

Mild Cognitive Impairment

Concepts, cut-offs, and clinical relevance

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Just a perfect day

Drink sangria in the park

And then later, when it gets dark

We go home

From "Perfect day" by Lou Reed

Voor Neil, mijn rots in de branding

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Abstract

Mild cognitive impairment (MCI) is a diagnosis frequently used in dementia research and in memory clinics. MCI is meant to identify patients without dementia, but with cognitive decline beyond what is considered normal, and with an increased risk of progressing to dementia. Typically, cognitive test performance 1.5 standard deviations (SD) or more below normal controls is considered impaired. To account better for heterogeneity in etiology and prognosis in MCI, clinical subtypes of MCI have been suggested; MCI with or without memory impairment as one dimension, and impairment in one or more than one cognitive domain as another dimension. The aim of this thesis is to clarify the prognostic value of MCI and MCI subtypes in memory-clinic patients.

All participants in papers I-III were either patients seeking care at the Sahlgrenska memory clinic in Mölndal, or healthy controls examined at the same unit.

Paper I included 317 patients, 55 of whom progressed to dementia. Paper II included 358 patients, 68 of whom progressed to dementia. Paper III included 383 patients, 70 of whom progressed to dementia. All patients included in paper I were also included in papers II and III, all patients included in paper II were also included in paper III.

In paper I, 317 patients were followed for 2 years, and 168 patients were followed for 4-6 years. The probability of a patient progressing to dementia after 2 years was 17%, and 14% after 4-6 years. One-third of the memory-clinic patients did not meet standard criteria for MCI at baseline, and had a reduced probability of progressing to dementia (from 17% to 1% within 2

years and from 14% to 9% after 4-6 years). Meeting standard criteria for MCI only slightly increased the risk of progressing to dementia (from 17% to 26% after 2 years and from 14% to 20% after 4-6 years). Amnesic multi-domain MCI was the only subtype that significantly increased a patient's probability of progressing to dementia (from 18% to 46% after 2 years and from 14% to 37% after 4-6 years). A more liberal MCI cut-off (i.e. 1.0 SD instead of 1.5 SD or 2.0 SD) did not improve the prognostic accuracy of MCI or the MCI subtypes.

In paper II, amnesic multi-domain MCI was associated with a much larger increase in probability of progression to dementia in younger patients under 65 with more than 12 years of education than in other demographic groups, as compared with patients with other subtypes and those who did not meet MCI criteria.

In paper III, cognitive subtypes derived from a latent profile analysis differentiated between patients who two years after baseline progressed to Alzheimer's disease dementia vs. dementia with subcortical vascular features, where the traditional MCI subtypes did not.

In conclusion, a large group of memory-clinic patients do not display significant cognitive impairments and have a very low probability of progressing to dementia. Prognosticating progression to dementia is easier in younger patients with more years of education than in other demographic groups. However, even among younger patients with more years of education, it may be better to use absence of amnesic multi-domain MCI to rule out progression to dementia, than to use presence of amnesic multi-domain MCI to find patients who will progress. Statistically derived cognitive subtypes may separate the risk of AD dementia from the risk of dementia with subcortical vascular features where the established MCI subtypes do not.

Keywords: mild cognitive impairment, cognition, dementia, Alzheimer's disease, memory clinic, diagnostic assessment.

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Sammanfattning på svenska

Lindrig kognitiv störning, eller mild cognitive impairment (MCI) på engelska, är en diagnos framtagen för att på ett tidigt stadium identifiera personer som har en förhöjd risk för att utveckla demens. Lindrig kognitiv störning kan delas in i undergrupper baserat på vilken sorts kognitiv nedsättning en patient har, samt om patienten har flera olika sorters nedsättningar eller inte. Generellt brukar en nedsättning i förmågan att lära in och komma ihåg nytt material, en minnesstörning, vara förknippad med en högre risk för att utveckla demens jämfört med andra sorters nedsättningar, särskilt om minnesnedsättningen framträder i kombination med andra sorters kognitiva nedsättningar. Flera olika nivåer av nedsättning kan användas för att bedöma om en person har lindrig kognitiv störning eller inte, och ett syfte med den här avhandlingen var att utvärdera om någon nivå är bättre än de andra. Ett andra syfte var att undersöka om den ökade risken för framtida demens som lindrig kognitiv störning innebär är lika stor bland äldre och yngre personer, och bland personer med högre och lägre utbildningsnivå. Ett tredje syfte var att med hjälp av statistiska metoder undersöka vilka kognitiva undergrupper som faktiskt är vanliga bland patienter som söker vård på en minnesmottagning, eftersom de undergrupper som oftast används är skapade utifrån teoretiska antaganden.

Studierna i avhandlingen är baserade på undersökningar av patienter vid minneskliniken på Sahlgrenska universitetssjukhuset, och friska kontrollpersoner. Studierna visade att patienter på en minnesmottagning som inte uppvisar tydliga kognitiva nedsättningar jämfört med friska äldre personer sannolikt inte utvecklar demens inom de närmaste åren. Bland patienter på en minnesmottagning är det lättare att ge en korrekt prognos till dem som är yngre än 65 och har mer än 12 års utbildning, än till andra patienter. Undergrupper framtagna med hjälp av statistiska metoder är bättre än de teoretisk framtagna undergrupperna på att skilja mellan patienter som kommer att utveckla demens orsakad av Alzheimers sjukdom och demens orsakad av småkärlsjukdom.

List of papers

This thesis is based on the following studies, referred to in the text by their Roman numerals.

- I. Göthlin, M., Eckerström, M., Rolstad, S., Wallin, A., Nordlund, A.
Prognostic accuracy of Mild Cognitive Impairment subtypes at different cut-off levels
Dementia & Geriatric Cognitive Disorders 2017; 20: 121-133.
- II. Göthlin, M., Eckerström, M., Rolstad, S., Kettunen, P., Wallin, A.
Better prognostic accuracy in younger MCI patients with more years of education
Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 2018; 10; 402-412.
- III. Göthlin, M., Eckerström, M., Lindwall, M., Rolstad, S., Eckerström, C., Jonsson, M., Kettunen, P., Svensson, J., Wallin, A.
Latent cognitive profiles differ between incipient Alzheimer's disease and dementia with subcortical vascular lesions in a memory clinic population
Manuscript.

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Abbreviations

AD	Alzheimer's disease
ADL	Activities of daily living
ADNI	Alzheimer's disease neuroimaging initiative
aMCI-md	Amnesic multi-domain mild cognitive impairment
aMCI-sd	Amnesic single-domain mild cognitive impairment
APOE	Apolipoprotein
A β ₁₋₄₂	β -amyloid protein
BNT	Boston naming test
CDR	Clinical dementia rating
CI	Confidence Interval
CIND	Cognitive Impairment No Dementia
COWAT	Controlled oral word association test
CUI-	Clinical utility index for negative test results
CUI+	Clinical utility index for positive test results
cVaD	Cortical vascular dementia
DSM	Diagnostic and Statistical Manual of Mental Disorders
FN	False negative observations
FP	False positive observations
FU-time	Follow-up time
GDS	Global Deterioration Scale

HSD	Honestly significant difference
I-FLEX	Investigation of flexibility
ICD	International Classification of Diseases
LPA	Latent Profile Analysis
LR-	Likelihood ratio for negative test results
LR+	Likelihood ratio for positive test results
m	Mean
MCI	Mild cognitive impairment
MixD	Mixed dementia, in this thesis a mix of AD and SVD
MMSE	Mini mental state examination
naMCI-md	Non-amnestic multi-domain mild cognitive impairment
naMCI-sd	Non-amnestic single-domain mild cognitive impairment
NPV	Negative predictive value
P-tau	Phosphorylated tau protein
PaSMO	Parallel serial mental operations
PPV	Positive predictive value
RAVLT	Rey auditory verbal learning test
RCF	Rey complex figure
SD	Standard deviation
Sens.	Sensitivity
Spec.	Specificity

STEP	Stepwise comparative status analysis
SVD	Subcortical vascular dementia
T-tau	Total tau protein
TMT	Trailmaking test
TN	True negative observations
TOMC	Translational outpatient memory clinic
TP	True positive observations
VaD	Vascular dementia
VaD-S	Dementia with subcortical vascular features (MixD + SVD)
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

Definitions in short

Biomarker	A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.
Dementia	A syndrome characterized by a decline in cognitive functions severe enough to interfere with independence in daily life. Can have different causes.
Diagnosis	Disease classification based on signs and symptoms. Typically used to guide treatment decisions and to give prognostic estimates.
Episodic memory	Memory of personally experienced events, in dementia research usually operationalized as the delayed recall of word lists or stories.
Etiology	Cause or causes of a disease.
False negative	An incorrect indication of the absence of a target condition, based on a binary diagnostic test, i.e. a sick person incorrectly identified as healthy.
False positive	An incorrect indication of the presence of a target condition, based on a binary diagnostic test, i.e. a healthy person incorrectly identified as sick.
Mild cognitive impairment	A syndrome characterized by a recent decline in cognitive functions greater than that of comparable peers, and different from mild dementia in that activities of daily life are intact or only minimally disturbed.
Memory clinic	Secondary-care facility, usually outpatient, where people concerned about their cognitive

functioning and progression to dementia are remitted.

