Subjective cognitive decline: An early sign of mild cognitive impairment and dementia?

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Subjective Cognitive Decline (SCD) – recently proposed as a possible preclinical stage of Alzheimer’s disease (AD) 

Jessen et al. 2014. Alzheimer’s & Dementia, 10(6), 844–852.
Why study Subjective Cognitive Decline (SCD)?

1. Interventions to prevent/modify Alzheimer’s disease (AD) and other forms of dementia thought to be most effective very early in the disease process: *Consequently, a need to find early markers for pre-clinical dementia among otherwise cognitively normal persons.*

2. In the context of searching for early markers for pre-clinical dementia, *persons with SCD are of special interest as SCD may be an early trigger for help-seeking.*
Why is it important to identify early markers?

Dementia is a massive problem:

- 5.4 million in the US have AD (Alzheimer’s Association 2016, alz.org)
- About 5.2 million above 65 years
- Approximately 200,000 below 65 (younger-onset AD).
- One in nine people age 65 and older has AD
- Increased longevity - larger problem tomorrow: Risk of AD doubles every 5 years between 65 and 85

- Early identification considered important as preventive measures and disease modifying treatments may be developed

Until recently, mild cognitive impairment (MCI) considered an early marker

- **MCI**: Intermediate stage between the expected cognitive decline of normal aging and the more-serious decline of dementia.

- Can involve problems with memory, language, thinking and judgment.

- Mild cognitive impairment is not meant to reflect lifelong low cognitive functioning (normal variation) - it is meant to reflect a change for this individual person

- **MCI** may increase risk of later progression to dementia, caused by Alzheimer's disease or other neurological conditions.

- Some people with MCI never get worse, some get better.

Petersen, R. Continuum (Minneap Minn) 2016;22(2):404–418
Mild cognitive impairment (MCI): Suggested stage between normal cognitive aging and dementia.

- First formal diagnostic criteria introduced by Petersen et al. 1999:

**TABLE.**

<table>
<thead>
<tr>
<th>MCI Original Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Memory complaint, preferably qualified by an informant</td>
</tr>
<tr>
<td>2. Memory impairment for age</td>
</tr>
<tr>
<td>3. Preserved general cognitive function</td>
</tr>
<tr>
<td>4. Intact activities of daily living</td>
</tr>
<tr>
<td>5. Not demented</td>
</tr>
</tbody>
</table>

Key Symposium criteria (still in use) (Stockholm 2003).

- First Key Symposium criteria demonstrating the syndromic phenotypes and how they can be paired with possible etiologies to assist the clinician in making a diagnosis.

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Amnestic MCI</th>
<th>Amnestic MCI</th>
<th>Nonamnestic MCI</th>
<th>Nonamnestic MCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degenerative</td>
<td>AD Single domain</td>
<td>AD Multiple domain</td>
<td>FTD Single domain</td>
<td>DLB Single domain</td>
</tr>
<tr>
<td>Vascular</td>
<td>Depression</td>
<td>Depression</td>
<td>Depression</td>
<td>Depression</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>Depression</td>
<td>Depression</td>
<td>Depression</td>
<td>Depression</td>
</tr>
<tr>
<td>Medical</td>
<td>Depression</td>
<td>Depression</td>
<td>Depression</td>
<td>Depression</td>
</tr>
</tbody>
</table>

AD = Alzheimer disease, DLB = dementia with Lewy bodies, FTD = frontotemporal dementia, MCI = mild cognitive impairment, VCI = vascular cognitive impairment.
**Neuropsychological profiles: MCI-PD and MCI-AD**

While MCI is of interest, because it represents the first objective evidence of decline - clinical trials – at this stage or later - aimed at development of disease-modifying interventions for AD have mostly failed.

A recent review of more than 400 clinical trials conducted the last decade revealed a failure rate of 99.6% (Cummings et al., 2014).

Thus, a shift of interest has taken place in the quest to find biological and possibly subtle cognitive markers for pre-clinical AD among cognitively normal persons with only subjective complaints (SCD).

Proposed disease development Alzheimer’s disease (AD)

- A prevailing (not undisputed) model suggest AD to start with deposition Amyloid b (Ab) protein in cortex - leading to:
  1. synaptic dysfunction
  2. neurodegeneration
  3. cognitive changes (MCI)
  4. and functional decline associated with early dementia (Jack et al., 2010, Sperling et al., 2011).

