Azienda Ospedaliero Universitaria Careggi

UNIVERSITÀ DEGLI STUDI FIRENZE
NEUROFARBA
DIPARTIMENTO DI NEUROSCIENZE, PSICOLOGIA, AREA DEL FARMACO E SALUTE DEL BAMBINO

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

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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 [1]
- 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[2]
- Older people with SCD are twice as likely to develop dementia as individuals without SCD[3]
- 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[4]

[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

[2] Stewart R et al. (2011) Longitudinal neuroimaging correlates of subjective memory impairment: 4-year prospective community study. Br. J. Psychiatry J. Ment. Sci.

[3] Mendonça MD et al. (2016) From Subjective Cognitive Complaints to Dementia: Who is at Risk?: A Systematic Review. Am. J. Alzheimers Dis. Other Demen.

[4] Paradise MB,et al. (2011) Subjective memory complaints, vascular risk factors and psychological distress in the middle-aged: a cross-sectional study. BMC Psychiatry

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

1. Comprehensive familial and clinical history
2. General and neurological examination
3. Extensive neuropsychological investigation
4. Assessment of depression (HDRS)
5. APOE genotype analysis (109)
6. Personality traits and leisure activities (60)

Inclusion Criteria	Exclusion Criteria
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

Satisfied criteria for Mild Cognitive Impairment[1]?

No → **110 SCD**

Yes → **109 MCI**

[1]Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: reccomandation from the National Institute on Aging-Alzheimer's Association workgroup on diagnostic guidelines for Alzheimer's disease. Alzheimer Dement. 2011.

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)*[1]
Composite Memory Score 2 (CMS 2)[1]**

*(-0.069)/FI24 + (-0.188)PM + (-0.027)PWA + (-0.023)MC + (-0.050)Orientation + 2.546
** (-0.129)FI24 + (0.169) PM + (-0.188)PWA + (0.072)MC + (0.032)Orientation – 2.804

Personality Traits (36 subjects)

Big Five Factors Questionnaire[2]:
- Emotional stability
- Energy
- Conscientiousness
- Agreeableness
- Openness to culture and experience

Cognitive Reserve

Leisure Activities[4] (36 subjects)
- Intellectual Activities (INT)
- Social Activities (SOC)
- Physical Activities (PHY)

Education
Schooling (in years)

Premorbid Intelligence
Test di Intelligenza Breve (TIB)[3]