Negative likelihood ratio	Describes the change in odds of progressing to dementia for a patient with a negative test result, as compared with the odds among all patients.
Negative predictive value	The number of true negatives divided by the sum of the number of false negatives and true negatives, or the ratio of true negative test results to all negative test results.
Positive likelihood ratio	Describes the change in odds of progressing to dementia for a patient with a positive test result, as compared with the odds among all patients.
Positive predictive value	The number of true positives divided by the sum of the number of true positives and false positives, or the ratio of true positive test results to all positive test results. The same as post-test probability for a positive test.
Sensitivity	True positive rate, the number of true positive observations divided by the number of positive observations.
Sign	A clinical manifestation of a disease or disorder observed by a clinician.
Specificity	True negative rate, the number of true negative observations divided by the number of negative observations.
Symptom	A clinical manifestation of a disease or disorder observed by the patient.
Syndrome	A condition characterized by a group of signs and/or symptoms occurring together.

True negative

A correct indication of the absence of a target condition, based on a binary diagnostic test, i.e. a healthy person correctly identified as healthy.

True positive

A correct indication of the presence of a target condition, based on a binary diagnostic test, i.e. a sick person correctly identified as sick.

1. Introduction

Mild cognitive impairment (MCI) is a clinical syndrome, different from normal aging in that it entails a recent decline in cognitive function greater than that of comparable peers, and different from mild dementia in that activities of daily life (ADL) are intact or only minimally disturbed. Dementia is also a syndrome, characterized by multiple cognitive deficits severe enough to cause impairment in occupational or social functioning [1]. In 2015, the estimated number of people suffering from dementia worldwide was 47 million, an increase of 11 million since 2010. The worldwide yearly costs of dementia have been estimated at 818 billion dollars in 2015. The majority of the costs occur in the social sector and in informal care [2]. Dementia is among the top 10 conditions contributing to disability worldwide [3].

Alzheimer's disease (AD) is the most common cause of dementia [4]. Clinically, AD dementia is typically characterized by severely impaired episodic memory, with impaired test results on delayed recall and recognition. In AD dementia, impairments in naming ability, verbal fluency, executive functions, and visuospatial functions are also commonly observed [5].

Aggregation of intracellular tau protein in neurofibrillary tangles and extracellular aggregation of beta amyloid protein into plaques can be observed on autopsy [6] and are regarded as the cause of AD [7]. Measuring total tau (T-tau), phosphorylated tau (P-tau), and β -amyloid protein ($A\beta_{1-42}$) in cerebrospinal fluid (CSF) provides an in vivo estimate of the underlying pathologies, and can help differentiate healthy controls from persons with both incipient [8] and manifest AD dementia [8,9]. As of yet, no treatments targeting amyloid plaques have reached clinical endpoints, and only symptomatic treatments are available for AD dementia.

Another common cause of dementia is vascular disease, e.g. stroke, resulting in vascular dementia (VaD). At the Sahlgrenska memory clinic (the clinical setting for this thesis), stroke related VaD is very uncommon. Subcortical vascular disease, or small vessel disease, in which blood flow in deep brain tissue is compromised, leading to white-matter lesions and micro infarctions, is a sometimes overlooked vascular condition [10], but is also an important cause of dementia [11]; subcortical vascular dementia (SVD). In many cases, subcortical vascular lesions and AD pathology are both present and both contribute to the emergence of cognitive symptoms and subsequent

dementia. Incipient SVD is separable from non-progressing MCI using neurofilament light, and has a different profile of T-tau, P-tau, and A β ₁₋₄₂ than incipient AD dementia [12].

Carrying the apolipoprotein E (APOE) ϵ 4 allele is the greatest known genetic risk factor for sporadic AD dementia [13]. Carrying the APOE ϵ 4 allele is also associated with an increased risk for cerebral amyloid angiopathy, common in elderly people with dementia and associated with white-matter lesions [14].

Other dementia disorders include Lewy-body dementia, and frontotemporal dementia, but a dementia syndrome can be caused by almost any disease or injury affecting the brain (e.g. HIV, Parkinson's disease, head trauma, substance abuse) [1].

1.1.1 Mild cognitive impairment

In 1982, Reisberg used the term 'mild cognitive decline' [15], and later 'mild cognitive impairment' [16], when describing stage 3 of the Global Deterioration Scale (GDS), meant as a description of global clinical severity of the stages of Alzheimer's disease. In 1999, Petersen proposed criteria for MCI [17], where memory complaints and abnormal memory for age were mandatory for the category of MCI. Table 1. Other cognitive domains were not yet mentioned, other than stipulating "normal general cognitive function". Here, the first mention of a cut-off for impaired memory was made in the context of MCI, albeit descriptive and not normative. A cohort of patients with MCI were reported to perform around 1.5 standard deviations below the level of age-matched and education-matched controls on a test of episodic memory.

In 2001, Petersen [18] stated that

“All individuals who present clinically with mild cognitive symptoms may not share the same fate ultimately. Some may go on to develop AD, while others may progress to another dementia. It is possible that some of the subjects will never progress to any significant extent. This broad group of individuals with mild cognitive complaints could be considered as having MCI. Recognizing that there are multiple sources of heterogeneity in such a classification, it is desirable to further specify criteria for subsets of MCI.”

recognizing that the general phenotype of MCI may be too inclusive for the purpose of identifying patients likely to progress to AD dementia. This was one of the reasons for the introduction of four syndromal phenotypes, or

subtypes, of MCI; MCI with or without memory impairment as one dimension, and impairment in one or more than one cognitive domain as another dimension, later formalized by the International Working Group on Mild Cognitive Impairment [19,20]. The new classification used the categories amnesic single domain MCI (aMCI-sd), amnesic multi-domain MCI (aMCI-md), non-amnesic single domain MCI (naMCI-sd), and non-amnesic multi-domain MCI (naMCI-md).

Still, no strict cut-off for MCI was recommended, although 1.5 standard deviations was mentioned again. In 2009, Jak et al. [21] sought to characterize various diagnostic approaches better. They described four operationalizations of MCI; historical criteria (one or more memory test scores 1.5 SD below age appropriate norms), typical criteria (one or more test scores 1.5 SD below age-appropriate norms), comprehensive criteria (two or more test scores 1.0 SD or more below age-appropriate norms), and liberal criteria (one test score 1.0 SD or more below age-appropriate norms), all based on neuropsychological test results. Table 2.

In the fifth version of the Diagnostic and Statistical Manual of Mental Disorders [22], regardless of etiology, the terms MCI and dementia were replaced with Mild and Major Neurocognitive Disorder, respectively. The suggested range for Mild neurocognitive disorder, equivalent to MCI, was described as typically in the range of 1.0–2.0 SD below appropriate norms, in one or more cognitive domains. Primarily subtyped according to known or presumed etiology, "on the basis of a combination of time course, characteristic domains affected, and associated symptoms." Further criteria incorporating biomarkers intended to identify prodromal AD have been suggested, but without making use of the subtype paradigm. In 2011, Albert et al. [23] suggested "Objective evidence of impairment in one or more cognitive domains, typically including memory". In 2014, Dubois et al. [24] suggested episodic memory impairments, without mention of other cognitive domains.

Criteria for the diagnosis of mild cognitive disorders resulting from vascular disease (vascular cognitive impairment, VCI) have recently been proposed by the International Society of Vascular Behavioural and Cognitive Disorders (VASCOG) [25], with impairments in at least one of seven cognitive domains, either with "test performance ... typically in the range between 1 and 2 standard deviations below appropriate norms (or between the 3rd and 16th percentiles)", or equivalent level as judged by a clinician, in combination with evidence of a predominantly vascular etiology. Published consensus guidelines have suggested a brief neuropsychological test battery

to diagnose VCI [26], and the importance of studying etiological VaD subtypes such as subcortical small vessel disease have recently been highlighted [27]. However, there is to date no broad consensus concerning syndromal presentations in mild stages of either AD or VaD, or if MCI should be diagnosed based on neuropsychological test results or clinical judgment, or what cut-off should be employed if neuropsychological test results form the basis of the diagnosis.

Table 1. Clinical criteria for the MCI syndrome

	Petersen, 1999 [17]	Winblad, 2004 [20]	Albert, 2011 [23]	DSM-5, 2013 [22]
Criteria				
Self-reported or informant-reported memory complaint	X			
Self-reported or informant-reported cognitive complaint		X	X	X
Objective memory impairment	X			
Objective cognitive impairment		X	X	X
Essentially preserved general cognitive functioning	X			
Preserved independence in functional abilities	X	X	X	X
No dementia	X	X	X	X

Abbreviations: X, criterion required for diagnosis; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th edition.