- Suggested time span from detectable amyloid pathology until dementia 10-15 years or more (Perrin et al., 2009).

Theoretical model for manifestation of risk factors for development of AD (Sperling et al., 2011).

Neuropsychology mostly relevant in the clinical disease stage
Clinical trials aimed at disease modifying interventions – mostly failed

Previous failed focus of intervention

Current focus of intervention

Suggested time span from detectable amyloid pathology until dementia 10-15 years or more (Perrin et al., 2009).

Theoretical model for manifestation of risk factors for development of AD (Sperling et al., 2011).
Many MCI may have progressed too far for intervention

- Studies find that some MCI subtypes have high risk for conversion

- **Amnestic, multiple domain** - highest conversion rates

- **Amnestic only** - intermediate rate

- **Single non-memory impairment** - lowest conversion rates

### Development of MCI subtypes over 2-years - Gothenburg - Oslo MCI Study

<table>
<thead>
<tr>
<th>Baseline diagnosis</th>
<th>Follow-up after 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SCD (100)</td>
</tr>
<tr>
<td>SCD (%)</td>
<td>140 (46.4)</td>
</tr>
<tr>
<td>Executive MCI (%)</td>
<td>19 (6.3)</td>
</tr>
<tr>
<td>Amnestic MCI (%)</td>
<td>96 (31.8)</td>
</tr>
<tr>
<td>Multidomain MCI (%)</td>
<td>47 (15.6)</td>
</tr>
<tr>
<td>Total (%)</td>
<td>302 (100)</td>
</tr>
</tbody>
</table>

• Employing a comprehensive MCI criterion (Jak. et al. 2009) we found atrophy in perirhinal and entorhinal cortices in amnestic MCI (aMCI) and significantly more affection of the hippocampal subfields in multiple domain MCI (mdMCI), probably representing a clinical progression relative to amnestic MCI coupled with hippocampal subfield affection.
In quest for earliest markers, SCD have become a major focus. SCD is very frequent and how often related to pathological decline and dementia?

**Approximate prevalence of subjective cognitive decline (SCD), MCI and dementia 60-80 years**

<table>
<thead>
<tr>
<th>Condition</th>
<th>&lt;80 years</th>
<th>60-80 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCD</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>MCI</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Dementia</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>


## Estimated Weighted Prevalence of Memory Complaint

<table>
<thead>
<tr>
<th></th>
<th>Unweighted N</th>
<th>Memory Complaint, % (SE)</th>
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<tbody>
<tr>
<td><strong>Total population</strong></td>
<td>810</td>
<td>22.1(1.9)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>286</td>
<td>20.6(3.1)</td>
</tr>
<tr>
<td>Female</td>
<td>524</td>
<td>23.4(2.3)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>463</td>
<td>24.1(2.6)</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>347</td>
<td>18.3(2.6)</td>
</tr>
<tr>
<td><strong>Age, yr</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–44</td>
<td>396</td>
<td>14.5(2.2)</td>
</tr>
<tr>
<td>45–64</td>
<td>186</td>
<td>19.6(3.6)</td>
</tr>
<tr>
<td>65–74</td>
<td>132</td>
<td>42.7(5.9)</td>
</tr>
<tr>
<td>75–84</td>
<td>80</td>
<td>50.8(7.8)</td>
</tr>
<tr>
<td>85+</td>
<td>16</td>
<td>88.3(3.6)</td>
</tr>
</tbody>
</table>

Mean: 61% memory complaint
Subjective memory impairment in a general population: HUNT study, Norway – also including younger subjects


Nine items about memory included in the questionnaire for participants aged 30 – 80+ in the large population based HUNT Study (n= 37405) (2006-08)

Subjective memory impairment among 30-80+ year olds
Why is SCD so common?
Confounders, other than dementia related variables (1)

Depression:
Depression and anxiety frequent in persons with subjective
cognitive complaints and no cognitive or biological evidence for
neurodegeneration

Muftuler løndalen T. Fladby D. Aarsland (2014). Neurobiological correlates of depressive symptoms in people with

Psychosocial stress:
Vague term, but psychosocial stress often considerable in persons
with subjective cognitive impairment in the general population (Ostberg
and up to 71% in SCD memory clinic patients, compared to 18% in
MCI patients (Elfgren C. (2010). Subjective memory complaints, neurpsychological performance and psychoatric
variables in memory clinic attendees. *Arch Gerontol Geriatr*. 51: 110-114)
Why is SCD so common?
Confounders, other than dementia related variables (2)