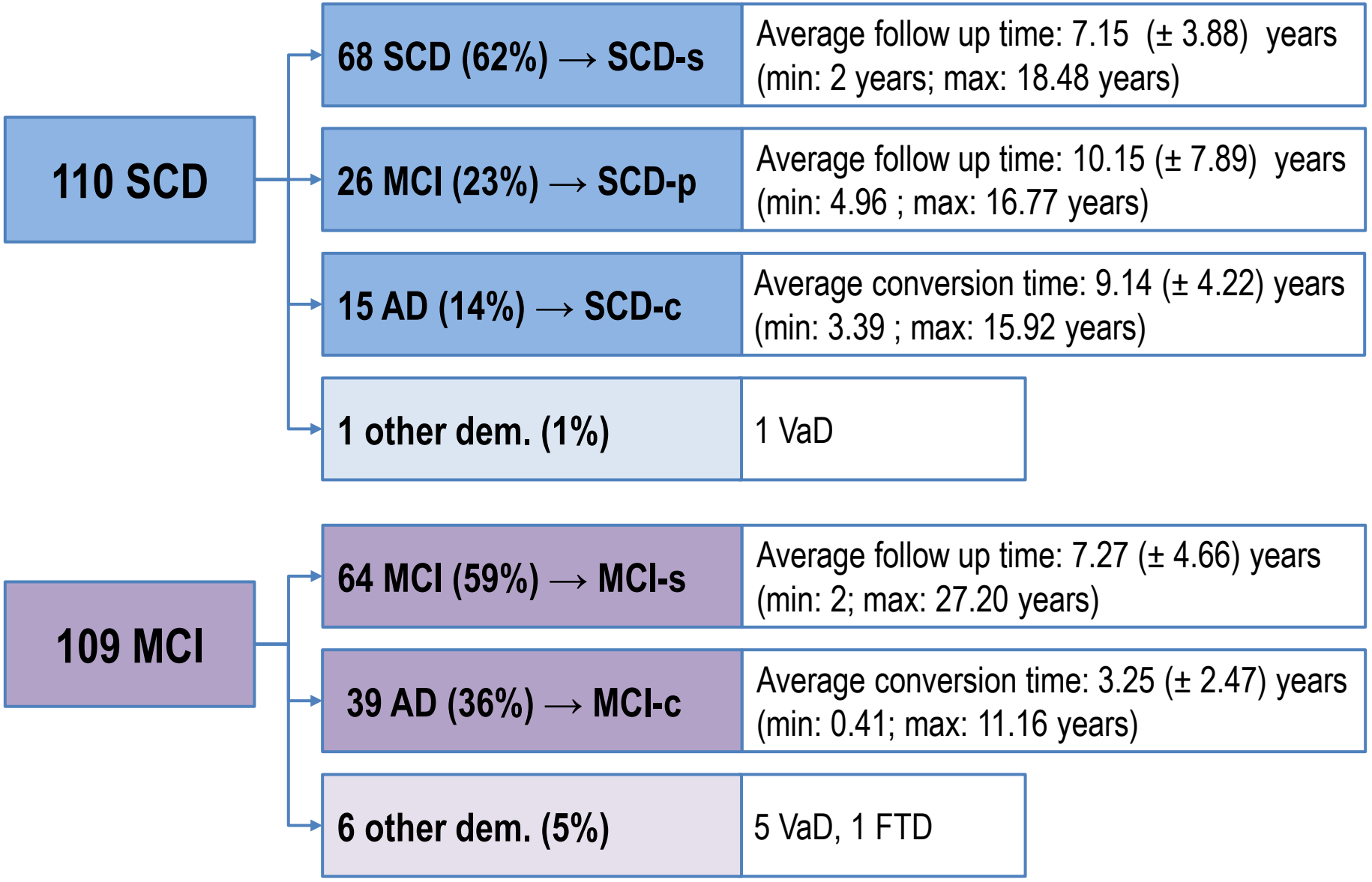
[1]Bracco L, et al. (1990) Italian Multicentre Study on Dementia (SMID): a neuropsychological test battery for assessing Alzheimer's disease. *J. Psychiatr. Res.*

[2]Goldberg LR , et al.(1992) The development of markers for the Big-Five factor structure. Psychol. Assess.

[3]Colombo L, et al.(2002) Stima del quoziente intellettivo tramite l'applicazione del TIB (Test Breve di Intelligenza). G. Ital. Psicol.

[4]Yarnold PR, et al.(1995) Cross-sectional psychometric assessment of the Functional Status Questionnaire: use with geriatric versus nongeriatric ambulatory medical patients. Int. J. Psychiatry Med.