Table modified from Petersen, 2014 [28].

Table 2. Operationalizations of MCI criteria

	Historical criteria	Typical criteria	Comprehensive criteria	Liberal criteria	Conservative criteria
Cognitive domain	Memory	Any	Any	Any	Any
n of tests under cut-off required for MCI	≥1	≥1 per domain	≥2 per domain	≥1 per domain	≥1 in ≥2 domains
Cut-off (SD)	1.5	1.5	1	1	1.5

Abbreviations: n, number; MCI, mild cognitive impairment; SD, standard deviation.

Operationalizations adapted from Jak et al. [21].

In parallel with the development of the MCI concept, several other similar concepts have been described. Kral's state of "benign senescent forgetfulness" was characterized by the inability to recall "relatively unimportant data", accompanied by lower scores on a memory test as compared with their age-group, between normal memory function and 'malignant senescent forgetfulness', which today might be called dementia or major neurocognitive disorder [29]. In 1986, a working group suggested a new diagnostic term for a decline in memory in healthy older individuals, and called it Age-Associated Memory Impairment [30]. Memory test performance at least 1 SD below the mean of young adults was one of the criteria, in contrast to Kral's concept, which compared individuals with others of the same age.

In the ICD-10 research criteria presented in 1993 [31], Mild Cognitive Disorder was introduced, and comprised difficulties in learning, recall, concentration, thinking, or language, and abnormal performance on neuropsychological tests, as well as 'evidence and/or history of cerebral disease, damage or dysfunction, or of systemic physical disorder known to cause cerebral dysfunction'. This category was intended to capture persons with significant cognitive decline who did not have dementia.

In 1994, Levy et al. proposed the concept of Aging-associated cognitive decline (AACD) [32], intended to identify persons who did not fulfill criteria for Mild Cognitive Disorder. The criteria were similar, but instead of the *presence* required the *absence* of cerebral disease, damage, or dysfunction or of systemic physical disorder known to cause cerebral dysfunction. Cognitive

performance at least 1 SD below appropriate norms, in one of the cognitive domains memory and learning; attention and concentration; thinking, language, or visuospatial functioning [32], was required.

In 1997, another competing concept was introduced by Graham et al. They called it cognitive impairment, no dementia, or CIND [33]. CIND was based on the population study The Canadian Study of Health and Aging, and was diagnosed in the absence of dementia, and consisted of the sub-categories delirium, chronic alcohol and drug use, depression, psychiatric illness, mental retardation, circumscribed or limited memory impairment, and "other" cognitive impairments.

MCI is by far the most commonly used term according to a search in Title/Abstract on PubMed. Table 3.

Table 3. PubMed search for MCI and related terms (2019-03-19)

Term, in Title/Abstract on PubMed.gov	n
Mild cognitive impairment	14350
Mild cognitive impairment OR MCI	21696
Cognitive impairment, no dementia OR CIND	361
Senescent forgetfulness	21
Age-Associated Memory Impairment OR AAMI	648
Mild cognitive disorder	58
Ageing-associated cognitive decline OR AACD	101
Mild neurocognitive disorder	113

Abbreviations: MCI, mild cognitive impairment; CIND, cognitive impairment, no dementia; AAMI, age-associated memory impairment; AACD, aging-associated cognitive decline.

1.2 Prognostic accuracy of MCI

Early clinical studies suggested that MCI defined using the original Petersen criteria from 1999 [17] (amnesic MCI; aMCI) in the majority of cases would progress to AD dementia [17,34], and MCI has been suggested as a valid target population for treatment trials [18,35]. A later meta-analysis reported a yearly progression rate of 10% and a cumulative progression to all-cause

dementia of 39% in specialist memory clinic settings [36] using the Petersen MCI criteria from 1999 [17]. Corresponding figures in community samples with MCI were an annual progression rate of 5% and 22% total progression to all-cause dementia. The mean observation time for the combined clinical and community samples was 4.6 years (SD 2.1). Farias et al. reported a yearly conversion rate of 13% in a memory clinic sample and 3% in a community sample [37], both groups fulfilling the updated MCI criteria from 2004 [20]. The annual conversion rate to dementia may decrease over time [34,36,38], perhaps reflecting the heterogeneity of MCI [39]; some MCI patients have incipient dementia and progress quickly, others may have other underlying reasons for their cognitive impairments and will not progress to dementia; some may even improve over time [38].

Many studies published on the topic of predicting dementia in memory-clinic patients with MCI have not reported sensitivity, specificity, and related parameters, nor true positive, false positive, true negative, and false negative observations [40-51], making it difficult to say how well the construct of MCI actually performs as a predictor of dementia.

Visser et al. reported sensitivity of 66% and a specificity of 73% for progression to AD dementia after 5 years for aMCI [52], and a sensitivity of 78% and a specificity of 74% also for aMCI with progression to AD dementia after 5 years, in a different sample [53].

1.2.1 Prognostic accuracy of MCI subtypes

A few papers reporting the prognostic accuracy of all four established MCI subtypes in memory-clinic samples have been published. Generally, aMCI-md has had the highest prognostic accuracy. Various cut-off levels have been used to diagnose MCI subtype, but have not been compared with each other regarding prognostic accuracy. Visser and Verhey [53] used Petersen's criteria for aMCI [17], with aMCI-sd and aMCI-md pooled, setting the cut-off for impairment 1.5 SD below the mean of a reference group. They followed 320 patients over 5 years. They reported a sensitivity of 78% and a specificity of 74% for AD dementia at follow-up for the aMCI group. Sensitivity and specificity for the other subtypes were not reported. Rasquin et al. [51] followed 118 memory-clinic patients without dementia for 2 years. They defined cognitive impairment as a score lower than the 10th percentile of scores in a reference group, equivalent to 1.28 SD, or a Mini-Mental State Examination (MMSE) score lower than 80% of the maximum score per item used. They reported that aMCI-md had a sensitivity of 65% and a specificity of 62% for detecting dementia, and the other categories performed poorly,

with very low sensitivities. However, using scores derived from the MMSE, which is insensitive to subtle cognitive impairments [54], may have affected the results. Nordlund et al. reported a sensitivity of 80% and a specificity of 79% for progression to all-cause dementia after 2 years for aMCI-md, in an earlier and smaller version of the patient sample used in this thesis [55].

1.2.2 Demographic differences in prognostic accuracy

Visser et al. reported that the positive predictive values for various definitions of MCI in predicting AD dementia 5 years later were higher in patients older than 65 years [52], and attributed their findings to a higher prevalence of pre-dementia in the older group. The results are somewhat conflicting and can also be interpreted as a better prognostic accuracy among younger participants. In a larger patient sample from the same memory clinic, Visser et al. [53] reported good prognostic accuracy for subsequent AD dementia only for aMCI in patients 70–85 years, compared with patients under 55 and between 55 and 69. Thus, it is unclear how patient age influences the prognostic accuracy in MCI. However, both neuritic plaques and neurofibrillary tangles measured post-mortem [56,57], and in-vivo CSF AD-biomarkers [58] are more weakly associated with an AD diagnosis in older people, indicating an increasing difficulty to distinguish between different states with increasing age. To the best of our knowledge, the prognostic accuracy in different education groups or in age and education levels simultaneously has not been investigated in clinical samples.

1.2.3 Data-driven subtypes of MCI

The MCI subtypes as suggested by Petersen [19] and Winblad et al. [20] are top-down categories, based on clinical experience and observation. As an alternative approach, several researchers have attempted to create cognitive subgroups of MCI patients based on data, using various data-driven methods of analysis.

Using various types of cluster analysis, several studies have reported between 3 or 4 cognitive clusters in memory-clinic patients. Some of the studies only included cross-sectional data [59-61]. Damian et al. [62] found an amnesic-executive cluster to predict progression to AD dementia best, Edmonds et al. [63] and Bondi et al. [64], both studying the ADNI cohort, found a dysexecutive and a dysexecutive/mixed class to predict progression to all-cause dementia best.

Four studies using latent profile analysis (LPA) to find latent cognitive subtypes in memory-clinic patients have been published. One study was

cross-sectional and also included neuropsychiatric features and functional impairments in the model [65]. The other three studies reported 3-5 latent classes [66-68]. Eppig et al. found a mixed MCI class to be most predictive of progression to all-cause dementia [68]. Köhler et al. [66] found a primary non-memory impairment class to have the highest prognostic accuracy for progression to all-cause dementia, and McGuinness et al. [67] found a class with deficits in multiple domains, including memory, to best predict progression to all-cause dementia. McGuinness et al. also compared to MCI subtypes using typical criteria [21] (Table 2). Of the established MCI subtypes, aMCI-md performed best, but was outperformed by their LPA-derived multiple deficits class. Eppig et al. [68], Köhler et al. [66], and McGuinness et al. [67] did not report sensitivity and specificity for progression to dementia.

