5.6)
		1.5	—	—	—	16 (20.0)	0 (0)	0 (0)
	Modified	1.0	—	—	—	74 (21.4)	4 (5.4)	7 (9.5)
		1.5	—	—	—	27 (18.8)	1 (3.7)	2 (7.4)
Unstable course	Original	1.0	62 (8.9)	1 (1.6)	2 (3.2)	18 (11.0)	1 (5.6)	3 (7.3)
		1.5	31 (4.0)	1 (3.2)	3 (9.7)	3 (3.8)	0 (0)	2 (66.7)
	Modified	1.0	78 (15.1)	2 (2.6)	3 (3.8)	45 (13.0)	2 (4.4)	4 (8.9)
		1.5	44 (6.1)	0 (0.0)	3 (6.8)	10 (6.9)	1 (10.0)	3 (30.0)
Total no. of cases	Original	1.0	699 (100)	32 (4.6)	117 (16.7)	164 (100)	12 (7.3)	41 (25.0)
		1.5	783 (100)	40 (5.1)	138 (17.6)	80 (100)	4 (5.0)	20 (25.0)
	Modified	1.0	517 (100)	26 (5.0)	83 (16.1)	346 (100)	18 (5.2)	75 (21.7)
		1.5	719 (100)	37 (5.1)	128 (17.8)	144 (100)	7 (4.9)	30 (20.8)

* Only participants with at least one follow-up are included.

† Number in brackets: number of persons with a diagnosis of dementia, who were already deceased (dc) at time of follow-up assessment.

‡ $\chi^2 = 53.2$, $df = 1$, $p = 0.000$.

§ $\chi^2 = 31.8$, $df = 1$, $p = 0.000$.

|| $\chi^2 = 42.6$, $df = 1$, $p = 0.000$.

¶ $\chi^2 = 39.6$, $df = 1$, $p = 0.000$.

MCI = mild cognitive impairment.

Table 4 Outcome of four clinical MCI subtypes (*n* = 863)*

Outcome	Diagnostic criteria	Severity level in SD	Amnesic–single domain	Nonamnesic–single domain	Amnesic–multiple domains	Nonamnesic–multiple domains
Diagnosis of dementia, all <i>n</i> (%)†						
	Original	1.0	17 (43.6)	20 (33.9)	25 (53.2)	4 (21.1)
		1.5	13 (52.0)	18 (40.0)	3 (37.5)	1 (50.0)
	Modified	1.0	26 (32.9)	35 (23.6)	40 (44.9)	5 (16.7)
		1.5	19 (43.2)	25 (31.3)	9 (60.0)	3 (60.0)
AD, <i>n</i> (%)‡						
	Original	1.0	7 (41)	12 (60)	14 (56)	2 (50)
		1.5	7 (54)	12 (67)	3 (100)	0 (0)
	Modified	1.0	13 (50)	20 (57)	25 (63)	2 (40)
		1.5	11 (58)	18 (72)	9 (100)	1 (33)
VD, <i>n</i> (%)‡						
	Original	1.0	3 (18)	3 (15)	6 (24)	0 (0)
		1.5	0 (0)	5 (28)	0 (0)	0 (0)
	Modified	1.0	5 (19)	7 (20)	8 (20)	0 (0)
		1.5	1 (5)	5 (20)	0 (0)	1 (33)
Other dementias, <i>n</i> (%)‡						
	Original	1.0	7 (41)	5 (25)	5 (20)	2 (50)
		1.5	6 (46)	1 (5)	0 (0)	1 (100)
	Modified	1.0	8 (31)	8 (23)	7 (17)	3 (60.0)
		1.5	7 (37)	2 (8)	0 (0)	1 (33)
Deceased, no diagnosis of dementia, <i>n</i> (%)†						
	Original	1.0	10 (25.6)	14 (23.7)	9 (19.1)	3 (15.8)
		1.5	6 (24.0)	12 (26.7)	2 (25.0)	0 (0.0)
	Modified	1.0	22 (27.8)	36 (24.3)	22 (24.7)	4 (13.3)
		1.5	14 (31.8)	26 (32.5)	2 (13.3)	0 (0.0)
Stable diagnosis, <i>n</i> (%)†						
	Original	1.0	2 (5.1)	0 (0.0)	4 (8.5)	2 (10.5)
		1.5	3 (12.0)	2 (4.4)	1 (12.5)	0 (0.0)
	Modified	1.0	6 (7.6)	9 (6.1)	15 (16.9)	7 (23.3)
		1.5	4 (9.1)	3 (3.8)	1 (6.7)	1 (20.0)
Improvers (MCI to non-MCI), <i>n</i> (%)†						
	Original	1.0	6 (15.4)	17 (28.8)	7 (14.9)	6 (31.6)
		1.5	3 (12.0)	12 (26.7)	1 (12.5)	0 (0.0)
	Modified	1.0	16 (20.3)	48 (32.4)	5 (5.6)	5 (16.7)
		1.5	4 (9.1)	21 (26.3)	2 (13.3)	0 (0.0)
Unstable course, <i>n</i> (%)†						
	Original	1.0	4 (10.3)	8 (13.6)	2 (4.3)	4 (21.1)
		1.5	0 (0.0)	1 (2.2)	1 (12.5)	1 (50.0)
	Modified	1.0	9 (11.4)	20 (13.5)	7 (7.9)	9 (30.0)
		1.5	3 (6.8)	5 (6.3)	1 (6.7)	1 (20.0)
Total no. of cases, <i>n</i> (%)†						
	Original	1.0	39 (100)	59 (100)	47 (100)	19 (100)
		1.5	25 (100)	45 (100)	8 (100)	2 (100)
	Modified	1.0	79 (100)	148 (100)	89 (100)	30 (100)
		1.5	44 (100)	80 (100)	15 (100)	5 (100)

