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Subclassifications for mild cognitive impairment: prevalence and predictive validity

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ABSTRACT

Background. Mild cognitive impairment (MCI) is associated with an increased risk of developing dementia. Recently published results of the Current Concepts in MCI Conference suggested subclassifications for MCI (MCI-amnestic, MCI-multiple domains slightly impaired, MCI-single nonmemory domain) based on the recognized heterogeneity in the use of the term. These subclassifications have not been empirically validated to date.

Method. A community sample of 1045 dementia-free individuals aged 75 years and over was examined by neuropsychological testing in a three-wave longitudinal study. The prevalences and the predictive validities for the subclassifications of MCI and their modifications (original criteria except for the report of subjective decline in cognitive function) were determined.

Results. The prevalence was 1 to 15% depending on the subset employed. Subjects with a diagnosis of MCI progressed to dementia at a rate of 10 to 55% over 2·6 years, depending on the subset employed. MCI-amnestic achieved the highest positive predictive power (PPP). ROC curves of the subclassifications for MCI indicate that all but one subset for MCI failed to predict dementia (MCI-multiple domains slightly impaired-modified: AUC = 0·585, $P < 0{\cdot}01$, 95% CI, 0·517–0·653). The use of modified criteria for MCI (original criteria except for the report of subjective decline in cognitive function) is associated with a higher diagnostic sensitivity but also with a reduction in diagnostic specificity and PPP.

Conclusions. Modified criteria should be applied if a concept for MCI with a high sensitivity is required and the original criteria (including subjective cognitive complaint) if a concept with high specificity and high PPP is required.

INTRODUCTION

Mild cognitive impairment is associated with an increased risk of developing dementia. Patients with this condition develop dementia at a rate of 10–15% per year, while the rate for healthy controls is only 1–2% per year (Shah *et al.* 2000). However, data on the prevalence of mild cognitive impairment and the conversion rate to dementia vary widely, depending on the different definitional criteria applied (Dawe & Procter, 1998). The current lack of agreement on terminology and specific diagnostic criteria poses problems both for clinicians in their work with patients and their families and for investigators studying the phenomenon. Furthermore, research into possible treatments for cognitive decline requires that agreement be reached on clearly specified high risk populations and their diagnostic criteria.

Definitions of mild cognitive impairment such as 'benign senescent forgetfulness' (BSF) (Kral, 1962) and 'age-associated memory impairment' (AAMI) as introduced by Crook *et al.* (1986) have been criticized for their unclear criteria (BSF) and for referring to far too heterogeneous a group of people to be of clinical use (AAMI)

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(Hanninen & Soininen, 1997). Other concepts such as 'mild cognitive decline' as established by the Global Deterioration Scale (GDS, GDS = 3) (Reisberg *et al*. 1982), or 'questionable dementia' as measured by the Cognitive Dementia Rating Scale (CDR, CDR = 0·5) (Hughes *et al*. 1982) have unspecified operational criteria for cognitive examination. Consequently, studies using such concepts can still vary greatly in their definitions of cases. Addressing criticism of earlier constructs, the International Psychogeriatric Association (in collaboration with the World Health Organization) suggested a new category termed 'aging-associated cognitive decline' (AACD) (Levy, 1994).

Several research centres use the term 'Mild Cognitive Impairment' (MCI), which is one of the most widely used concepts in empirical studies (Petersen *et al*. 2001). However, there seems to be little agreement on its diagnostic algorithms (Ritchie & Touchon, 2000). For example, it remains unclear whether cognitive decline is established only in relation to age-specific norms or also to education-specific norms, and also whether or not MCI should be limited exclusively to isolated memory impairment. It is argued that memory impairment commonly occurs together with other cognitive deficits (Ritchie & Touchon, 2000). Moreover, the criterion of deficits in cognitive domains other than memory has been supported by recent research on the prediction of dementia (Bozoki *et al*. 2001). The concept of MCI would therefore be more useful if the cognitive criteria were not restricted to an isolated decline in memory but included a significant decline in any cognitive function (Ritchie & Touchon, 2000). In addition to this criticism of the concept, recent empirical results obtained by Ritchie *et al*. (2001) in a population-based sample suggest that MCI has a very low sensitivity in the detection of dementia and a poor relative predictive power for the onset of dementia.

