From Subjective Cognitive Decline to Alzheimer’s Disease: the predictive role of neuropsychological, personality and cognitive reserve features. A 7-years Follow-Up study.

S. Mazzeo *, V. Bessi *, S. Padiglioni *, C. Piccini ‡, B. Nacmias *, S. Sorbi *, L. Bracco *

* Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Florence, Italy.
‡ Local Health Care Units Toscana 10.
Introduction

Mild Cognitive Impairment (MCI)
Transitional stage between normal aging and dementia (Petersen 1999)

- Associated with an increased risk of positive AD biomarkers
- Increased annual conversion rate of 5%-17% to AD
- Neurodegenerative or non-degenerative conditions may underlie MCI

Subjective Cognitive Decline (SCD)
Self-experienced persistent decline in cognitive capacity with normal performance on standardized cognitive tests (SCD-Initiative, 2014)

- Associated with an increased risk of positive biomarkers for Alzheimer’s pathology
- Older people with SCD are twice as likely to develop dementia as individuals without SCD
- Associated with depression, anxiety, personality traits, sleep problems and concurrent medication use
- Large community-based studies estimated prevalence in the order of 12% in 45-64 aged adults and of 50% to 60% in older adults which increases with age

1 Ward A et al. Rate of conversion from prodromal Alzheimer’s disease to Alzheimer’s dementia: a systematic review of the literature. Dement Geriatr Cogn Dis Extra. 2013
## Materials and methods

### 284 subjects

Auto-referred to the Centre for Alzheimer’s Disease and Adult Cognitive Disorders of Careggi Hospital in Florence between March 1990 and March 2017

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
</table>
| 1. Complaint of cognitive decline ≥6 months in duration  
2. Not satisfied criteria for dementia at baseline  
3. Attainment of the clinical endpoint (i.e. conversion to MCI or to AD during follow up) or a follow up longer than 2 years in those who did not convert | 1. History of head injury  
2. Current neurological and/or systemic disease  
3. Symptoms of psychosis or major depression  
4. Alcoholism or other substance abuse  
5. Age at the end of follow up <65 years |

### Inclusion Criteria

- Comprehensive familial and clinical history
- General and neurological examination
- Extensive neuropsychological investigation
- Assessment of depression (HDRS)
- APOE genotype analysis (109)
- Personality traits and leisure activities (60)

### Exclusion Criteria

1. History of head injury
2. Current neurological and/or systemic disease
3. Symptoms of psychosis or major depression
4. Alcoholism or other substance abuse
5. Age at the end of follow up <65 years

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# Neuropsychological Assessment

**Short- and long-term verbal memory**
- Digit Span (DS)
- Five Items (FI) and Paired Words (PW) Acquisition and Recall after 10 min and 24-h
- Babcock Immediate (BS) and Delayed Recall (BSR)

**Language**
- Token Test (TT)
- Set Test (SET)
- Phonemic Fluency Test (PFT)

**Visuo-motor functions**
- Copying Drawings (CD)
- Copy of Rey-Osterrieth Complex Figure test (RFR)

**Visuo-spatial memory**
- Recall of Rey-Osterrieth Complex Figure test (RFR)

**Attention/executive functions**
- Dual Task (DT)
- Trail Making Test (TMT)

**Everyday memory**
- Rivermead Behavioral Memory Test (RMBT)

**Composite Memory Score 1 (CMS 1)**

**Composite Memory Score 2 (CMS 2)**

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### Personality Traits (36 subjects)

**Big Five Factors Questionnaire**
- Emotional stability
- Energy
- Conscientiousness
- Agreeableness
- Openness to culture and experience

### Cognitive Reserve

**Leisure Activities**
- Intellectual Activities (INT)
- Social Activities (SOC)
- Physical Activities (PHY)

**Education**
- Schooling (in years)

**Premorbid Intelligence**
- Test di Intelligenza Breve (TIB)

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Results

110 SCD

- 68 SCD (62%) → SCD-s
  - Average follow up time: 7.15 (± 3.88) years
    (min: 2 years; max: 18.48 years)

- 26 MCI (23%) → SCD-p
  - Average follow up time: 10.15 (± 7.89) years
    (min: 4.96; max: 16.77 years)