None of the above studies have reported true positives, false positives, true negatives, false negatives, sensitivities, or likelihood ratios, and none have investigated progression to dementia with subcortical vascular features.

1.2.4 Prognostic accuracy of biomarker-based classifications

Prognostic accuracy of neurochemical biomarkers is typically evaluated in patients who fulfill criteria for MCI (Table 4), either the Petersen criteria from 1999 [17], which require memory impairments, or later criteria, which may also base the MCI categorization on impairments in other cognitive domains.

T-tau, P-tau, and A β ₁₋₄₂ can discriminate between manifest AD dementia and healthy controls with high sensitivity and specificity [69]. However, discriminating between incipient AD dementia and stable MCI, i.e. giving a reliable prognosis to a patient, is more difficult. As can be seen in Table 4, most attempts to predict progression to AD dementia using CSF biomarkers fail to achieve a simultaneously high sensitivity and specificity, even though all samples consist of only patients with MCI, and some use optimized cut-offs derived from the sample under study. In a review of studies predicting progression to probable AD dementia, Mitchell et al. found that CSF biomarkers, in general, slightly increased the positive predictive value, and decreased the negative predictive value as compared with clinical assessment alone [70].

There is a difference between using pre-defined and optimized cut-offs. Optimized cut-offs, obtained typically using ROC analysis, which produce the optimal cut-off value to distinguish between two groups on a continuous

variable, risk overestimating the prognostic or diagnostic accuracy of the marker investigated. A pre-defined cut-off, either derived from a previous publication using a different sample, or derived from a training data-set and tested in a validation data-set, is preferable.

Table 4. Sensitivity and specificity of CSF AD biomarkers for progression to AD dementia

Study	n	Marker	Sens./spec.	FU-time	Cut-off	Sample
Brys, 2009 [71]	65	P-tau	73/83	2 years	1	aMCI
Brys, 2009	65	T-tau	68/91	2 years	1	aMCI
Hansson, 2007 [41]	131	\square A β ₁₋₄₂ /A β ₁₋₄₀	87/78	4-6 years	1	aMCI
Hansson, 2007	131	A β ₁₋₄₂	93/53	4-6 years	1	aMCI
Herukka, 2005 [46]	78	A β ₁₋₄₂	70/76	4 years	1	MCI
Herukka, 2005	78	A β ₁₋₄₂ /P-tau	61/88	4 years	1	MCI
Herukka, 2005	78	P-tau	87/60	4 years	1	MCI
Herukka, 2005	78	T-tau	87/56	4 years	1	MCI
Hansson, 2006 [72]	134	A β ₁₋₄₂ & T-tau	95/83	4-6 years	2	aMCI
Hertze, 2010 [73]	159	A β ₁₋₄₂	90/71	4.7 years	2	MCI
Hertze, 2010	159	A β ₁₋₄₂ & T-tau	88/82	4.7 years	2	MCI
Hertze, 2010	159	P-tau	42/90	4.7 years	2	MCI
Hertze, 2010	159	T-tau	73/77	4.7 years	2	MCI
Mattsson, 2009 [74]	750	A β ₁₋₄₂	79/65	≥ 2 years	2	MCI
Mattsson, 2009	750	A β ₁₋₄₂ , T-tau & P-tau	83/72	≥ 2 years	2	MCI
Mattsson, 2009	750	P-tau	84/47	≥ 2 years	2	MCI
Mattsson, 2009	750	T-tau	86/56	≥ 2 years	2	MCI
Prestia, 2013	57	A β ₁₋₄₂	79/27	3 years	2	aMCI

ADNI [75]

Prestia, 2013 ADNI	57	T-tau	46/61	3 years	2	aMCI
Prestia, 2013 TOMC [75]	36	A β_{1-42}	94/50	2.2 years	2	aMCI
Prestia, 2013 TOMC	36	T-tau	61/83	2.2 years	2	aMCI
Vos, 2013 [76]	61	A β_{1-42}	55/71	2 years	2	naMCI
Vos, 2013	130	A β_{1-42}	75/58	2 years	2	aMCI
Vos, 2013	61	T-tau	60/78	2 years	2	naMCI
Vos, 2013	130	T-tau	74/61	2 years	2	aMCI
Vos, 2013	61	A β_{1-42} /T-tau	90/54	2 years	2	naMCI
Vos, 2013	130	A β_{1-42} /T-tau	98/38	2 years	2	aMCI

Abbreviations: Sens., sensitivity; spec., specificity; A β_{1-42} , β -amyloid protein; P-tau, phosphorylated tau protein; T-tau, total tau protein; ADNI, Alzheimer's disease neuroimaging initiative; TOMC, Translational outpatient memory clinic; FU-time, follow-up time; MCI, mild cognitive impairment; aMCI, amnesic mild cognitive impairment; naMCI, non-amnesic mild cognitive impairment.

Cut-off: 1 means that the optimal cut-off value for separating progressing and non-progressing patients was found and used in the same data. Cut-off: 2 means that the cut-off value for separating progressing and non-progressing patients was pre-defined, either taken from the literature or derived from other data, e.g. by finding the optimal cut-off value for separating healthy controls from patients with manifest dementia. When combinations are shown, they are the best performing combinations from each paper.

2. Aim

The objective of this thesis is to clarify the prognostic value of MCI and MCI subtypes in memory-clinic patients.

- The aim of paper I was to evaluate the prognostic accuracy of three different cut-off levels for classifying MCI and MCI subtypes in relation to diagnosis of dementia syndrome after 2 and 4–6 years.
- The aim of paper II was to investigate the influence of years of age and education on the prognostic accuracy of MCI subtypes over a 2-year period.
- The aim of paper III was to create data-driven individual-based cognitive subtypes using LPA and investigate the derived classes not only in terms of conversion to AD dementia, but also in terms of conversion to vascular dementia of the subcortical type.

3. Patients and Methods

3.1 Participants

All participants were patients at the Sahlgrenska memory clinic, or healthy controls, and included in the prospective Gothenburg MCI study [38]. Consecutive patients were invited to participate in the Gothenburg MCI study if they were between 40 and 79 years of age and presented with self-reported and/or informant-reported cognitive decline with a duration of at least 6 months, without obvious relation to somatic or psychiatric disorders or trauma. Healthy control participants were recruited mainly from information meetings about dementia and senior-citizen organizations, and were included using the same criteria, but without self-reported or observed cognitive decline.

Examinations in the Gothenburg MCI study included methods from various modalities. The cognitive modality consisted of neuropsychological testing comprising speed and attention, learning and episodic memory, visuospatial functions, language functions, and executive functions. Further, blood and CSF were sampled, and all participants underwent brain magnetic resonance imaging examinations.

3.2 Diagnostic procedures

In the Gothenburg MCI study, the Global Deterioration Scale (GDS) [15,77] was used to determine the cognitive stage of the patients. The GDS describes seven stages, from cognitively and functionally normal (GDS 1), to very severe cognitive decline or severe dementia (GDS 7); in the Gothenburg MCI study GDS 1 (equivalent to cognitively healthy); GDS 2 (equivalent to very mild or subjective cognitive decline); GDS 3 (equivalent to MCI); and GDS 4 (equivalent to mild dementia) were used [38]. Table 5.

In the Gothenburg MCI study operationalization, GDS comprised the MMSE [78], the Clinical Dementia Rating (CDR) [79], Comparative Status Analysis (STEP) [80], and Investigation of Flexibility (I-FLEX), which is a short form of the executive interview EXIT [81]. Table 5.

Table 5. Rating on the global deterioration scale (GDS) in the Gothenburg MCI study

	STEP	I-FLEX	CDR	MMSE
GDS 1 - cognitively healthy	0	0	≤1 x 0.5	≥29
GDS 2 - very mild or subjective cognitive impairment	0	<3	≤1 x 0.5	≥28
GDS 3 - MCI	≥1	≥3	>1 x 0.5	≥26
GDS 4 - mild dementia	>1	>3	>1.0	≤25

Abbreviations: GDS, Global Deterioration Scale; STEP, Stepwise Comparative Status Analysis; I-FLEX, Investigation of flexibility; CDR, Clinical Dementia Rating; MMSE, Mini Mental State Examination; MCI, mild cognitive impairment.

For GDS 2, cognitive complaints reported in clinical interview are mandatory.

STEP combines neurologic and psychiatric examination methods and relies on observations made by a physician. It comprises 50 common dementia symptoms, and aims to determine a patient’s brain regional symptom profile [80]. Eight items from the STEP tool (item 13. memory disturbance, 14. disorientation, 15. reduced capacity for abstract thinking, 16. visuospatial disturbance, 17. poverty of language, 18. sensory aphasia, 19. visual agnosia, and 20. apraxia) associated with dementia in general were used in the GDS assessment. In an inter-rater reliability analysis of the STEP [82], items 13-17 and item 20 had kappa >0.8, item 19 had kappa 0.66, and item 18 had kappa 0.4).