A recently published article presenting the results of the 'Current Concepts in MCI Conference' discusses the criticism raised against the term and proposes subclassifications for MCI that cover a significant decline in any cognitive function (Petersen *et al*. 2001). Three subsets of MCI are suggested: 'MCI-amnestic', 'MCI-multiple domains slightly impaired' and 'MCI-single nonmemory domain'. To our knowledge, no empirical validation of this subclassification has been carried out to date. It is the purpose of the present study to establish prevalences and predictive validities for the subclassifications of MCI in a representative general population sample aged 75 years and older. We also introduce slightly modified criteria for the three subsets of MCI by excluding the report of subjective decline of cognitive function by the individual or a reliable informant from the necessary diagnostic criteria. The importance of a subjective report of cognitive decline in the prediction of dementia is questionable and may not be of additional predictive value within a concept of mild cognitive impairment (Jorm *et al*. 1997). Since the newly established subclassifications of MCI suggest that each of the three subsets for MCI is associated with an increased risk of developing a particular type of dementia such as Alzheimer's disease (AD) or vascular dementia (VD), we also provide data on the differential diagnosis of dementia (Petersen *et al*. 2001).

METHOD

Subjects

The data was derived from the Leipzig Longitudinal Study of the Aged (LEILA 75+), a population-based study on the epidemiology of dementia and mild cognitive impairment. A total of 1500 community-dwelling individuals aged 75 and over and resident in the Leipzig-South district, Germany, were identified by systematic random sampling from an age-ordered list provided by the local registry office. Institutionalized individuals were included in the study on a proportional basis ($N = 192$). The study design of the Leipzig Longitudinal Study of the Aged has been described in detail elsewhere (Riedel-Heller *et al*. 2000, 2001).

Of the overall sample of 1692 subjects, 242 (14·2%) declined to participate, 57 (3·4%) had died and 15 (0·9%) were not traceable. Information on 113 (6·7%) study subjects shielded by their relatives was obtained solely by proxy interviews. Clinical interviews incorporating neuropsychological assessment were conducted with 1265 (74·8%) participants. These 1265 study subjects did not differ significantly from the remainder of the sample in regard to age ($U = 263\,553$, $P = 0{\cdot}455$), gender ($\chi^2 = 0{\cdot}391$, df = 1,

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$P = 0{\cdot}532$) or marital status ($\chi^2 = 5{\cdot}027$, df = 3, $P = 0{\cdot}170$). Two hundred and twenty (17·4%) of these 1265 subjects were suffering from dementia as defined by the DSM-IV. The following analysis is based on the remaining 1045 non-demented participants.

Instruments

Structured clinical interviews were conducted by trained psychologists and physicians during visits to the subjects' homes. The main instrument employed was the SIDAM (Structured Interview for Diagnosis of Dementia of Alzheimer-Type, Multiinfarct Dementia and Dementia of other Etiology according to the ICD-10, DSM-III-R and DSM-IV) (Zaudig *et al.* 1991). The SIDAM consists of a neuropsychological test battery including the MMSE, a section for clinical judgement and third party information on psychosocial impairment. The SIDAM was constructed on the basis of operationalized criteria from the DSM-III-R, DSM-IV and ICD-10. SIDAM diagnostic algorithms (Zaudig *et al.* 1991) based on DSM-IV diagnostic guidelines were used to derive DSM-IV diagnosis of dementia (dementia of the Alzheimer type (AD), vascular dementia (VD), dementia not further specified). Hachinski and Rosen scores were used to aid in the diagnosis of VD. The diagnosis of dementia types was not supported by neurological investigation, imaging or autopsy.

Data on sociodemographic variables, possible risk factors for dementia and mild cognitive impairment, the ability to perform activities of daily living and complaints of a subjective decline in cognitive function were also collected. In addition, structured third party interviews were conducted, mainly in order to obtain information on cognitive and psychosocial functioning.

Cognitive testing with the SIDAM covered six different areas of neuropsychological functioning: orientation, memory, intellectual abilities, verbal abilities and calculation, constructional abilities, aphasia and apraxia. For each cognitive domain age- and education-specific norms were employed in the evaluation of impairment in cognitive function. Depressive symptoms were assessed on the CES-D (Center of Epidemiological Studies Depression) Scale (Radloff, 1977) and SCID (Structured Clinical Interview for DSM-III-R, Spitzer *et al.* 1987).