Results



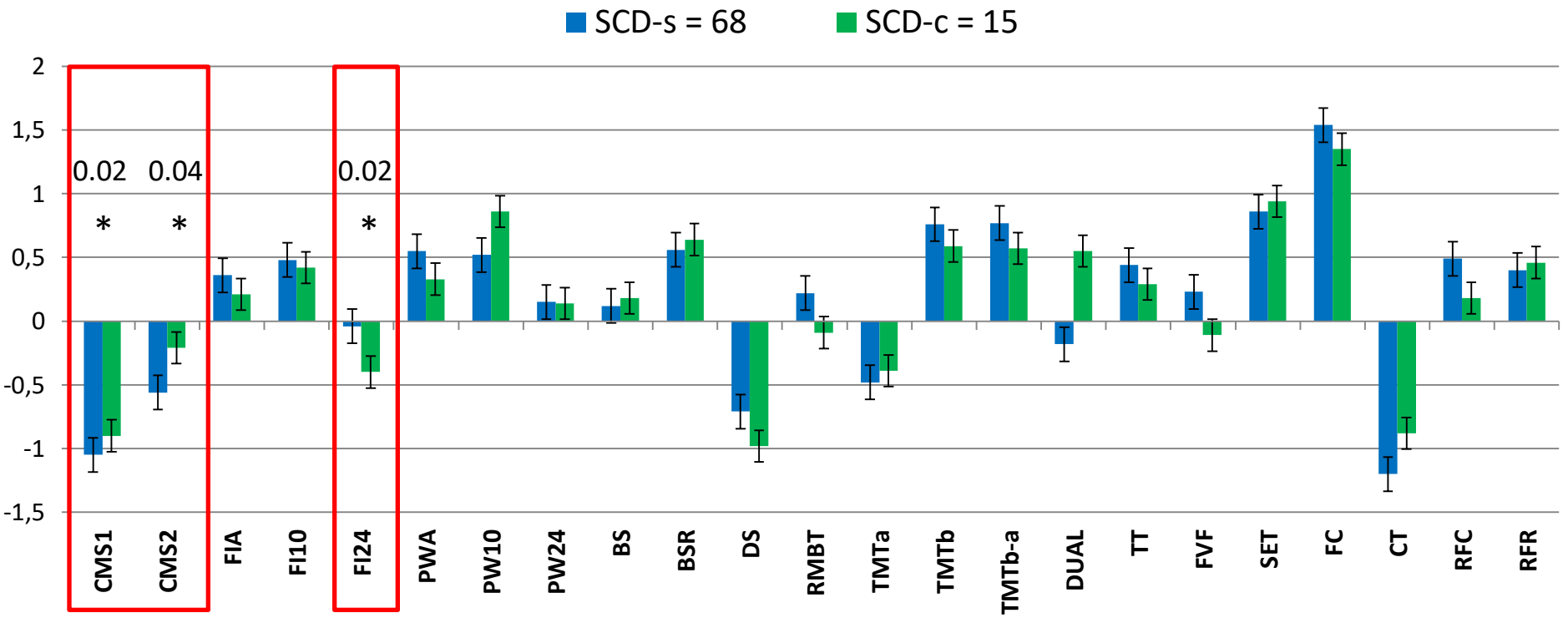
McKhann GM, et al. (2011) The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement. J. Alzheimers Assoc.* **7**, 263–269.

Demographic and cognitive features

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

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 significanze for comparison between MCI-n and AD.
*In MCI and AD groups follow up indicates conversion to MCI and to AD time.