The CDR [79,83] is a standardized clinical interview conducted with the patient and an informant. It covers memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care. In the Gothenburg MCI study, a simplified version of CDR was used, where the rater used the clinical and anamnestic information available to score, however not results from the neuropsychological test battery.

The MMSE [78] test was originally intended as a cognitive status test in psychiatry patients, and is frequently used in dementia and MCI research. The MMSE tests orientation, immediate recall, attention, delayed recall, language, and copying of pentagons.

I-FLEX is an assessment of executive function, with 6 parts: a number-letter task (1A to 5E), a word fluency task (≥10 words in one minute considered

unimpaired), anomalous sentence repetition (5 sentences), an interference task (the word 'blue' in black letters, the patient has to correctly state the colour of the letters), 2 Luria hand sequences, and a counting task.

For patients with GDS 4, the following criteria were used for an etiological dementia diagnosis: Alzheimer's disease was diagnosed using the 1984 National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria for AD [84]. Vascular dementia forms are either SVD or cortical vascular dementia (cVaD). SVD was diagnosed using the Erkinjuntti criteria [85], and cVaD using the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria [86].

To date, no patients in the Gothenburg MCI study have progressed to a mix of AD and cortical vascular dementia (cVaD) [38]. A MixD diagnosis in the Gothenburg MCI study might be either a combination of AD and SVD or AD and cVaD, although the latter has been rare (one patient with AD/cVaD and two with AD and both cVaD and SVD at baseline, none among the converters). In both cases, the patient must also fulfill clinical AD symptomatology according to established criteria [84] (i.e., parietotemporal lobe syndrome). Additionally, white-matter changes must be either (1) moderate/severe, with no predominant frontal lobe syndrome or (2) mild, and in combination with a marked frontal lobe syndrome (in addition to the parietal lobe syndrome).

3.3 Neuropsychological testing

In the Gothenburg MCI study, a neuropsychological test battery was administered to patients and controls in each biennial study round. Some tests have been removed, added, or had their versions changed in the course of the study, often based on clinical considerations. A full description of the tests and the changes to the test battery over time is beyond the scope of this thesis.

The test battery was administered by a licensed psychologist, or a psychologist-in-training supervised by a licensed psychologist during two sessions of 1 to 2 hours. The test order was standardized, and verbal tests were varied with nonverbal in each session. Tasks administered between immediate and delayed recall on the memory tests that should not influence performance on delayed recall were chosen.

The test battery was designed to cover the cognitive domains speed and attention, learning and episodic memory, visuospatial functions, language functions, and executive functions. In the full battery, several cognitive subfunctions were assessed within each cognitive domain.

Episodic memory. The Rey Auditory Verbal Learning test (RAVLT) is a word-recall test considered to have a high test-retest reliability [87,88]. A 15-item word-list is read to the patient five times, each time the number of recalled items is registered. Next, a 15-item distraction list is read to the patient, and then the patient is asked to repeat the original list. After 30 minutes of distraction (i.e. other tests) delayed recall of the original items are registered, followed by a recognition task. The delayed recall trial was used in papers I-III. In the Wechsler's logical memory test (WLM) [89] the patient is read two short stories and asked to repeat them immediately and after 30 minutes of distraction. The delayed recall trial was used in papers I and II.

Speed and attention. In the Digit Symbol test (from the Wechsler Adult Intelligence Scale (WAIS), revised [90] or WAIS-III [91]), the patient enters symbols corresponding to numbers according to a symbol key. Number of correct items after 90 (WAIS-r version) or 120 seconds (WAIS-III version) are recorded. Both versions were used in paper I.

In the Trailmaking test part B (TMT B) [92], the patient draws a line on a sheet of paper, from 1 to A, to 2, to B etc until they reach the final number 13. The time required to complete the task is noted. TMT B is a test of complex alternating attention, and can also be construed as a test of executive function.

Working memory or attention span. In Digit Span from the Wechsler Adult Intelligence Scale [90], the patient is asked to repeat series of digits of increasing length forward and backward. In paper III, the sum of the number of digits repeated forward and backward was used.

Language functions. The controlled oral word association test (COWAT) F-A-S is a test of letter-fluency, where the patient is asked to say as many words as they can in 60 seconds, starting with the letters F, A, and S, respectively, with certain exceptions [93]. In paper III, the sum of correct items for letters F-A-S were used. The Token test [94] is a test of language comprehension, where the patient is given verbal instructions on how to manipulate 10 plastic tokens, 5 circles and 5 squares with different colors. In papers I and II, a version with 22 items [95] was used. The Boston naming test (BNT) [96] is a test of naming ability, where the patient is presented with

sixty drawings of increasing difficulty. In paper I, items 30-60 were used, because items 1–29 were not administered to all patients [97].

Visuospatial functions. The copying task of the Rey complex figure test (RCF) [98] is a test of spatial orientation and construction. In papers I and II, the number of correct items copied were used. In the silhouettes subtest of the Visual Object and Space Perception battery (VOSP) [99], the patient is asked to identify 30 silhouettes of everyday objects and animals. The test measures spatial perception and was used in papers I-III.

Executive functions. The parallel serial mental operations (PaSMO) [39] test entails the patient rattling off the Swedish alphabet from A to Ö, with each letter followed by its corresponding increasing number. The test is similar to a verbal version of TMT B, but without any visual aid. The test measures mental control. Response time in seconds was used in papers I-III. The Stroop color word test (Stroop III) is a test of inhibition of automated responses. The patient is asked to name the font color of a non-matching color word. Response time in seconds was used in papers I and II. In Table 6, the cognitive tests used in this thesis are listed.

Table 6. Neuropsychological tests used in paper I-III

Neuropsychological domains and tests	Paper		
	I	II	III
Episodic memory			
RAVLT delayed recall (correct items)	X	X	X
WLM delayed recall (correct items)	X	X	
Speed and attention			
Digit Symbol WAIS-r (correct items after 90 seconds)	X	X	
Digit Symbol WAIS-III (correct items after 120 seconds)	X	X	
TMT B (response time in seconds)	X	X	X
Language functions			
COWAT F-A-S (correct items after 60 seconds per letter)			X
Token test (correct items)	X	X	
BNT 30-60 (correct items)	X		
Visuospatial functions			
RCF copy (correct items)	X	X	
VOSP silhouettes (correct items)	X	X	X
Executive functions			
PaSMO II (response time in seconds)	X	X	X
Stroop III (response time in seconds)	X	X	
Working memory or attention span			
Digit span (items correct backward + forward)			X

Abbreviations: RAVLT, Rey auditory verbal learning test; WLM, Wechsler logical memory; WAIS-r, Wechsler Adult Intelligence Scale revised; WAIS-III, Wechsler Adult Intelligence Scale third edition; TMT B, Trailmaking test part B; COWAT F-A-S, Controlled oral word association test letters F-A-S; BNT, Boston naming test; RCF copy, Rey complex figure copying; VOSP silhouettes, the silhouettes subtest from the Visual Object and Space Perception battery; PaSMO II, Parallel serial mental operations part II.

3.4 Classification of MCI subtypes

For the papers presented in this thesis, MCI subtypes were determined using neuropsychological test data, in accordance with Jak et al's [21] typical criteria (Table 2), if not otherwise noted. aMCI-sd was operationalized as having at least one memory test score below the cut-off score, and all non-memory domain test scores above; aMCI-md as having at least one memory test score as well as at least one non-memory test score below the cut-off score; naMCI-sd as having at least one test score in any non-memory domain below the cut-off score, and having both memory test scores above it; naMCI-md as having at least two test scores in any two or more non-memory domains below the cut-off score and having both memory scores above it. Further, all patients with any one test under the cut-off were also analyzed as non-subtyped MCI and patients with no test result under the cut-off were categorized as 'no impairment'.

In paper I, we dichotomized the test results of the healthy controls based on age ≥ 65 and ≤ 64 , and used the means and standard deviations in each group to classify patients. In paper II, we dichotomized only those test results where there were significant differences among the healthy controls when they were dichotomized based on age (≥ 65 or ≤ 64) and education (≥ 13 or ≤ 12) and used the means and standard deviations in each group to classify patients. Tests with no significant differences in the control group were not dichotomized. In paper I and II, we used percentiles rather than standard deviations to classify the patients. In paper III, we used regression-based formulas to calculate individual z-values controlled for years of age and education, which were then used to categorize each patient according to criteria mentioned above.

In paper I, our MCI classifications correspond to the liberal, typical, and conservative criteria suggested by Jak et al. (2009). In paper II and III, our classification of MCI corresponds to the typical criteria.

3.5 Cerebrospinal fluid AD-markers and APOE

CSF and APOE data were only used in paper III. All CSF samples were collected by lumbar puncture in the L3/L4 or L4/L5 interspace at the standardized time point 8.30–9.00 am. The first 12 mL of CSF was collected in a polypropylene tube and immediately transported to the local laboratory for centrifugation at $2.000 \times g$ at $+4^\circ\text{C}$ for 10 min. The supernatant was pipetted off, gently mixed to avoid possible gradient effects, and aliquoted in polypropylene tubes that were stored at -80°C pending biochemical analyses, without being thawed and re-frozen.