Following the proposals discussed at the Current Concept in Mild Cognitive Impairment conference three subclassifications for MCI were examined: 'MCI-amnestic', 'MCI-multiple domains slightly impaired' and 'MCI-single nonmemory domain' (Petersen *et al.* 2001). 'MCI-amnestic', which emphasizes memory loss, is defined by the criteria established by Petersen *et al.* (1999). Subjects who were found to have a memory impairment of $>1{\cdot}0$ S.D. compared with the age- and education-specific norms and showed no difficulty in any other area of cognitive functioning received a diagnosis of 'MCI-amnestic' if all other criteria for 'MCI-amnestic' were met (complaints of subjective memory decline, preserved general intellectual functioning, intact ability to perform activities of daily living, absence of dementia). 'MCI-multiple domains slightly impaired' was diagnosed if at least two cognitive domains showed an impairment of $>1{\cdot}0$ S.D. below the mean of the respective age- and education-matched population and the individual or a reliable informant reported cognitive decline, but a diagnosis of dementia could not be given. If only a single domain other than memory was impaired (impairment of $>1{\cdot}0$ S.D. below the age and education appropriate mean), the subject was not demented and a subjective cognitive decline was reported, 'MCI-single nonmemory domain' was diagnosed.

In addition to the cut-off of 1·0 S.D. below the age- and education-specific mean for defining MCI, the different MCI subtypes were determined according to different severity levels: cognitive performance 1·5 S.D.s and 2·0 S.D.s below the mean of age- and education-matched control subjects.

Study subjects who met the exclusion criteria for mild cognitive impairment defined by Levy (1994) (any present or past medical or psychiatric condition, or psychoactive substance use, that can cause cerebral dysfunction) were excluded from the study to rule out the possibility of cognitive impairment due to medical or psychiatric conditions.

In addition to the three subclassifications, modified subsets for MCI were evaluated: 'MCI-amnestic-modified', 'MCI-multiple domains slightly impaired-modified' and 'MCI-single nonmemory domain-modified'. Each of these modified subsets included the same criteria

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as the original subclassifications, excepting the report of a subjective decline of cognitive function by the individual or a reliable informant.

Structured clinical interviews were conducted at baseline between January 1997 and June 1998. Study participants were requested to take part in two follow-up assessments, which were conducted 18 and 36 months after the baseline assessment, respectively. If it was not possible to administer the SIDAM at follow-up (e.g. owing to death or severe weakness or because relatives of study subjects refused participation on behalf of the elderly person in their care), we offered the option of a fully structured proxy interview. This included the Clinical Dementia Rating Scale (CDR) (Hughes *et al*. 1982) for assessment of cognitive function, instead of cognitive testing.

Consensus conferences of physicians and psychologists were held on each subject to discuss clinical judgement and psychosocial and cognitive impairment. The clinical diagnosis of dementia was made according to the DSM-IV criteria (American Psychiatric Association, 1994). Cognitive criteria of dementia diagnosis were either based on cognitive testing or CDR data (in case of proxy interviews). The reported prevalence-rates for mild cognitive impairment are based on those individuals who performed cognitive testing at baseline. Reported predictive validities of the three subclassifications for MCI include subjects of which only CDR data were available at follow-up.

Analysis

The frequencies of the subsets of MCI at baseline are given as percentage prevalences. Receiver operating characteristic (ROC) analysis was applied to evaluate the relative predictive powers of the different subsets of MCI in the prediction of future dementia. In addition, the positive predictive power (PPP) of each subset was calculated as the proportion of subjects who received a diagnosis of MCI at baseline and also developed dementia before the follow-up assessment (true positives) over all subjects of which information (including CDR data) were available at follow-up who had had a diagnosis of MCI at baseline (true and false positives).