Demographic factors
SCD is very common in healthy older adults – between 25 and 50%

Somatic and other conditions
SCD reported and very frequent in TBI, epilepsy, stroke, MS, cancer, bipolar disorder, post cancer treatment, heart surgery and ECT – to mention a few (Nilsson Wallin, Wahlund. *Kognitiv medicin:* Norsteds; 2011)

Personality traits
High neuroticism, low level of percieved self efficacy, high level of agreeableness, anxiety proneness, low level of extraversion, achievement-striving and dutiful persons - are all more likely to report SCD (Eckerström M. *Subjective cognitive decline in memory clinic patients.* Doctoral Thesis, Sahlgrenska Academy, University of Gothenburg, 2017)

Agreement on key points:
1. Evidence that SCD occurs in preclinical AD and may be a symptomatic indicator because:
   (a) Longitudinal data support SCD as a risk factor for future cognitive decline as well as for MCI and AD dementia
   (b) There is cross-sectional biomarker evidence for an increased prevalence of preclinical AD in those with SCD
   (c) Individuals with SCD and biomarker evidence for AD are at increased risk of cognitive decline and progression to MCI and AD dementia.

2. Current knowledge insufficient to define the specific features of SCD in preclinical AD. The characteristics of SCD in preclinical AD are probably variable and heterogeneously expressed.

3. Preclinical AD is, by definition, a biomarker diagnosis, and SCD is neither required for the diagnosis of preclinical AD nor is it necessarily present in all cases of preclinical AD. SCD by itself may never be sufficient to diagnose preclinical AD.

4. Numerous causes of SCD other than preclinical AD exist. These include, but are not limited to, SCD in MCI due to AD, dementia, normal aging, psychiatric and neurologic disorders other than AD, or related to effects of medication and substance use.
Research criteria for pre-MCI subjective cognitive decline (SCD-I)

1 Self-experienced persistent decline in cognitive capacity in comparison with a previously normal status and unrelated to an acute event.
2 Normal age-, gender-, and education-adjusted performance on standardized cognitive tests, which are used to classify mild cognitive impairment (MCI) or prodromal AD.

1 and 2 must be present

Exclusion criteria:
1 Mild cognitive impairment, prodromal AD, or dementia
2 Can be explained by a psychiatric* or neurologic disease (apart from AD), medical disorder, medication, or substance use

Abbreviation: AD, Alzheimer’s disease.

* Individual symptoms of depression or anxiety, which do not reach the threshold of a disorder, are not considered exclusion criteria.
SCD-I - Features that increase the likelihood of preclinical AD in individuals with SCD according to current data: **SCD plus (preclinical AD)**

- Subjective decline in memory, rather than other domains of cognition
- Onset of SCD within the last 5 years
- Age at onset of SCD ≥60 years
- Concerns (worries) associated with SCD
- Feeling of worse performance than others of the same age group

If available or possible to obtain in the respective study:

- Confirmation of cognitive decline by an informant
- Presence of the APOE ε4 genotype
- Biomarker evidence for AD (defines preclinical AD) See next slide

Abbreviations: AD, Alzheimer’s disease; SCD, subjective cognitive decline.

The evolution of preclinical Alzheimer’s disease:
Implications for prevention trials.

**Stage 0**
No biomarker abnormalities

**Stage 1**
Asymptomatic amyloidosis
- High PET amyloid retention
- Low CSF Aβ\textsubscript{1-42}

**Stage 2**
Amyloidosis + Neurodegeneration
- Neuronal dysfunction on FDG-PET/fMRI
- High CSF tau/p-tau
- Cortical thinning/Hippocampal atrophy on sMRI

**Stage 3**
Amyloidosis + Neurodegeneration + Subtle Cognitive Decline
- Evidence of subtle change from baseline level of cognition
- Poor performance on more challenging cognitive tests
- Does not yet meet criteria for MCI

**SNAP**
Suspected non-Alzheimer pathology
- Neurodegeneration markers without evident amyloidosis

**Stage 1** begins with cerebral amyloidosis.

**Stage 2** is amyloidosis plus markers of neurodegeneration + normal cognitive function.

**Stage 3** is amyloidosis + neurodegeneration + subtle cognitive and behavioral decline not sufficient for MCI or dementia due to AD.