* Only cases with at least one follow-up are included.

† Percentage related to the number of mild cognitive impairment (MCI) cases in the column.

‡ Percentage related to the total number of dementia cases in the column.

AD = Alzheimer disease; VD = vascular dementia.

Table 5 Different outcomes and their preceding courses (*n* = 863)

Outcome	Course of cognitive diagnosis before outcome			Total no., n (%)†
	Stable non-MCI, n (%)*	Stable MCI, n (%)*	Unstable diagnosis, n (%)*	
Dementia				
Original criteria				
1.0 SD	58 [9]‡ (33.9)	86 [6] (50.3)	27 [4] (15.8)	171 [19] (19.8)
1.5 SD	102 [11] (59.6)	49 [6] (28.7)	20 [2] (11.7)	171 [19] (19.8)
Modified criteria				
1.0 SD	29 [6] (17.0)	127 [11] (74.3)	15 [2] (8.8)	171 [19] (19.8)
1.5 SD	83 [9] (48.5)	69 [9] (40.4)	19 [1] (11.1)	171 [19] (19.8)
Deceased, no dementia				
Original criteria				
1.0 SD	135 (69.2)	45 (23.1)	15 (7.7)	195 (22.6)
1.5 SD	159 (81.5)	25 (12.8)	11 (5.6)	195 (22.6)
Modified criteria				
1.0 SD	86 (44.1)	89 (45.6)	20 (10.3)	195 (22.6)
1.5 SD	133 (68.2)	48 (24.6)	14 (7.2)	195 (22.6)
No dementia				
Original criteria				
1.0 SD	351 (70.6)	60 (12.1)	86 (17.3)	497 (57.6)
1.5 SD	432 (86.9)	37 (7.4)	28 (5.6)	497 (57.6)
Modified criteria				
1.0 SD	237 (47.7)	96 (19.3)	164 (33.0)	497 (57.6)
1.5 SD	394 (79.3)	48 (9.7)	55 (11.1)	497 (57.6)
Total no.				
Original criteria				
1.0 SD	544	191	128	863 (100)
1.5 SD	693	111	59	863 (100)
Modified criteria				
1.0 SD	352	312	199	863 (100)
1.5 SD	610	165	88	863 (100)

* Percentage related to the total number of each outcome (*n* = 171, 195, 497).

† Percentage related to *n* = 863 (total number of subjects).

‡ Number in brackets: number of persons with a diagnosis of dementia, who were already deceased at time of follow-up assessment; these persons are included in the total number of dementia cases.

MCI = mild cognitive impairment.

mains was very small. Participants who met diagnostic criteria of nonamnestic MCI—multiple domains at baseline more likely progressed to non-AD dementia than the other three MCI subtypes. However, here the number of participants was also very small. Conversion rates to dementia (all dementia types) were higher for the amnesic MCI types than for the nonamnestic MCI types.

The highest rate of improvement was found in participants with nonamnestic MCI (single domain) at baseline (approximately 30%). Participants with a diagnosis of amnesic MCI at baseline (single domain as well as multiple domains) improved their cognitive status more seldom (15% or lower).

Prediction of dementia. Table 5 shows the course of cognitive status at preceding examinations for different

outcomes (incidence of dementia, deceased without a diagnosis of dementia during lifetime, living without dementia diagnosis). Depending on which set of diagnostic criteria was applied, 29% to 74% of the 171 demented participants had stable MCI before dementia diagnosis. Of all diagnostic criteria for MCI, the criteria of “MCI-modified, 1.0 SD” showed the highest sensitivity (sensitivity = 74%) and “MCI original, 1.5 SD” showed the lowest sensitivity (sensitivity = 29%) in the detection of dementia.