RESULTS

Baseline evaluation

One hundred sixteen of the 1045 non-demented study subjects met the exclusion criteria for mild cognitive impairment defined by Levy (1994) to rule out the possibility of cognitive changes due to medical or psychiatric conditions (e.g. any neurologic disorder that could produce cognitive deterioration, a current diagnosis of any major psychiatric disorder). Nine hundred and twenty-nine subjects remained for baseline examination. Baseline characteristics of the sample are given in Table 1. The study population had an average age of 81·5 years (S.D. = 4·9). Three-quarters of the sample were woman. Institutionalized individuals were older, had a lower MMSE-baseline-score and a lower level of education compared to those individuals living in private households.

Table 2 shows the proportions of subjects meeting the original and modified criteria of one of the three subsets for MCI according to different degrees of severity of cognitive impairment (1·0, 1·5 and 2·0 S.D.s below the mean of age- and education-matched control subjects). The original criteria of all three subsets for MCI were diagnosed in 15% of the study participants (prevalence of 3–6% in each subset) if a cut-off of 1·0 S.D. was chosen.

If the criterion of a subjective report of cognitive decline was excluded (modified criteria), the baseline prevalence increased to 32% for all three subsets (cut-off of 1·0 S.D.). No impairment of cognitive domains was found in the remaining 68% of subjects. For 'MCI-amnestic-modified' the prevalence was lowest (5%), for 'MCI-multiple domains slightly impaired-modified' the prevalence was 12% and for 'MCI-single nonmemory domain-modified' 15%.

If a severity level of 1·5 or 2·0 S.D.s was chosen, the prevalence of all subsets together (original or modified) decreased by 50% (S.D. = 1·5) and two-thirds (S.D. = 2·0).

Examination at follow-up

Seventy-seven subjects were lost to follow-up. These 77 study subjects did not differ significantly from the remainder of the sample ($N = 852$) in regard to age ($U = 29\,823$, $P = 0{\cdot}186$), gender ($\chi^2 = 0{\cdot}337$, df = 1, $P = 0{\cdot}068$) or complaints of impaired memory expressed by the

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Table 1. *Characteristics of the baseline and follow-up population*

	Private households	Institutions	All
Baseline sample			
Number of cases	858	71	929
Age			
Range	75–99	76–99	75–99
Mean (S.D.)	81·2 (4·6)	86·0 (5·4)	81·5 (4·9)
MMSE score, mean (S.D.)	27·1 (2·1)	26·0 (1·9)	27·0 (2·1)
Gender, *N* (%)			
Male	211 (24·6)	13 (18·3)	224 (24·1)
Female	647 (75·4)	58 (81·7)	705 (75·9)
Level of education, *N* (%)			
Low	181 (21·1)	27 (38·0)	208 (22·4)
Middle	550 (64·1)	41 (57·7)	591 (63·6)
High	125 (14·6)	1 (1·4)	126 (13·6)
Missing	2 (0·2)	2 (2·8)	4 (0·4)
Drop-outs after baseline, *N* (%)	74 (8·6)	3 (4·2)	77 (8·3)
Follow-up sample			
Number of cases	784	68	852
Age at baseline			
Range	75–99	76–99	75–99
Mean (S.D.)	81·1 (4·6)	85·9 (5·4)	81·5 (4·9)
MMSE baseline score, mean (S.D.)	27·2 (2·0)	26·0 (1·9)	27·1 (2·1)
Gender, *N* (%)			
Male	199 (25·4)	13 (19·1)	212 (24·9)
Female	585 (74·6)	55 (80·9)	640 (75·1)
Level of education, *N* (%)			
Low	160 (20·4)	25 (36·8)	185 (21·7)
Middle	500 (63·8)	40 (58·8)	540 (63·4)
High	122 (15·6)	1 (1·5)	123 (14·4)
Missing	2 (0·3)	2 (2·9)	4 (0·5)

individual or significant others at the baseline assessment ($\chi^2 = 2{\cdot}773$, df = 3, $P = 0{\cdot}428$). However, drop-outs had a slightly lower level of education ($\chi^2 = 7{\cdot}941$, df = 3, $P = 0{\cdot}019$) and a significantly lower MMSE score at baseline ($U = 26\,919$, $P = 0{\cdot}009$).

The remaining 852 subjects were reassessed at at least one follow-up time point. Sample characteristics are given in Table 1. The average follow-up period was 2·6 years (S.D. = 0·73). The statistical analysis was based on the diagnosis established at the final follow-up visit at which the subject was available.