**SNAP** or Suspected Non-Alzheimer Pathology has evidence of neurodegeneration without apparent amyloidosis.
Predictors of Conversion: Protein biomarkers in CSF

- Protein biomarkers in CSF predict progression to AD:
  - Low CSF Aβ related to beta amyloid plaques
  - High tau levels, total tau (T-tau) and phosphorylated tau (P-tau) related to neurofibrillary tangles
  - Result of these two processes – is that the neuron die

(Jack et al., 2010, Sperling et al., 2011).
Imaging

- Medial temporal lobe atrophy on MRI tends to predict progression

- A hypometabolic pattern consistent with AD on fluorodeoxyglucose-PET (FDG-PET) may also predict progression

- Several studies have indicated that individuals with MCI who have a positive amyloid PET scan are more likely to progress rapidly.
A requirement is that SCD is not associated with objective Mild Cognitive Impairment (MCI).

So how do we separate between normal cognitive function and MCI?

Where we set the cut off is a key question in the definition of SCD, and has obvious consequences for prognosis.
Percentage of SCD in the Norwegian Dementia Disease Initiation SCD/MCI Cohort (Fladby et al. 2017) based on strict or mild interpretation of prevailing MCI criteria.

- Prevailing MCI diagnostic criteria: At least 1 test 1 - 1.5 SD below mean.
- Recommended testing: memory, executive, attention, language or visuospatial skills.

American Psychiatric Association/National Institute of Aging and Alzheimers Association (Albert et al., Alzheimers Dement. 2011 May;7(3):270-9.)
Concern regarding a change in cognition
- Compared to prior level. Obtained from patient, close informant or skilled clinician

Impairment in 1 or more cognitive domains
- More than expected from age/education.
- If repeated assessments, decline should be evident. Change can occur in several cognitive domains recommended to be tested (according to Key Symposium criteria): memory, executive, attention, language or visuospatial skills.
- Impairment in episodic memory most common in MCI patients who subsequently progress to AD
- Impairment criterion: 1 to 1,5 SD or more below normative mean

Preservation of independence in functional abilities
- Only mild problems performing complex functional tasks: paying bills, preparing meals, shopping

Not demented
- No evidence of significant impairment in social or occupational function
In brief neuropsychological assessment, amnestic MCI is associated with CSF biomarkers for cognitive decline in contrast to the prevailing NIA-AA MCI criterion


**Dependent variable: NIA Stage 2: Path. CSF Ab42 and path. T-tau or P-tau**

**Multivariate analysis**

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>OR (95 % CI)</th>
<th>P- value</th>
</tr>
</thead>
<tbody>
<tr>
<td>One test or more &lt; T=40, including at least one memory test</td>
<td>4.4 (1.9 – 10.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Age at inclusion</td>
<td>1.1(1.0 – 1.1)</td>
<td>0.007</td>
</tr>
<tr>
<td>Two or more tests &lt; T=40 in any cognitive domain</td>
<td>2.2 (0.9-5.5)</td>
<td>0.093</td>
</tr>
<tr>
<td>One test or more &lt; T=35 in any cognitive domain (NIA-AA MCI criterion)</td>
<td>0.5(0.2 – 1.5)</td>
<td>0.243</td>
</tr>
</tbody>
</table>
Separation between SCD and MCI rely on cut off scores

• A cut off score in neuropsychology aim at discrimination between results that represents normal and abnormal brain functions

• However, a sharp dichotomization between normal/abnormal can never reflect a true description of how the brain functions

• The aim is to achieve the best balance between specificity and sensitivity
So what is best the best cut-off score???

Neuropsychological impairment
1, 1.5 or 2 standard deviations (SD) below premorbid function?

Advantages and disadvantages:

1 SD below expected: increased sensitivity (true impaired), however increased risk for false positive findings.

1.5 or 2 SD below expected: lower sensitivity and increased risk for false negative findings.
Distribution of Average Impairment Rating T-Scores for normal and brain-damaged groups (Taylor & Heaton, JINS, 2001)

Cut off at T=30

Or

Cut off at T=40
Inverse Relationship Between Specificity (true normals) and Sensitivity (true impaired)

Theoretical T-score distributions illustrating the tradeoff between sensitivity and specificity.