Neuropshycological assessment - SCD



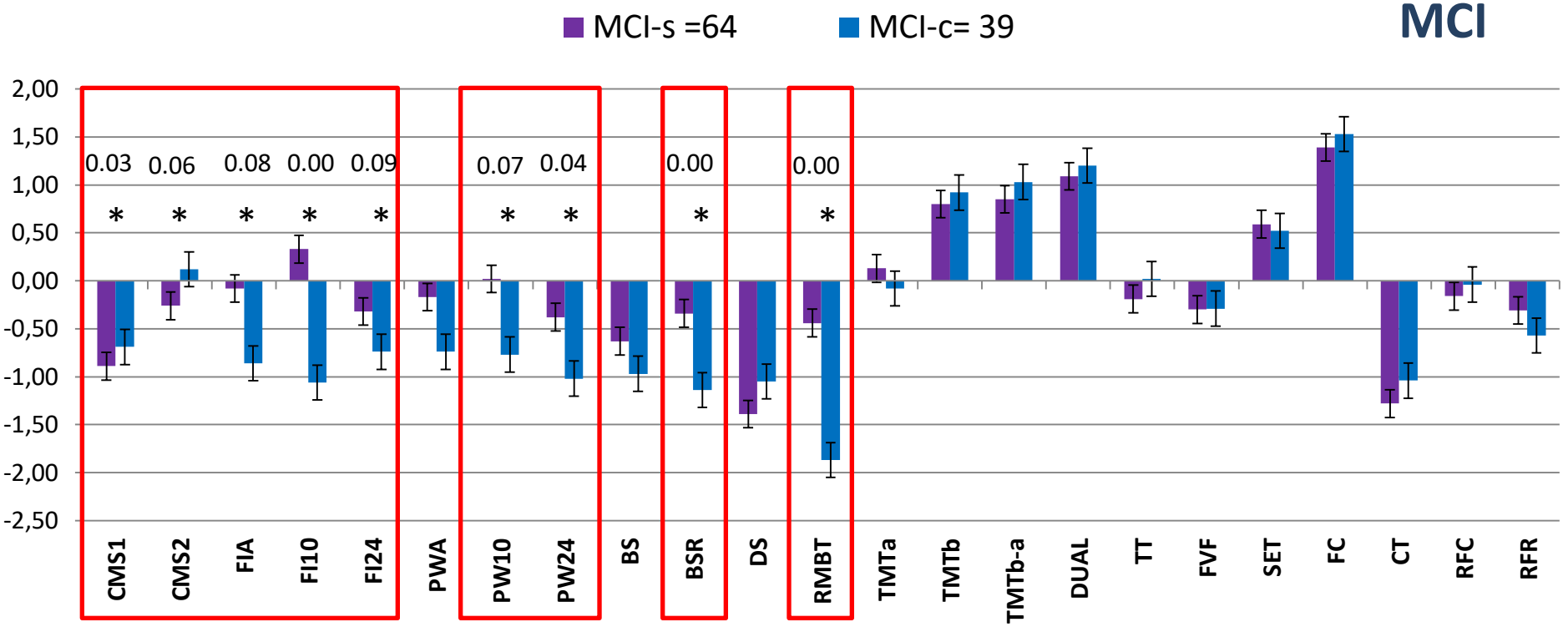
	AUC	Cut-off*	Sens.	Spec.
CMS1	0.679	-0.93	60.0%	72.1%
CMS2	0.671	-0.32	60.0%	73.5%
FI24	0.683	0.02	86.7%	44.4%

*expressed as **z-scores**

SCD to AD	*B*	Wald	*p*	HR	95% CI
CMS1	3.415	4.089	0.043	30.427	(1.111;833.617)

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

MCI



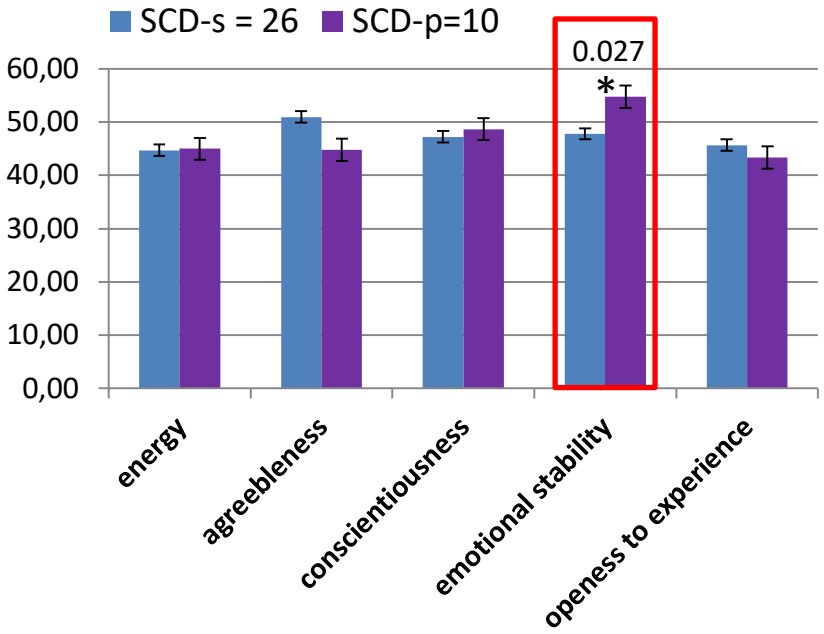
	AUC	Cut-off*	Sens.	Spec.
CMS2	0.794	-0.035	73.2%	72.7%
RMBT	0.788	-0.93	72.7%	80.5%
BSR	0.785	-0.74	77.3%	65.9%
CMS1	0.782	-0.74	68.2%	78.0%
FI10	0.761	-0.05	68.2%	78.0%
FI24	0.739	-0.58	63.6%	65.9%
FIA	0.738	-0.15	68.2%	61.0%
PW10	0.710	0.11	68.2%	65.9%
PW24	0.669	-0.58	63.6%	68.3%