The positive predictive power (PPP) for subsequent dementia for each of the subsets of MCI and varying degrees of severity (S.D. of 1·0, 1·5 and 2·0) are given in Table 2. Subjects with a diagnosis of MCI progressed to dementia at a rate of 13% to 33% over 2·6 years (5% to 13% per year), depending on the subset employed, whereas healthy subjects converted at a rate of 7% to 8% over the same time period (3% per year) if a severity degree of cognitive impairment of 1·0 S.D. was chosen. The conversion rate to dementia over 2·6 years was relatively low for subjects with 'MCI-single non-memory domain' (original and modified criteria: 18% and 13%). The PPP for subsequent dementia was highest for the original criteria of 'MCI-amnestic' (33%) and 'MCI-multiple domains slightly impaired' (29%) and slightly lower for the modified diagnoses of these subsets for MCI (23% and 24%). The PPP increased in almost all subsets if a severity degree of cognitive impairment of 1·5 or 2·0 S.D.s was chosen. MCI-amnestic achieved the highest PPP: >50% of MCI-amnestic cases (1·5 or 2·0 S.D.s) developed subsequent dementia within 3 years.

There was no difference in the duration of follow-up between participants who had become demented by the follow-up assessment and those who had not. There was also no difference between the lengths of the follow-up periods of the subjects with an MCI subclassification and those who had no cognitive impairment.

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Table 2. *Original and modified* subclassifications for mild cognitive impairment (MCI): baseline prevalences and development of dementia within 3 years (PPP, positive predictive power†)*

MCI subclass	Criteria	Severity level of MCI s.d.‡	Baseline prevalence		PPP	
			N	%	*N*	%
Amnestic	Original	1·0	29	3·1	9	33·3
		1·5	23	2·5	12	54·5
		2·0	17	1·8	9	52·9
	Modified	1·0	47	5·1	10	22·7
		1·5	39	4·2	13	37·1
		2·0	29	3·1	11	40·7
Multiple domains slightly impaired	Original	1·0	53	5·7	14	28·6
		1·5	17	1·8	3	18·8
		2·0	5	0·5	1	20·0
	Modified	1·0	112	12·1	24	24·0
		1·5	31	3·3	8	28·6
		2·0	10	1·1	4	40·0
Single non-memory domain	Original	1·0	57	6·1	9	17·6
		1·5	39	4·2	7	19·4
		2·0	24	2·6	5	22·7
	Modified	1·0	143	15·4	17	13·1
		1·5	86	9·3	8	10·1
		2·0	47	5·1	6	13·6
All	Original	1·0	139	15·0	32	25·2
		1·5	79	8·5	22	29·7
		2·0	46	5·0	15	34·1
	Modified	1·0	302	32·5	51	18·6
		1·5	156	16·8	29	20·4
		2·0	86	9·3	21	25·9
Normal ageing§	Original	1·0	790	85·0	57	7·9
		1·5	850	91·5	67	8·6
		2·0	883	95·0	74	9·2
	Modified	1·0	627	67·5	38	6·6
		1·5	773	83·2	60	8·5
		2·0	843	90·7	68	8·8

* Original subclassifications of MCI according to Petersen *et al.* (2001), modified subclassifications exclude the criterion of a subjective complain of cognitive impairment.

† PPP, Positive predictive power: calculated as the proportion of subjects who received a diagnosis of mild cognitive impairment at baseline and developed dementia before follow-up (true positives) over all subjects of which information were still available at follow-up who had had a diagnosis of mild cognitive impairment at baseline (true and false positives).

‡ The different MCI subtypes were determined according to different severity levels: cognitive performance 1·0 s.d., 1·5 s.d. and 2·0 s.d. below the mean of age- and education-matched control subjects.

§ No impairment in cognitive domains.