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<table>
<thead>
<tr>
<th></th>
<th>1 SD</th>
<th></th>
<th>1.5 SD</th>
<th></th>
<th>2 SD</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Spec</td>
<td>Sens</td>
<td>Spec</td>
<td>Sens</td>
<td>Spec</td>
<td>Sens</td>
</tr>
<tr>
<td>Verbal Comprehension</td>
<td>85.2</td>
<td>46.0</td>
<td>93.6</td>
<td>26.2</td>
<td>97.7</td>
<td>9.5</td>
</tr>
<tr>
<td>Perceptual Organization</td>
<td>84.3</td>
<td>56.3</td>
<td>92.9</td>
<td>41.3</td>
<td>97.8</td>
<td>18.3</td>
</tr>
<tr>
<td>Processing Speed</td>
<td>84.6</td>
<td>73.8</td>
<td>93.9</td>
<td>63.5</td>
<td>98.0</td>
<td>43.7</td>
</tr>
<tr>
<td>Working Memory</td>
<td>84.4</td>
<td>57.9</td>
<td>92.7</td>
<td>45.2</td>
<td>97.2</td>
<td>27.0</td>
</tr>
<tr>
<td>Auditory Memory</td>
<td>83.6</td>
<td>69.0</td>
<td>93.0</td>
<td>58.7</td>
<td>97.7</td>
<td>46.0</td>
</tr>
<tr>
<td>Visual Memory</td>
<td>82.7</td>
<td>82.5</td>
<td>93.0</td>
<td>69.8</td>
<td>97.7</td>
<td>53.2</td>
</tr>
</tbody>
</table>

(Taylor & Heaton, JINS, 2001)

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Frequency of “abnormal” test-scores (T score ≤ 39) for 1189 neurological healthy persons on a neuropsychological test battery (HRB-25 measures) (Heaton et al. 2004)

About 9% of healthy persons (not MCI) have 4 «abnormal» scores, defined as T-scores < 39.
Principles for Selecting a Test Score Cutoff for Neurodiagnostic Purposes

- Specificity (true normals) must be reasonably high (suggest >80%).
- False positive and false negative errors should be as balanced as possible.
- Main task: Be correct as often as possible.
Jak et al. (2009) and Bondi et al. (2014) validated a «comprehensive» MCI criterion:

- 5 cognitive domains (memory, attention, language, visuospatial function and executive function), 3 to 5 subtests within each cognitive domain.

- **Criterion: Impairment on 2 or more tests in one domain- more than 1 SD below mean.**

- Normal if only 1 test in one domain below cut off.

MCI based on comprehensive criteria significantly associated with CSF AD markers and more dementia converters than MCI based on typical classification: *impairment in at least 1 test 1-1.5 SD below mean.* (National Institute of Aging – Alzheimer’s Association task force criteria for MCI (Albert et al. 2011))
Is subjective complaints associated with objective impairment/MCI?
- Cognitive disorders **underestimate** memory complaints (MCI)
- Affective, adjustment and anxiety disorders **overestimate** memory complaints (SCI)

Mean discrepancy scores (self-rating minus informant-rating) for all 39 items on the Ecog (Questionnaire about cognitive function.)

- A positive score indicates one is overestimating their cognitive decline relative to their study-partner’s report, while a negative score indicates one is underestimating their cognitive decline.

Some longitudinal findings in subjective cognitive impairment/subjective cognitive cognitive decline

- Examined whether subjective memory impairment (SMI) predicts all-cause dementia or Alzheimer's disease (AD) in a population-based study with long-term follow-up.

- A total of 2043 initially dementia-free participants (≥ 60 years) made three memory ratings ("compared with others", "compared with five years ago", and "complaints from family/friends") at baseline. During follow-up (median = 10 years), 372 participants developed dementia (208 with AD).

- Cox regression revealed that subjective memory impairment ratings predicted:
  1. all-cause dementia in models adjusting for age and sex (Hazard ratio or HR from 2.04 to 3.94)
  2. even higher values for AD (HR from 2.29 to 5.74).

- The result persisted in models including other covariates, including baseline episodic memory performance, and in analyses restricted to participants with long time to dementia diagnosis (≥ 5 years).

- The findings underscore the usefulness of subjective memory assessment in combination with other factors in identifying individuals at risk for developing dementia.

- Similar findings in other studies, e.g.:
Effect of amyloid on memory and non-memory decline from preclinical to clinical Alzheimer’s disease
Yen Ying Lim et al., Brain Jan 2014, 137 (1) 221-231

- Healthy individuals, MCI and AD underwent PET imaging for beta-amyloid.

- Cognitive assessments at baseline, and 18- and 36-month follow-ups.