Blood samples were drawn in the morning in the fasted state. Plasma samples for determination of APOE concentrations were stored at -80°C pending biochemical analyses, without being thawed and re-frozen.

3.6 Statistical methods

Differences in continuous variables were tested with the Tukey-Kramer HSD test for multiple comparisons (papers I-III), differences in categorical variables were tested with the chi-square test for dichotomous comparisons (paper II) or the Steel-Dwass for multiple comparisons (papers I-III).

In paper III, we performed multiple logistic regression to confirm results from estimates of sensitivity and specificity while controlling for years of age and education.

In paper III, LPA was performed using Mplus software (version 7.1). LPA is an individual-based analytic approach, which means that it analyzes patterns of values on variables within each individual participant, rather than patterns among the variables themselves, as in the more traditional variable-based analytic approach. LPA is a sub-class of mixture modelling. Mixture modelling is considered an individual-centered approach, and factor models, or variable-based models, are not actually competing but complementary perspectives or approaches. Mixture models can be used to find latent (unobserved) groups of individuals with measurement patterns that are similar to each other, and factor analysis looks for latent or unobserved variables assumed to underpin measurements on groups of variables [100]. LPA uses maximum likelihood estimation to model the classification uncertainty of the individual to a latent class, and the choice of number of clusters is considered less arbitrary than in cluster analysis using k-means clustering [101].

The various items on the MMSE do not necessarily have the same value, e.g. a score of 0 on the delayed recall item may not mean the same thing as a score of 0 on the comprehension item. MMSE also displays a pronounced roof effect when used in individuals with normal cognitive functioning or even mild cognitive impairment; it has a negative skew. However, in using MMSE descriptively, as was the case in papers I-III, parametric statistics (the Tukey-Kramer HSD test) were applied to test for differences across subgroups. Differences in years of education were also tested with parametric tests when used descriptively in papers I-III. Parametric statistical methods have been shown to be robust for use in data that is not normally distributed, and in ordinal data [102].

3.6.1 Evaluation of diagnostic tests

Table 7. Confusion matrix

Test (e.g. MCI)	Outcome (e.g. progression to dementia)		
	Outcome positive	Outcome negative	
Test positive	True positive (TP)	False positive (FP)	= TP + FP
Test negative	False negative (FN)	True negative (TN)	= FN + TN
	= TP + FN	= FP + TN	n = TP + FN + FP + TN

Abbreviations: MCI, mild cognitive impairment; TP, true positive; FP, false positive; FN, false negative; TN, true negative.

In order to evaluate the prognostic accuracy of a binary diagnostic test, we first determine the number of true positive, false positive, false negative, and true negative observations. A true positive observation is one where the test (e.g. does the patient have MCI or not) is positive, and the outcome (e.g. did the patient progress to dementia) is also positive. A false positive observation is one where the test is positive, and the outcome is negative. A false negative observation is one where the test is negative, and the outcome is positive. A true negative observation is one where both the test and the outcome are negative. Table 7.

Sensitivity is calculated by dividing the number of true positive observations by the number of positive outcomes. Sensitivity tells us the percentage of patients with a positive outcome that are correctly identified by the test.

Specificity is calculated by dividing the number of true negative observations with the number of negative outcomes. Specificity tells us the percentage of patients with a negative outcome that are correctly identified by the test.

The positive likelihood ratio (LR+) is calculated by dividing sensitivity by the false positive rate ($FP / (FP + TN)$). The LR+ tells us the magnitude of multiplication of the odds of having a positive outcome when the test is positive, as compared to the odds of a positive outcome before any test is applied.

The negative likelihood ratio (LR-) is calculated by dividing the false negative rate ($FN / (TP + FN)$). The LR- tells us the magnitude of

multiplication of the odds of having a positive outcome when the test is negative, as compared with the odds of a positive outcome before any test is applied.

The pre-test probability of having a positive outcome is the same as the prevalence (outcome positive / n). Odds can be calculated from probabilities by dividing probability by (1 - probability); probability can be calculated from odds by dividing the odds by (1 + odds).

The clinical utility index for a positive test (CUI+) is calculated by multiplying the sensitivity and the positive predictive value ($PPV = TP / \text{test positive}$) of a test. The clinical utility index for a negative test (CUI-) is calculated by multiplying the specificity and the negative predictive value ($NPV = TN / (FP + TN)$) of a test. The CUI was developed as an alternative to likelihood ratios and takes prevalence into account. CUI+ and CUI- can be interpreted as a test having excellent (≥ 0.81), good (≥ 0.64), satisfactory (≥ 0.49), or poor (< 0.49) clinical utility [103].

In papers I-III, the number of true positive, false positive, false negative, and true negative observations are reported for each condition, along with corresponding sensitivity, specificity, and likelihood ratios. In papers I and II, pretest probability (or prevalence) and post-test probabilities for a positive and a negative test are also reported. In paper II, CUI+ and CUI- [103] are also reported. In paper II, a graphic method for comparing diagnostic tests was used [104]. With this method, the true positive rate is plotted over the false positive rate.

When true and false positives and negatives are reported, the reader has the opportunity to calculate all the desired parameters of prognostic accuracy themselves.

3.7 Ethical considerations

The Gothenburg MCI study was approved by the local ethics committee before start of data-collection (diary number: L091-99, 15 March 1999) and again after protocol changes (diary number: T479-11, 8 June 2011). Written informed consent was obtained from all participants upon inclusion.

The title of the updated application from 2011 was "Early detection of dementia and its impact on the understanding of the nature of the dementia disorders and their treatment" (author's translation from Swedish). Further, the primary research aim was "to attempt to identify the most common

dementia disorders in a very early phase, i.e. before patients display the clinical picture currently required for a diagnosis of dementia to be given." (author's translation from Swedish). Papers I-III fall within the scope of the ethical approval.

At the Sahlgrenska memory clinic, neuropsychological and clinical assessment is part of clinical routine. Sampling and analysis of CSF is also part of clinical routine, however in most cases not for patients with only subjective cognitive complaints. Genetic (APOE) testing is not part of clinical routine, and was performed exclusively for research purposes. Results of APOE testing were not shared with the participants. All assessments of the healthy controls were done exclusively for research purposes.

4. Results

4.1 Paper I

The main objective of paper I was to compare the prognostic accuracy of MCI and MCI subtypes at three different cut-offs: 1.0, 1.5, and 2.0 SD under the mean of a normal control group.

At all three cut-offs, patients with aMCI-md had an increased risk of progressing to all-cause dementia. For aMCI-md, sensitivity increased and specificity decreased when the cut-off was lowered from 2.0 to 1.5 and 1.0 SD. MCI without subtyping had a high sensitivity, but a low specificity at all three cut-offs. We further investigated which cognitive domain that was most predictive of all-cause dementia when combined with a memory impairment. When present together with memory impairments, impairments in speed/attention and executive function showed the best predictive values in general, but there was a lot of variation when cut-off and follow-up time differed.

Our results suggest that aMCI-md is the only viable subtype for predicting dementia for follow-up times up to six years. Lowering the cut-off decreases the positive predictive value, and increases the negative predictive value of aMCI-md. None of the three cut-offs were clearly better than the other ones.

aMCI-md was the most common subtype among patients progressing to AD dementia, to SVD, and to MixD. Further, the Petersen subtypes may fail to account in full for the neuropsychological differences between prodromal probable AD dementia and SVD.

When using 2.0 SD as the cut-off for aMCI-md, although LR⁺ was high, sensitivity was low. Further, we question the utility of using 2.0 SD as the cut-off score to predict progression to dementia since clinical judgment would likely already suggest a high risk of deterioration for aMCI-md 2.0 SD. It is also possible that patients with aMCI-md 2.0 SD already fulfill clinical dementia criteria.

4.2 Paper II

The main objective of paper II was to estimate if and how the prognostic accuracy of aMCI-md differs between older and younger patients, and patients who have shorter and longer education. We found that the prognostic accuracy of aMCI-md among younger patients with more years of education was very good, and poor in the three remaining patient groups, the poorest in older patients with fewer years of education. Conversely, conversion rates to dementia were the lowest in younger patients with more years of education and the highest in older patients with fewer years of education. I.e., even if the risk of developing dementia is rather high among older patients with fewer years of education, testing positive for aMCI-md does not increase the probability by much, whereas younger patients with more years of education have a low pre-test probability of progressing to dementia, which is sharply increased if they test positive for aMCI-md.