The receiver operating characteristic (ROC) curves indicate that almost all subclassifications of MCI failed to predict dementia (Table 3). Only the ROC curve for 'MCI-multiple domains slightly impaired-modified (severity level = 1·0 s.d.)' indicates a significant predictive power (AUC = 0·585, $P = 0·009$). Of all three subsets, 'MCI-multiple domains slightly impaired-modified (severity level = 1·0 s.d.)' showed the highest sensitivity in the detection of dementia (sensitivity = 27%). Sensitivity decreased for almost all MCI criteria if the cut-off of MCI severity was 1·5 or 2·0 s.d.s. Specificity increased for all MCI criteria if the cut-off of MCI severity was 1·5 or 2·0 s.d.s. For all levels of MCI severity, the use of modified criteria (i.e. no need for subjective complaint) was associated with a higher diagnostic sensitivity and a reduction in diagnostic specificity.

The relative prognostic power in predicting the development of dementia in the following 2·6 years was the highest (optimal relation of sensitivity and specificity) for all three subsets of MCI (modified criteria, severity level = 1·0 s.d.) taken together (sensitivity = 57%, specificity = 71%, AUC = 0·640, $P = 0·000$). Fifty-one (57%) of the total of 89 dementia cases diagnosed at follow-up were detected before the onset of the disease by the modified MCI subsets (severity level = 1·0 s.d.). Thirty-eight of the 89 dementia

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Table 3. *Results of the receiver operating characteristics analysis conducted to evaluate the relative predictive powers of the different subclassifications for MCI (original and modified)* to predict the onset of dementia*

Subclassifications for MCI	Criteria	Severity level of MCI S.D.†	Sensitivity %	Specificity %	AUC	S.E.	Asymptotic significance	95% CI
Amnestic	Original	1·0	10·1	97·6	0·539	0·034	0·231	0·472–0·605
		1·5	13·5	98·7	0·561	0·035	0·060	0·493–0·629
		2·0	10·1	99·0	0·545	0·034	0·161	0·478–0·612
	Modified	1·0	11·2	95·5	0·534	0·034	0·295	0·468–0·600
		1·5	14·6	97·1	0·559	0·035	0·070	0·491–0·626
		2·0	12·4	97·9	0·551	0·034	0·113	0·484–0·619
Multiple domains slightly impaired	Original	1·0	15·7	95·4	0·556	0·034	0·085	0·488–0·623
		1·5	3·4	98·3	0·508	0·033	0·797	0·444–0·573
		2·0	1·1	99·5	0·503	0·033	0·926	0·439–0·567
	Modified	1·0	27·0	90·0	0·585	0·035	0·009	0·517–0·653
		1·5	9·0	97·4	0·532	0·034	0·325	0·466–0·598
		2·0	4·5	99·2	0·519	0·033	0·567	0·453–0·584
Single nonmemory domain	Original	1·0	10·1	94·5	0·523	0·033	0·476	0·458–0·588
		1·5	7·9	96·2	0·520	0·033	0·530	0·455–0·585
		2·0	5·6	97·8	0·517	0·033	0·600	0·452–0·582
	Modified	1·0	19·1	85·2	0·521	0·033	0·507	0·457–0·586
		1·5	9·0	90·7	0·498	0·032	0·961	0·435–0·562
		2·0	6·7	95·0	0·509	0·033	0·785	0·445–0·573
All	Original	1·0	36·0	87·5	0·618	0·034	0·000	0·550–0·685
		1·5	24·7	93·2	0·590	0·035	0·006	0·521–0·658
		2·0	16·9	96·2	0·565	0·035	0·044	0·497–0·633
	Modified	1·0	57·3	70·8	0·640	0·032	0·000	0·578–0·703
		1·5	32·6	85·2	0·589	0·034	0·006	0·522–0·656
		2·0	23·6	92·1	0·579	0·035	0·015	0·511–0·647

* Original subclassifications for MCI according to Petersen *et al.* (2001), modified subclassifications for MCI exclude the criterion of a subjective complaint of cognitive impairment.

† The different MCI subtypes were determined according to different severity levels: cognitive performance 1·0 S.D., 1·5 S.D. and 2·0 S.D. below the mean of age- and education-matched control subjects.