- Compared with amyloid-negative healthy - amyloid-positive healthy, and amyloid-positive MCI and AD showed moderate and equivalent decline in verbal and visual episodic memory over 36 months (Effect sizes = 0.47–0.51).

- Amyloid negative with MCI did not show any cognitive decline over 36 months.

Thus, a subgroup of normals/SCD (amyloid-positive) may be of particular interest

127 patients with SCD (age 60 ± 10 years, 61 [48%] females, MMSE 29 ± 1).

SCD/MCI distinction based on prevailing MCI criteria (Albert et al. 2011), followed for 3.9 yrs.

At baseline, Aβ42 and tau were abnormal in 20 patients (both 16%), and ptau in 32 patients (25%).

Thirteen (10%) progressed to MCI (n = 11) or AD (n = 2) over 3.9 years.

Aβ42 was the strongest predictor of progression to MCI or AD with an adjusted hazard ratio (HR) of 16.0 (3.8-66.4).

The adjusted HR associated with tau was 2.8 (0.9-9.2) and with ptau 2.6 (0.8-8.2).

Combinations of biomarkers had a lower predictive value than Aβ42 alone.

Results in line with the hypothesis that the cascade of pathologic events starts with deposition of Aβ42, whereas neuronal degeneration and hyperphosphorylation of tau are more downstream events, closer to clinical manifestation of AD.
Subjective cognitive decline (SCD) and relation to subsequent objective mild cognitive impairment (MCI) and dementia –

Slightly different outcome in two longitudinal studies of SCD based on the Gothenburg-Oslo MCI study cohort (GO-MCI)

The memory clinics at Sahlgrenska University Hospital in Gothenburg and Akershus University Hospital (Ahus) in Oslo employ:

• The same inclusion and exclusion criteria
• Similar clinical assessments
• Similar neuropsychological test batteries
Exclusion criteria:
- Major depressive and other severe psychiatric disorders
- Neurological disease
- History of moderate/severe TBI
- Cardiovascular accident
- Other severe somatic illness or current substance abuse
- Dementia: significant impairment in social or occupational function and/or a score < 25 on MMSE

Inclusion criteria:
- Subjective and objective (verified by an informant) evidence for progressive cognitive impairment for more than 6 months.
- Mild objective cognitive symptoms according to screening procedures (Cognistat, MMSE 25-30)

Included patients classified by Global Deterioration Scale (Reisberg et al. 1988)(GDS) with scores 2 (subjective cognitive decline (SCD) and 3 (objective MCI).
Background/Aims: This study observed memory clinic patients with subjective cognitive decline (SCD) and normal cognitive function at baseline. The primary aim was to address SCD as a potential risk factor for cognitive decline. The secondary aim was to address potential relation between (1) baseline CSF biomarkers and (2) decline in memory performance over the first two years of follow-up, with possible cognitive decline after six years.

Methods: 81 patients (mean age 61 years) with SCD were recruited from university memory clinics and followed for 6 years.
Introduction: Subjective cognitive decline (SCD) and biomarker-based “at-risk” concepts such as “preclinical” Alzheimer’s disease (AD) have been developed to predict AD dementia before objective cognitive impairment is detectable. We longitudinally evaluated cognitive outcome when using these classifications.

Methods: Memory clinic patients ($n = 235$) were classified as SCD ($n = 122$): subtle cognitive decline ($n = 36$) and mild cognitive impairment ($n = 77$) and subsequently subclassified into SCDplus and National Institute on Aging–Alzheimer’s Association (NIA-AA) stages 0 to 3. Mean (standard deviation) follow-up time was 48 (35) months. Proportion declining cognitively and prognostic accuracy for cognitive decline was calculated for all classifications.
Neuropsychological SCD/MCI algorithm in the 6 year follow up. N=81, Age 61(SD=7.5):

Memory tests:
- RAVLT, delayed recall
- RCFT, delayed visual reproduction

“Executive” measures:
- TMT-B
- COWAT

Results converted to T-scores. Commercially available norms employed.
- Cut off set to T=37
- Any score < 37 = MCI or more severe
- All scores ≥ 37 = SCD

Similar criterion employed in several MCI studies (Chao et al. 2009, Grambaite et al. 2011, Hessen et al 2014 etc).
Neuropsychological SCD/MCI algorithm in the 4 year follow up. N=235. Age 63 (SD=9):