- 15 AD (14%) → SCD-c
  - Average conversion time: 9.14 (± 4.22) years
    (min: 3.39; max: 15.92 years)

- 1 other dem. (1%)
  - 1 VaD

109 MCI

- 64 MCI (59%) → MCI-s
  - Average follow up time: 7.27 (± 4.66) years
    (min: 2; max: 27.20 years)

- 39 AD (36%) → MCI-c
  - Average conversion time: 3.25 (± 2.47) years
    (min: 0.41; max: 11.16 years)

- 6 other dem. (5%)
  - 5 VaD, 1 FTD

# Demographic and cognitive features

<table>
<thead>
<tr>
<th>Features</th>
<th>SCD-s (68)</th>
<th>SCD-p (26)</th>
<th>SCD-c (15)</th>
<th>p (1)</th>
<th>p (2)</th>
<th>MCI-s (64)</th>
<th>MCI-c (39)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at baseline (± SD)</td>
<td>64.45 (± 6.63)</td>
<td>63.80 (± 8.85)</td>
<td>66.91 (± 5.75)</td>
<td>0.960</td>
<td>0.161</td>
<td>67.21 (± 7.025)</td>
<td>71.97 (± 5.12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age at onset (± SD)</td>
<td>55.65 (± 8.91)</td>
<td>60.56 (± 7.41)</td>
<td>62.53 (± 7.07)</td>
<td>0.813</td>
<td>0.281</td>
<td>62.89 (± 7.41)</td>
<td>68.59 (± 5.95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (females/males)</td>
<td>44/24</td>
<td>19/7</td>
<td>11/4</td>
<td>0.440</td>
<td>0.764</td>
<td>41/22</td>
<td>26/13</td>
<td>0.870</td>
</tr>
<tr>
<td>Familiarity (%)</td>
<td>52.94%</td>
<td>53.85%</td>
<td>46.46%</td>
<td>0.937</td>
<td>0.778</td>
<td>54.68%</td>
<td>51.28%</td>
<td>0.737</td>
</tr>
<tr>
<td>Follow up/Conversion time</td>
<td>7.15 (± 3.88)</td>
<td>6.53 (± 3.11)*</td>
<td>9.14 (± 4.22)*</td>
<td>0.892</td>
<td>0.106</td>
<td>7.27 (± 4.66)</td>
<td>3.25 (± 2.47)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Disease duration (± SD)</td>
<td>4.26 (± 3.84)</td>
<td>3.98 (± 3.24)</td>
<td>4.40 (± 4.08)</td>
<td>0.640</td>
<td>0.731</td>
<td>4.32 (± 3.24)</td>
<td>3.38 (± 2.82)</td>
<td>0.092</td>
</tr>
<tr>
<td>Schooling (± SD)</td>
<td>11.25 (± 4.77)</td>
<td>9.54 (± 4.17)</td>
<td>11.20 (± 5.39)</td>
<td>0.117</td>
<td>0.795</td>
<td>8.58 (± 4.46)</td>
<td>9.05 (± 4.57)</td>
<td>0.615</td>
</tr>
<tr>
<td>MMSE (± SD)</td>
<td>28.31 (± 1.83)</td>
<td>28.07 (± 2.04)</td>
<td>27.23 (± 2.56)</td>
<td>0.601</td>
<td>0.069</td>
<td>26.72 (± 2.15)</td>
<td>25.82 (± 2.21)</td>
<td>0.083</td>
</tr>
<tr>
<td>APOE e4+ (%)</td>
<td>21.56 %</td>
<td>33.33%</td>
<td>54.54%</td>
<td>0.319</td>
<td>0.056</td>
<td>12.12%</td>
<td>61.90%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDRS (± SD)</td>
<td>26.67 (± 4.19)</td>
<td>26.38 (± 3.91)</td>
<td>26.33 (± 3.69)</td>
<td>0.909</td>
<td>0.932</td>
<td>27.10 (± 4.62)</td>
<td>26.42 (± 3.97)</td>
<td>0.556</td>
</tr>
<tr>
<td>TIB (± SD)</td>
<td>111.48 (± 6.24)</td>
<td>109.43 (± 8.77)</td>
<td>110.58 (± 6.64)</td>
<td>0.281</td>
<td>0.409</td>
<td>103.73 (± 12.62)</td>
<td>107.15 (± 10.751)</td>
<td>0.241</td>
</tr>
</tbody>
</table>

Values quoted in the table are mean (±SD). Age at baseline, age at onset, disease duration, follow up time and schooling are expressed in years. p (1) indicates level of significance for comparison between SCD-nc and MCI; p (2) indicates level of significance for the comparisons between SCD-nc and AD; p indicates level of significance for comparison between MCI-n and AD.