AUC, Area under the curve.

cases found at follow-up were not detected at the baseline assessment by one of the modified MCI subsets. Of these 38 cases, 22 developed dementia between the baseline assessment and the first follow-up assessment and seven of these suffered a stroke between baseline assessment and the first follow-up. The other 16 cases received a diagnosis of dementia between the first and second follow-up interviews. Seven of these 16 dementia cases received the diagnosis of one of the three modified MCI subsets at the first follow-up: two 'MCI-amnestic-modified', two 'MCI-single nonmemory domain-modified' and three 'MCI-multiple domains slightly impaired-modified'. One subject with dementia suffered a stroke between the first and second follow-up assessments. Fifteen of the 38 dementia cases with no MCI diagnosis at baseline were at a clinically detectable risk before dementia onset due to stroke or MCI diagnosed (modified criteria) at the first follow-up visit. In sum, 66 out of 89 dementia cases (74%) were detected before the onset of dementia by a diagnosis of stroke or one of the three modified subsets of MCI (MCI severity = 1·0 S.D.).

Among the subjects who had had a diagnosis of 'MCI-amnestic-modified, (MCI severity = 1·0 S.D.)' at baseline and developed dementia at follow-up, 50% of the dementia cases were suffering from AD, 10% from VD, while the remaining 40% could not be assigned to a specific aetiology (dementia not further specified). Of those subjects who had had a diagnosis of 'MCI-multiple domains slightly impaired-modified (MCI severity = 1·0 S.D.)' at baseline and developed dementia at follow-up, 67% of the dementia cases developed AD, 12% VD, and no specification was possible for the remaining 21% (dementia not further specified). The distribution of different types of dementia

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was similar for study participants with a diagnosis of 'MCI-single nonmemory domain-modified, (MCI severity = 1·0 S.D.)' at baseline and subsequent dementia (70% AD, 12% VD, 18% not further specified).

DISCUSSION

With the subclassifications of MCI proposed at the Current Concepts in MCI Conference in 1999 (Petersen *et al.* 2001) a number of shortcomings of the classical MCI concept was addressed. Cognitive impairment is now clearly related to age- and education-specific norms and is not limited exclusively to isolated memory impairment.

However, none of the three subclassifications alone proved to have significant relative predictive power in the prediction of dementia. Only a relatively small number of subjects met the original criteria for each subset of MCI and thus the sensitivities of the respective subsets in the detection of dementia were very low. As a result of poor sensitivity, only a small proportion of subjects developing future dementia will be detected and given examination or treatment. The main proportion of subjects developing future dementia would remain unrecognized and not be given intervention if these criteria are applied.

The annual conversion rate of 'MCI-amnestic' to dementia obtained in our study falls within the range of results published for small clinical samples to date (10–15%) (Petersen *et al.* 2001). However, similarly to Ritchie *et al.* (2001) in their population-based sample, we found only a small percentage of 'MCI-amnestic' cases in our non-demented population and a poor sensitivity of 'MCI-amnestic' criteria. Population-based validation studies have thus far failed to demonstrate a predictive validity (with an acceptable sensitivity and specificity) of 'MCI-amnestic'. Thus, population-based studies are of utmost importance in the evaluation of diagnostic criteria for mild cognitive impairment.

However, the results of our study indicate that all three subsets of MCI together are required to obtain significant predictive power for the onset of dementia. Thirty-six per cent of all subjects in which dementia was diagnosed at follow-up had met the diagnostic criteria of one of the three subsets of MCI as defined by the Current Concepts in MCI Conference at the baseline assessment. Since our follow-up period was only 3 years, results might be different after further follow-ups. When following subjects for a longer period of time, also a single subset of MCI could possibly achieve significant predictive power.

However, our study suggests that the predictive validities of the three subsets of MCI improve if the criterion of a subjective decline in cognitive functioning reported by the subjects or significant others is excluded from the diagnostic criteria for MCI. 'MCI-multiple domains slightly impaired-modified' was the only subset of MCI that yielded a significant relative predictive power for onset of dementia. The highest relative predictive power and the best relation of sensitivity and specificity were found for all three modified subsets taken together.