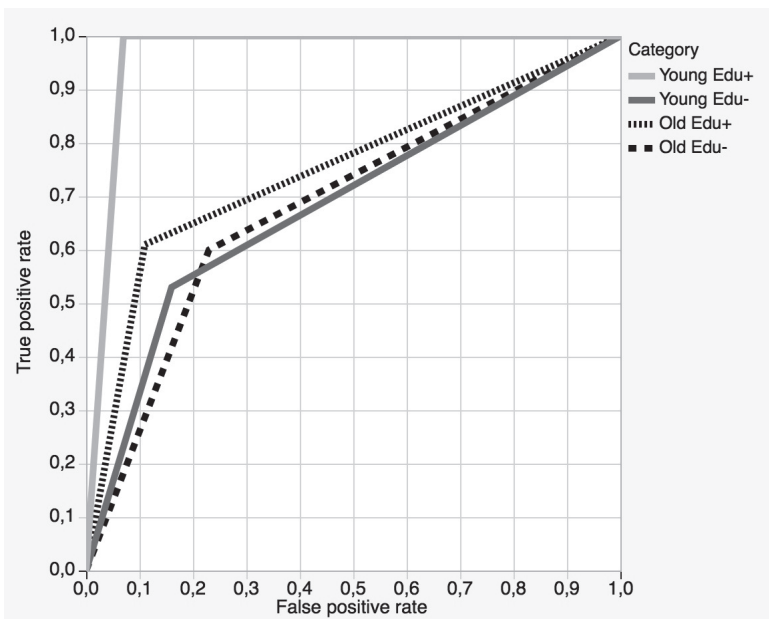


Figure 1. Prognostic accuracy of aMCI-md for progression to all-cause dementia after 2 years in the different demographic groups, true positive rate over false positive rate. Abbreviations: Young Edu+, age ≤ 64 and education ≥ 13 ; Young Edu-, age ≤ 64 and education ≤ 12 ; Old Edu+, age ≥ 65 and education ≥ 13 ; Old Edu-, age ≥ 65 and education ≤ 12 ; aMCI-md, amnesic multi-domain mild cognitive impairment.

4.3 Paper III

The established MCI subtypes do not distinguish between incipient dementia etiologies very well. It is unclear if latent cognitive profiles can distinguish between VaD-S (a combined group of SVD and MixD) and AD dementia at the incipient stage. In paper III, we therefore aimed to create LPA classes based on neuropsychological tests, and to investigate if they differed in terms of progression to dementia of different etiologies.

The LPA resulted in two classes with impaired cognition (Moderate and Severe impairments) and two classes with normal cognition (Normal-Low and Normal-High cognition). Belonging to the Moderate class predicted progression to all-cause dementia and to AD; belonging to the Severe class predicted progression to all-cause dementia, AD and VaD-S. Of the Petersen MCI subtypes, only amnesic multi-domain MCI predicted progression to all-cause dementia, AD, and VaD-S.

There were more APOE e4 carriers in the Severe and the Moderate classes than in the Normal-low class. Further, T-tau was higher and $A\beta_{1-42}$ was lower in the Severe and Moderate classes than in the two normal classes, but the biomarkers did not significantly differ between the Severe and the Moderate class.

Latent cognitive profiles separated between AD and VaD-S, while the Petersen subtypes did not. However, similar to the Petersen subtypes, LPA classes work better for ruling out progression to dementia than for case finding.

4.4 MCI subtype classification in paper I-III

In paper I-III, slightly different methods were used for classifying MCI and MCI subtypes (as described in detail in section 3.4). In order to compare the three different operationalizations of having a test result ≥ 1.5 SD below healthy controls, Cohen's kappa, a test of agreement, was estimated for the three methods, for all subtypes and for aMCI-md dichotomously. Table 8. These results are not presented in the papers. I also estimated sensitivity and specificity of aMCI-md as operationalized in the three different papers. Table 9.

Table 8. Classification agreement in papers I-III

MCI all subtypes	Observed agreement	Cohen's kappa
Paper I vs paper II	71%	0.63
Paper I vs paper III	60%	0.47
Paper II vs paper III	64%	0.52
aMCI-md		
Paper I vs paper II	95%	0.85
Paper I vs paper III	89%	0.66
Paper II vs paper III	89%	0.67

Abbreviations: MCI, mild cognitive impairment; aMCI-md, amnesic multi-domain MCI; vs, versus.

Table 9. Prognostic accuracy of the aMCI-md classifications in papers I-III

aMCI-md	Sensitivity	Specificity	LR+	LR-
Paper I	69 (55-80) %	83 (78-87) %	4.1 (3.0-5.6)	0.4 (0.3-0.6)
Paper II	66 (52-78) %	86 (82-90) %	4.8 (3.4-6.8)	0.4 (0.3-0.6)
Paper III	63 (49-75) %	90 (86-94) %	6.5 (4.2-10.0)	0.4 (0.3-0.6)

Abbreviations: aMCI-md, amnesic multi-domain mild cognitive impairment; LR+, positive likelihood ratio; LR-, negative likelihood ratio.

There is no universally accepted interpretation of the magnitude of Cohen's kappa, however it has been suggested that <0.00 could be interpreted as poor agreement, 0.00–0.20 as slight agreement, 0.21–0.40 as fair agreement, 0.41–0.60 as moderate agreement, 0.61–0.80 as substantial agreement, and 0.81–1.00 as almost perfect agreement [105]. With these figures as a guideline, the agreement between our own MCI subtype operationalizations can be interpreted as moderate to substantial, and the agreement between the aMCI-md operationalizations as substantial to almost perfect. Arguably, aMCI-md is the most important subtype to classify correctly, and the differences in operationalization produced results with a high level of agreement for this construct.

Using the same data, different operationalizations may result in slightly different classifications of MCI and MCI subtypes, as well as different accuracy in predicting progression. Using regression to estimate the influence of e.g. age and education or other variables of interest is probably more accurate than dichotomizing the control group, and further allows for keeping the full control group data set as comparison for all patients. Further, what a neuropsychological test measures, is somewhat unclear, and test choice likely influences all parameter estimates. We did not use the same neuropsychological tests, and we did not operationalize the cut-off in the same way, in the three papers, but all three papers adhered to the typical criteria (Table2) [21]. Thus, many different operationalizations of MCI can be used while still fulfilling general criteria.

This section highlights some of the problems inherent in MCI and dementia research. Differences in operationalization occur on many levels, apparently even within the thesis of a single person. How many tests are required to be impaired, how many tests are used, which tests are used, to what domain do you ascribe a test, what level of impairment is required (1.0, 1.3, 1.5, 2.0 SD etc.), and how do you operationalize the level of impairment (using published norms, or a healthy control group etc.), plus of course inclusion and inclusion criteria and procedures affect the make-up of the data-set.

5. Discussion

The objective of this thesis was to clarify what the prognostic value of MCI and MCI subtypes is in memory-clinic patients. MCI as defined by widely used criteria [17,20] has little prognostic value on its own. Amnesic multi-domain MCI can have clinical utility as a negative test, i.e. to rule out progression to dementia in the near future. As a positive test, to find cases with a high probability of progressing to dementia, the clinical utility of MCI as defined by criteria, of any subtype, in all age- and education groups, is poor at best (clinical utility index for a positive test result ≤ 0.49).

No previous studies have investigated the prognostic accuracy of multiple cut-off points for defining MCI subtypes in memory-clinic patients. Jak et al [21] did investigate stability over time of several different operationalizations of MCI and MCI subtypes (see Table 3 for a description of the various operationalizations), but they applied the criteria in a group of neurologically normal community-dwelling older adults, and no one progressed to dementia during the follow-up time.

It was previously unclear how the prognostic accuracy of MCI and MCI subtypes differed according to the age and education of patients. We have shown that the prognostic accuracy of particularly aMCI-md is superior in younger patients with more years of education in relation to other demographic groups. In two papers, Visser et al. concluded that the prognostic accuracy of aMCI is good only among memory clinic patients older than 65 [52] and older than 70 [53], respectively. Our results did not support this conclusion, and instead show that the prognostic accuracy of aMCI-md is better among younger than older patients. To a certain extent, the difference can be explained by difference in interpretation. In one of the studies by Visser et al. [52], the PPV was higher in the older group, however the NPV was much higher in the younger group, as was the LR+ (LR+ 12.8 in the age group 55-64, LR+ 2.1 in the age group 65-85. Author's own calculations). Thus, the results in Visser (2005) can be interpreted as being in congruence with our results, with a better prognostic accuracy among younger patients. In the other paper by Visser et al. [53], sensitivity, specificity, and PPV were higher among patients aged 70-85 than patients aged 55-69, and PPV was very low among patients aged 40-54. However, NPV was higher among younger patients, and the highest in the youngest group. There is no clear reason for the differences between Visser's and our results. The mean age for the patients with aMCI was 62, as compared with our patient mean age of around 65 for all MCI patients.

Our results are in congruence with Chary et al. [106], who in a population-based study showed that neuropsychological test results predicted all-cause dementia in participants with higher but not lower education level. No previous studies have investigated the influence of both patient age and education on the prognostic accuracy for progression to dementia.