Nine percent to 16% of demented participants had an unstable diagnosis (neither stable MCI nor stable non-MCI) before dementia onset. Seventeen percent to 60% of participants with dementia at follow-up were diagnosed as cognitively unimpaired at each assessment (stable non-MCI) before the onset of dementia.

Table 6 Relative predictive power of MCI to predict the onset of dementia (*n* = 863)

MCI criteria	Sensitivity, %	Specificity, %	AUC	SE	Asymptotic significance	95% CI
Original criteria						
1.0 SD	50.3	84.8	0.676	0.025	0.000	0.627–0.724
1.5 SD	28.7	91.0	0.598	0.026	0.000	0.548–0.649
Modified criteria						
1.0 SD	74.3	73.3	0.738	0.022	0.000	0.695–0.780
1.5 SD	40.4	86.1	0.632	0.026	0.000	0.582–0.683

MCI = mild cognitive impairment; AUC = area under the curve.

Before death, participants were diagnosed mainly as cognitively unimpaired. Seven percent to 19% of the survivors without a diagnosis of dementia met diagnostic criteria of MCI at each follow-up assessment (stable MCI).

The receiver operating characteristic curves indicate a significant relative prognostic power of stable MCI (all four subsets together) in predicting the development of dementia in the following 4.3 years (table 6). Sensitivity decreased if the cutoff of MCI severity was 1.5 SD as compared with 1 SD, and if original criteria as compared with modified criteria (i.e., no need for subjective memory impairment) were applied. However, the use of modified criteria and a cutoff level of 1 SD were associated with a reduction in diagnostic specificity. The “MCI- modified, 1.0 SD” criteria have the highest relative predictive power for the development of dementia (sensitivity = 74%, specificity = 73%, AUC = 0.738, *p* = 0.000).

Discussion. The study aimed to provide an empirical validation of the expanded MCI concept.²

There are only a few other studies empirically validating the expanded MCI concept.^{14,15} These studies should be examined with close attention to the exact diagnostic algorithm for MCI. In the expanded MCI concept,² it was not defined—besides the broad categories amnesic vs nonamnesic, single vs multiple domains—which specific cognitive domains are affected. In an earlier clinical study,¹⁴ nine cognitive domains were measured. In the Cardiovascular Health Study (CHS) Cognition Study,¹⁵ six cognitive domains were assessed. Both studies used several neuropsychological instruments. In this study, the diagnosis of MCI relied on cognitive testing with one instrument, the SIDAM. Consequently, the cognitive domains assessed within this study revolve around the composition of the SIDAM, which measures six domains (see Methods section). Generally, the accuracy of dementia prediction in persons with MCI might depend on the exact definition of affected domains and instruments used.

In this study, the prevalence rates for MCI ranged from 9% to 42% depending on the used MCI criteria (original or modified, 1.0 SD or 1.5 SD). The CHS Cognition Study,¹⁵ which used diagnostic criteria comparable to our criteria “MCI modified, 1.5 SD,” reported a prevalence rate of 19%, which is similar the rate reported in this study.

In this study, the proportion of participants with

amnesic MCI—single domain was small. Concordantly, earlier studies reported prevalence rates ranging from 1% to 6%.^{15,16–18} It seems that most persons with MCI have a range of cognitive deficits greater than only memory impairment. We found that MCI—single domain is more prevalent than MCI—multiple domains. This unusual finding might partly be driven by our SIDAM-based definition of cognitive domains. One would assume that having multiple domains slightly impaired might be as prevalent or more prevalent than having a single domain slightly impaired, and this was actually found in one clinical study.¹⁴ However, clinical populations are selective and probably more impaired than population-based samples. We found that the nonamnesic MCI type is as frequent as the amnesic MCI type.

The conversion rates of MCI (all subtypes together) to dementia were 31% to 44%, which is comparable to rates reported in other studies.² If the MCI subtypes were investigated separately, amnesic MCI types had higher conversion rates to dementia (all dementia types) than the nonamnesic MCI types. This supports findings of a clinical study.¹⁴ It has been proposed that each of the MCI subtypes is associated with an increased risk of developing a particular type of dementia such as AD or VD.² This assumption was supported by a clinical study.¹⁴ In contrast, in this study, AD was the most common dementia type at follow-up in all but one MCI subtype. Only persons with nonamnesic MCI—multiple domains were more likely to progress to a non-AD dementia.