In fact, the predictive power of subjective memory complaints has been questioned in view of both their multiple determinants (e.g. personality, depression and anxiety) and situational variables affecting the interaction between clinicians and patients (Jorm & Christensen, 2001). Based on the results of their empirical study, Jorm *et al.* (1997) conclude that it is inappropriate to include a subjective report of cognitive decline in diagnostic criteria for mild cognitive impairment. Neuropsychological screening at the primary care level could detect persons at risk even if they do not report subjective complaints. Cases of mild cognitive impairment could be missed, if the elderly persons do not admit cognitive impairment and no third party information can be obtained. On the other hand, the absence of a subjective memory complaint in people with demonstrable cognitive impairment due to multiple determinants (CIND) could characterize a subgroup of elderly people who still have the potential for cognitive improvement (Palmer *et al.* 2002). However, in persons without demonstrable cognitive impairment, subjective memory deficits may have prognostic value in the early detection of future dementia. This may apply especially to highly educated elderly people, owing to the ceiling effect of some cognitive tests (Jonker *et al.* 2000).

Based on our results it would be premature to suggest that in older subjects who show

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evidence of objective cognitive impairment the diagnostic criterion of a subjective cognitive decline has no additional predictive power. In our study the use of modified criteria for MCI (all three subclassifications together) (i.e. no need for subjective complaint) is associated with a higher diagnostic sensitivity but also with a reduction in diagnostic specificity and PPP.

Furthermore, sensitivity decreased and specificity increased for MCI (all three subclassifications together) if the level of MCI severity was 1·5 or 2·0 S.D.s compared to S.D. = 1·0.

In total, if a concept for mild cognitive impairment with a high sensitivity is requested, our results suggest that a lower severity level of MCI (S.D. = 1·0) and the modified criteria should be applied. If a concept with high specificity and high PPP is required, a higher severity level of MCI (S.D. = 1·5 or 2·0) and the original criteria (including subjective cognitive complaints) should be applied.

The purpose of the present study was to identify a concept with an optimal relation of sensitivity and specificity in the prediction of dementia. The concept should be specific enough not to detect too many false positives, which would then be given unnecessary medication. The concept should be sensitive enough to detect a meaningful subgroup to which intervention can be applied. Diagnostic criteria with a high sensitivity can serve as a first screening to detect patients in need of further neuropsychological assessment, e.g. at the primary care level. However, the decision on the prescription of medication should be based on highly specific criteria, especially when the medication is very expensive or has side-effects. Thus, the definition of the best proportion of sensitivity and specificity depends on the purpose. However, in addition to having a high conversion rate to dementia, diagnostic criteria of mild cognitive impairment should, ideally, demonstrate a high sensitivity and specificity to be of clinical use.

Our results failed to support the assumption of the Current Concepts in MCI Conference (Petersen *et al*. 2001) that each of the three subsets for MCI is associated with an increased risk of developing a particular type of dementia. Similar to the findings of Brayne *et al*. (1995) most of the cases with mild cognitive impairment developed AD. However, it is a limitation of our study that the diagnosis of dementia types was not supported by neurological examinations, imaging or autopsy. Thus, our differential diagnoses are less accurate than would have been the case in a specialized clinical setting. Moreover, only AD and VD were diagnosed, all other types of dementia such as Lewy body dementia or frontotemporal dementia were subsumed under the single broad category of 'Dementia not further specified'. However, AD and VD are not clearly defined categories and there is still no internationally accepted set of consensus diagnostic criteria for different types of dementia. Vascular and degenerative processes may both contribute to the development of dementia, especially in very old age, and either one or the other type of dementia is diagnosed, depending on the diagnostic tools employed. The traditional view of VD and AD as distinguishable entities is becoming steadily less tenable. Recent reports of overlapping symptomatologies suggest that the validity of the diagnoses is questionable, even if neuroimaging is used (Kalaria & Ballard, 1999; Stewart, 2002).

In order to increase sensitivity and specificity of concepts for MCI, further predictors of decline in subjects with MCI should be identified. Our study is limited by the failure to assess biological markers in order to examine their interactions with sociodemographic and neuropsychological measures in the prediction of dementia. For example, neuropsychological measures in combination with the ApoE genotype (Tierney *et al*. 1996) and atrophy of the medial temporal lobe (Visser *et al*. 1999) have proved to be of better predictive value than any of these variables alone. Further population-based studies are needed to establish the combination of cognitive tests and biological markers with the highest predictive value. Criteria with a high sensitivity and specificity for detecting dementia at an early stage will help to further develop effective pharmacological and behavioural interventions for delaying the onset and progression of the disease.

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