Memory tests:
- RAVLT, delayed recall
- RCFT, delayed visual reproduction

Non-amnestic tests:
- Boston Naming Test
- VOSP silhouettes (visuoperceptual task)

- Raw scores employed, not adjusted for age
- Cut off 1.5 SD below control means

SCD=All tests above cut-off
MCI = At least 2 (of 4) tests below cut off T < 35 (strict cut off!)
Cerebrospinal Fluid Biomarkers

6-year study:
Aβ_{42} considered pathological if ≤500 ng/l.
P-tau considered pathological if ≥80 ng/l.
T-tau level considered abnormal if T-tau >450 ng/l (Sjögren et al. 2001)

4-year study:
Aβ_{42} considered pathological if ≤482 ng/l.
P-tau considered pathological if ≥52 ng/l.
T-tau level considered abnormal if T-tau >320 ng/l (Mattson et al. 2009)
What happened to the SCD patients after 6 years:

• Hypothesis:

(1) That the majority of the patients would remain cognitively stable.

(2) Low Aβ42 at baseline would be the most powerful predictor of dementia development. We also assumed that other baseline CFS biomarkers would be more pathological in patients that developed dementia after 6 years.

(3) Patients with memory decline during the first 2 years of observation would be at higher risk of both further cognitive decline and development of dementia after 6 years.
Two year follow up of 122 SCD patients find indication of neurodegenerative cause for memory decline: Memory decline > 0.5 SD (but within the normal range) associated with significantly higher T-tau at baseline than the group with improved memory (T-tau 341 vs 260, p=0.04).

The baseline memory score of those who declined was significantly better than the baseline score of those who improved over two years (T-score 56 vs T-score 52, p=0.02).

Thus, a memory cut-off indicating low baseline memory, would not would have identified the declining group!
**Results 6 years:**

- 5% converted to dementia
- 11% declined to MCI
- In total 16% declined
- 84% remained cognitively stable or slightly improved

<table>
<thead>
<tr>
<th>Test point</th>
<th>GDS 2 (SCD)</th>
<th>GDS 3 (MCI)</th>
<th>GDS 4 (Dementia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDS baseline (N, %)</td>
<td>42 (52)</td>
<td>39 (48)</td>
<td>0</td>
</tr>
<tr>
<td>GDS after 6 years (N, %)</td>
<td>51 (63)</td>
<td>26 (32)</td>
<td>4 (5)</td>
</tr>
</tbody>
</table>

Global Deterioration Scale (Reisberg et al. 1988) (GDS). 2=SCD, 3= objectively measured MCI and 4= dementia.
Predictors of dementia (GDS ≥ 4) after 6 years in patients with only subjective cognitive complaints at baseline

<table>
<thead>
<tr>
<th>Baseline variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n=81)</td>
<td>OR</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Aβ_{42} ≤ 500 ng/L</td>
<td>14.54</td>
<td>0.025</td>
</tr>
<tr>
<td>Memory decline &gt; 0.5 SD/2yrs</td>
<td>9.83</td>
<td>0.054</td>
</tr>
<tr>
<td>Executive T-score ≤ 46.5</td>
<td>7.56</td>
<td>0.057</td>
</tr>
<tr>
<td>Ratio T-tau/Aβ_{42} &gt; 0.52</td>
<td>3.75</td>
<td>0.203</td>
</tr>
<tr>
<td>P-tau ≥ 80 ng/L</td>
<td>4.06</td>
<td>0.274</td>
</tr>
<tr>
<td>T-tau ≥ 450 ng/L</td>
<td>0.00</td>
<td>0.999</td>
</tr>
</tbody>
</table>

- (1) Low Aβ_{42} at baseline and (2) memory decline the first 2 years of follow up predicted dementia.
- Combined these variables associated with 50% risk of conversion to dementia.
- More dementia converters needed for strong analysis of etiological factors
Cognitive outcome at follow-up (4 years) for the subclassification groups.

Abbreviations: MCI, mild cognitive impairment; NIA-AA, National Institute on Aging–Alzheimer's Association; SCD, subjective cognitive decline.