*In MCI and AD groups follow up indicates conversion to MCI and to AD time.
Neuropsychological assessment - SCD

<table>
<thead>
<tr>
<th></th>
<th>AUC</th>
<th>Cut-off*</th>
<th>Sens.</th>
<th>Spec.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMS1</td>
<td>0.679</td>
<td>-0.93</td>
<td>60.0%</td>
<td>72.1%</td>
</tr>
<tr>
<td>CMS2</td>
<td>0.671</td>
<td>-0.32</td>
<td>60.0%</td>
<td>73.5%</td>
</tr>
<tr>
<td>FI24</td>
<td>0.683</td>
<td>0.02</td>
<td>86.7%</td>
<td>44.4%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SCD to AD</th>
<th>B</th>
<th>Wald</th>
<th>p</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMS1</td>
<td>3.415</td>
<td>4.089</td>
<td>0.043</td>
<td>30.427</td>
<td>(1.111;833.617)</td>
</tr>
</tbody>
</table>

Cox regression model controlled for age and APOE. $\chi^2= 7.91, p=0.020$

*expressed as z-scores
### MCI to AD

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>Wald</th>
<th>p</th>
<th>HR</th>
<th>[95% C.I.]</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMS2</td>
<td>1.469</td>
<td>5.322</td>
<td>0.021</td>
<td>4.346</td>
<td>[1.247;15.145]</td>
</tr>
<tr>
<td>BSR</td>
<td>1.161</td>
<td>4.281</td>
<td>0.039</td>
<td>3.194</td>
<td>[0.104;0.941]</td>
</tr>
</tbody>
</table>

Cox regression model controlled for age and APOE

χ² = 27.093, p<0.001

*expressed as z-scores
Personality traits - SCD

<table>
<thead>
<tr>
<th>SCD to MCI</th>
<th>B</th>
<th>Wald</th>
<th>p</th>
<th>HR</th>
<th>[95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>E.S.</td>
<td>0.086</td>
<td>5.442</td>
<td>0.013</td>
<td>1.089</td>
<td>(1.019;1.165)</td>
</tr>
</tbody>
</table>

Cox regression model controlled for age and APOE. $\chi^2 = 16.877$, $p = 0.010$

Cognitive reserve - SCD

<table>
<thead>
<tr>
<th>SCD to MCI</th>
<th>B</th>
<th>Wald</th>
<th>p</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>INT</td>
<td>-0.357</td>
<td>5.093</td>
<td>0.007</td>
<td>0.700</td>
<td>0.540; 0.907</td>
</tr>
</tbody>
</table>

Cox regression model controlled for age and schooling. ($\chi^2 = 12.122$, $p = 0.007$)
1. Slight differences in neuropsychological test scores between converters and non-converters are detectable up to 7 years before conversion to MCI and up to 9 years before conversion to AD.

2. Neuropsychological assessment may represent a reliable tool in outpatient evaluation to estimate the risk of progression to AD.

3. Composite scores are more accurate than single test scores and are not influenced by confounding factors (age, APOE).

4. Emotional stability is a risk factor for progression to MCI in subjects experiencing SCD.

5. Cognitive reserve (high Intellectual Activities and TIB) is a protective factor in the progression from SCD to MCI.
Department of Neurological and Psychiatric Sciences, University of Florence

Prof. Sandro Sorbi
Valentina Bessi
Camilla Ferrari
Gemma Lombardi
Giulia Lucidi
Federica Terenzi

Laboratory of Neurogenetics
Prof. Benedetta Nacmias
Silvia Bagnoli
Elena Cellini

Neuropsychologists
Sonia Padiglieni
Cristina Polito

Thank you for the attention