In this study, approximately one-fifth of the participants with MCI at baseline improved their cognitive status to normal. In earlier studies, between 15% and 44% improved.¹⁹ In this study, between 4% and 13% of persons with MCI had an unstable course. Petersen² reported that MCI cohorts in population-based studies show instability rates of 25% to 40%. Generally, the variability in outcomes of subjects with MCI might have different causes. It might be the result of different etiologies. This possibility was not investigated in this study, because there was no valid information about etiology. Second, it might be decisive if the diagnosis of MCI subtypes was based on—somewhat arbitrary—neuropsychological cutoff scores (as in this study). If a

clinical consensus diagnosis was used instead, there might have been a greater uniformity in outcomes.

The relative prognostic power of MCI was examined only for the combined MCI group (all for subtypes). In an earlier study by our working group, we found that the predictive power for future dementia is highest if all MCI subtypes are combined.²⁰ All diagnostic criteria of MCI applied in this study (original vs modified, 1 SD vs 1.5 SD) had a significant relative prognostic power in predicting dementia. The highest relative predictive power and the best relation of sensitivity and specificity were found for "MCI modified, 1.0 SD." However, between 17% and 60% of participants with dementia at follow-up were diagnosed as cognitively unimpaired at each assessment before the onset of dementia.

The predictive validities of the MCI concepts improved if the criterion of a subjective decline in cognitive functioning was excluded from the diagnostic criteria for MCI. The use of modified criteria for MCI was associated with a higher sensitivity but also with a reduction in specificity. The predictive power of subjective memory complaints has been questioned in view of their multiple determinants.²¹ It was argued that if subjective cognitive decline were included in diagnostic MCI criteria, some cases of MCI could be missed.^{22,23} However, in persons without demonstrable cognitive impairment, subjective memory deficits may have prognostic value in the early detection of future dementia.

In summary, if an MCI concept with high sensitivity is requested, modified MCI criteria and a low severity level (SD = 1.0) should be applied. If a concept with high specificity and high positive predictive power is requested, the original MCI criteria and a high severity level should be applied.

Limits of the study. The diagnosis of dementia types was not supported by neurologic examinations, imaging, or autopsy. Our differential diagnoses are less accurate than those in specialized clinical settings. The ultimate validity of our conclusions is somewhat diminished because of this potential lack of diagnostic accuracy. Moreover, only AD and VD were diagnosed; all other types of dementia were subsumed under the broad category of "other dementias." However, it has been recognized that AD pathology and vascular changes often coexist and may both contribute to the development of dementia, especially in very old age. Recent reports of overlapping symptomatology suggest that the validity of the diagnoses is questionable, even if neuroimaging is used.^{24,25} The exclusion of participants with PD might have led to the unintentional exclusion of persons with Lewy body disorder. There is a potential overlap between the two disorders.²⁶ Lewy body dementia is among those conditions persons with nonamnesic MCI might progress to.² Consequently, the prevalence of nonamnesic MCI might have been slightly underestimated in this study. Some might criticize our inclusion of persons with stroke and depression in the study. However, subjects with stroke

have an increased risk of developing VD. Their exclusion would result in an underrepresentation of subjects at risk for VD.¹⁴ Likewise, depression may be a risk factor for AD.²⁷ Their exclusion would result in an underrepresentation of subjects at risk for AD. Roughly one quarter of the subjects who developed dementia during the study were not reassessed directly, but by proxy. However, the inclusion of these subjects is a prerequisite for the exact estimation of the frequency of development of dementia, helping to avoid underestimation. A last limit of this study is that the impaired domains in persons with MCI have been defined using a relatively brief test and not a complete neuropsychological battery.

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NeuroImages

Minocycline-induced skin and dental pigmentations

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A 75-year-old man with amyotrophic lateral sclerosis was started on active treatment with minocycline hydrochloride, an investigational neuronal anti-apoptotic agent,¹ in February 2005 starting at 100 mg twice daily tapered up to 200 mg twice daily or identical placebo. Within 2 months he developed painless bluish-gray pigmentary lesions over the dorsum of the legs, arms, and face (figure, A); dark brown dental pigmentation appeared 3 months later (figure, B). The dose of study drug was subsequently reduced. Minocycline-induced skin pigmentation is caused by skin infiltration with pigment-loaded dermal macrophages, positive for melanin. The exact mechanism behind these minocycline-induced skin changes is not understood.²

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Figure. Minocycline-induced skin and dental changes. (A) Large confluent areas of non-tender dark (black) pigmentation over the forearms. (B) Areas of deep brown pigmentation over dental enamel. Such pigmentary changes are amenable to treatment with the Nd:YAG laser as well as the ruby laser treatments.

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Tahseen Mozaffar and Paul H. Gordon

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