Several studies have reported data-driven cognitive subtypes in memory-clinic patients, using either various cluster-analysis techniques, or latent profile analysis. The studies using LPA reported 3 [67,68], 5 [66], and 7 [65] classes, with groups largely similar to our classes; one or two groups displaying normal cognitive test scores; one or two groups with predominantly memory impairments, resembling our Moderate group, and one mixed group, similar to our Severe group. However, Köhler et al. [66] also identified a non-amnesic group with impairments in other domains, which we did not. We identified two impaired groups, both with memory test scores at or below -1.5 z, much like Eppig et al. [68]. Three studies using LPA reported progression data, Eppig et al. [68] to all-cause dementia, and Köhler et al. [66] also to other etiologies, but not to subcortical vascular dementia, and McGuinness et al. [67] to all-cause dementia. Thus, our results are the first reporting a difference in prognostic accuracy for statistically derived subgroups in prognostic accuracy for progression to AD and SVD dementias.

Studies investigating the prognostic accuracy of AD biomarkers and combinations of biomarkers are typically performed in patients with MCI, either according to Petersen's criteria from 1999 [17] (i.e. aMCI) or the updated criteria [20]. Table 4. This likely affects the results obtained. Even if it is unusual, some help-seekers who present without cognitive impairments still progress to dementia, and help-seekers without cognitive impairments but with positive AD biomarkers may have an increased risk of progressing to dementia [107]. And even though the comparison may be questionable because of differences in both outcome measures and inclusion criteria, sensitivity and specificity for aMCI-md (sensitivity 69% and specificity 83% for progression to all-cause dementia after 2 years, paper I) is not very different from the sensitivities and specificities reached using biomarkers in MCI patients (Table 4). Further, it can be argued that CSF biomarkers represent a more costly, more invasive, less widely available, and less tolerated option, resulting in a modest increase in prognostic accuracy at best [70,108].

Few studies on MCI and dementia use criteria for SVD. White-matter changes are often accepted as a part of AD, or may be described as atypical

AD, although there are data supporting the notion that SVD is a non-AD disorder [109]. Results from paper III and previous results from our group [110] show that dementia with subcortical features may be phenotypically and pathophysiologically different from AD.

5.1 Problematization of the MCI concept

The clinical relevance of the MCI concept can be questioned, since its utility in identifying patients likely to progress to dementia even within the near future is poor. Widely used criteria may, however, be used to identify patients with a very low probability (around 1 %, depending on cut-off choice) of progressing to dementia. It could be argued that giving a patient an MCI diagnosis is helpful in that it confirms the patient's own perception of cognitive decline. However, if this is the goal, perhaps a new set of criteria should be developed to this end. Since the MCI diagnostic entity gives little attention to functional impairments, only stating that these may not be severe enough to warrant a dementia diagnosis, criteria intended to capture the patient's own perceptions of impairment should pay more attention to instrumental activities of daily living as well. If MCI or a similar diagnostic entity (e.g. mild neurocognitive disorder) is to be applied in patient groups other than memory-clinic patients, e.g. younger patients with stress-induced cognitive impairments, taking functional impairments of a lesser magnitude into account may be of great importance. For example, difficulties with paying bills or maintaining the household may cause significant suffering for someone in their 40s.

Mental disorders are usually associated with either significant distress or disability [1,22,111]. MCI is defined by the absence of functional impairments severe enough to impede independence in functional abilities. Further, in the DSM V, it is stated that

"The diagnosis of a mental disorder should have clinical utility: it should help clinicians to determine prognosis, treatment plans, and potential treatment outcomes for their patients. However, the diagnosis of a mental disorder is not equivalent to a need for treatment."

However, MCI may not meet this criterion, since it may not help the clinician to determine a patient's prognosis, other than in its absence [112]. In combination with CSF and imaging biomarkers, a better prognostic accuracy could possibly be achieved, it has, however, not been unequivocally shown.

In the Gothenburg MCI study, a lot of patients opt out of the study after a few years (44% drop-out at the 6-year follow-up) [38]. However, progression to dementia seems to occur mostly within the first couple of years of the first visit [34,36,38]. Further, it can be argued that the first couple of years after first visit are also the most clinically important. Longer follow-up periods are important to understand the phenomena better, they are, however, notoriously difficult to carry out without significant loss to follow-up.

5.2 Societal impact of dementia

Though dementia diagnoses will certainly increase as populations across the world grow older, there is also accumulating evidence that incidence rates of dementia are falling, possibly due to e.g. better management of cardiovascular disease, improvements in education, healthcare etc. [113,114]. The results suggest improved healthcare early in life might benefit late-life cognitive health, and possibly reduce the risk of dementia. Further, dementia prevalence is still very low in the age groups studied in a typical memory-clinic research setting [115].

Estimates from Eurostat show that the population above 80 will increase, whereas the population between 50 and 80 (now target population in memory clinics and research) will start to decrease as early as 2025 [117]. In those over 80, we also start seeing a dramatic increase in prevalence, from around 7% among those aged 75-79, to 13% among those aged 80-84, and then sharply increasing to 43% among those aged 90+ [115]. The focus of memory clinics and the research conducted in memory clinics is typically on younger patients. Are we focusing on the right population? Some argue that we do not [116].

5.3 Evaluating diagnostic tests

The proper evaluation of a diagnostic test is a long-standing problem in medicine, and sensitivity, specificity, and likelihood ratios are not always easy to interpret [118].

It has been argued that the likelihood ratios are more useful for comparing tests, but more difficult to understand [119]. Another option, put forward by Biggerstaff [104], is graphically comparing tests. This method enables a simultaneous evaluation of several parameters of two or more binary diagnostic tests. When comparing two tests, they can be interpreted in relation to each other based on the position of their respective intercepts.

What is a desirable level of prognostic accuracy? This is difficult to say, and depends in part on the prognostic accuracy of competing markers or categorizations. A consensus report on molecular and biochemical markers of AD published in 1998 [120] suggested that a marker with sensitivity and specificity over 80% was desirable. However, a marker or categorization with e.g. both sensitivity and specificity of 85% would theoretically falsely tell 15% of patients with the disease that they do *not* have it, and likewise tell 15% of all patients without the disease that they *do* have it. The acceptability of such performance can be questioned, however it must be put into the context of what other categorizations are available to the clinician. If 85/85 is the best test available, then it is perhaps acceptable, or at least better than not being able to give any scientifically based prognosis at all.

Which value is more important, sensitivity or specificity? This depends on the setting, and the purpose of the classification. In a primary-care setting, a high sensitivity might be more important than a high specificity. I.e., we do not want to convey a message of low risk to a patient who actually does progress to dementia within a couple of years of the assessment. In recruitment to clinical trials, which often takes place at memory-clinic units, a high specificity might take precedent over a high sensitivity. It could be argued that it is unethical to administer an experimental drug treatment to a patient who does not actually have the disease in question, with the risks involved in terms of adverse effects, the costs, and the time and effort a participant in a clinical trial is required to spend. This does, however, raise the question of what we consider disease in this context. Is disease the display of biological markers associated with the manifest stage of the respective disease categories, but perhaps with a small or unknown likelihood of progression of symptom severity? Or is the disease the very high likelihood of imminent progression of symptom severity to the point of loss of independence of living? I.e., is the disease the biological substrate, or is it the symptom severity? Given the pervasive uncertainty of the biological mechanisms behind AD and other dementia disorders, and the fact that clinical criteria define disease as a syndrom of a certain severity, I argue that the latter is the case. This would mean that recruitment to clinical trials needs to be based not only on biological measurements, but more so on the display of characteristics associated with a high likelihood of progression of symptom severity.

6. Conclusions

Patients who do not meet standard criteria for MCI have a very low probability of progressing to dementia. The only MCI subtype that significantly increases the probability of progressing to dementia is aMCI-md. Prognosticating progression to dementia is easier in patients under 65 with more than 12 years of education than in other demographic groups. However, even among younger patients with more years of education, it may be better to use absence of amnesic multi-domain MCI to rule out progression to dementia than to use presence of amnesic multi-domain MCI to find patients who will progress. Cognitive profiles derived using LPA may be better suited for discriminating between those who progress to AD dementia and those who progress to VaD-S, than the traditional MCI subtypes.

7. Future perspectives

The most pressing issue in the field of MCI and dementia research is that of finding treatments for the most common underlying diseases. Further, there is still a lack of consensus surrounding MCI, how it should be operationalized, and with what instruments.

The clinical value of MCI is supposedly its ability to predict progression to dementia. If MCI, or mild neurocognitive disorder as it is called in the latest iteration of the DSM [22], is to be used in other populations than memory-clinic patients worried about developing dementia, perhaps a different diagnostic category should be formulated, outlining subjective and objective level of cognitive decline, as well as level of functional impairment, and the distress experienced by the patient.

Simultaneously, continued efforts are needed to formulate a category that has a better prognostic accuracy for progression to dementia than current concepts. However, MCI is still the best described of the various attempts to identify patients at a pre-dementia stage.

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