SCD total to dementia: 10%

NIA-AA = 2 to dementia (Pat. CSF = Ab42 + T-tau or P-tau): 24%

MCI to dementia: 52%

### Binary logistic regression. Baseline single predictors of cognitive decline in SCD patients (4 yrs)

<table>
<thead>
<tr>
<th></th>
<th>Prediction cognitive decline</th>
<th>Prediction dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1a</td>
<td>Model 2a</td>
</tr>
<tr>
<td><strong>Aβ42 ≤ 482</strong></td>
<td>&lt;.047</td>
<td>.027</td>
</tr>
<tr>
<td>T-tau ≥ 320</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>p-tau ≥ 52</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>APOE ε4 ≥ 1 allele</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Informant-reported memory decline</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Informant-reported subjective symptom onset age ≥ 60 years</td>
<td>ns</td>
<td>2.4 0.8–6.9</td>
</tr>
<tr>
<td>Informant-reported subjective symptom duration ≤ 5 years</td>
<td>ns</td>
<td>1.5 0.2–10.7</td>
</tr>
<tr>
<td><strong>95% CI for OR</strong></td>
<td>Lower-upper</td>
<td>Lower-upper</td>
</tr>
<tr>
<td>1.0–13.7</td>
<td>0.1–3.6</td>
<td>0.3–2.6</td>
</tr>
<tr>
<td>0.6–17.4</td>
<td>0.6–17.4</td>
<td>0.3–2.6</td>
</tr>
<tr>
<td>0.3–2.6</td>
<td>0.3–2.6</td>
<td>0.3–4.3</td>
</tr>
<tr>
<td>0.1–6.9</td>
<td>0.1–6.9</td>
<td>0.1–18.0</td>
</tr>
<tr>
<td>0.1–13.8</td>
<td>0.3–4.7</td>
<td>0.1–22.3</td>
</tr>
<tr>
<td>0.3–4.3</td>
<td>0.3–4.3</td>
<td>0.1–18.0</td>
</tr>
</tbody>
</table>
In summary, slightly different prognosis regarding dementia in 2 SCD studies from mainly the same cohort (Gothenburg – Oslo MCI cohort)

- 5% demented after 6 yrs (n=81) – 10% after 4 yrs (n=122)

- MCI criteria and test selection different: 1 test below T= 37 (n=81) versus 2 tests below T=35 (n=122) (4 tests)

- Different norms: Commercially available, partially demographically corrected (n=81) versus control group, not demographically corrected (n=122)

- Different CSF (Ab42, T-tau and P-tau) cut-off scores in the studies. Both based on «state of the art» litterature.
Percentage of SCD in the Norwegian Dementia Disease Initiation SCD/MCI Cohort (Fladby et al. 2017) based on strict or mild interpretation of prevailing MCI criteria.

- Prevailing MCI diagnostic criteria: At least 1 test 1 - 1.5 SD below mean.
- Recommended testing: memory, executive, attention, language or visuospatial skills.

Total N=452

- N=247
- N=196

American Psychiatric Association/National Institute of Aging and Alzheimers Association (Albert et al., Alzheimers Dement. 2011 May;7(3):270-9.)
Continued summary of findings from the 2 SCD studies from the Gothenburg – Oslo MCI cohort

- No convincing support for the SCD plus categories proposed by the SCD-I group (Jessen et al. 2014. *Alzheimer’s & Dementia*, 10(6), 844–852)

- CSF Aβ42 single most important predictor of cognitive decline and dementia in SCD groups of heterogeneous etiology

- The 4 year study (n=122) support use of biomarker-based classifications – specifically the NIA-AA ‘preclinical AD’ stage 2 or 2+3 - to predict cognitive decline, dementia and AD dementia, in memory clinic SCD patients
Does this mean that prediction of cognitive decline and dementia is all about biomarkers?

Not so sure, «pathological» AD biomarkers may be too frequent for precise prediction.
Neuropsychological recommendation:

(1) Patients in this age range
(2) Same recruitment criteria (SCD)
(3) Normal neuropsychology and no path. biomarkers for dementia, can usually be given a good prognosis

Some exceptions:

- Normal neuropsychology and “severe SCD” warrant monitoring
- Also those with high cognitive reserve
Take home messages

• Current evidence support some association between SCD and future dementia

• However, SCD is not specific enough to be a valid marker for cognitive decline on its own

• SCD patients with normal neuropsychology and biomarkers, can be given a good prognosis

• In the presence of pathological biomarkers, the risk for further decline in SCD patients is fairly high

• There is a strong association between SCD and symptoms of depression, anxiety and psychosocial stress

• Reduced awareness of cognitive difficulties may be present already at the MCI stage. Therefore, SCD should not be a required criterion for MCI
Thank you for your attention!