MCI to AD	*B*	Wald	*p*	HR	[95% C.I.]
CMS2	1.469	5.322	0.021	4.346	[1.247;15.145]
BSR	1.161	4.281	0.039	3.194	[0.104;0.941]

Cox regression model controlled for age and APOE
$\chi 2 = 27.093$, $p<0.001$

*expressed as **z-scores**

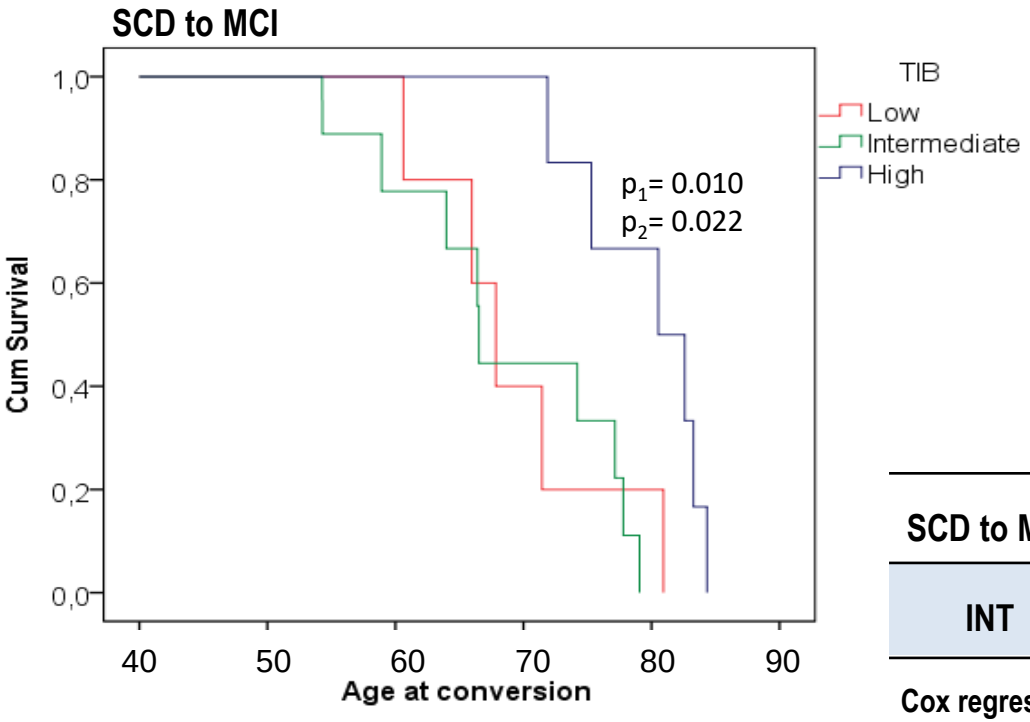
Personality traits - SCD

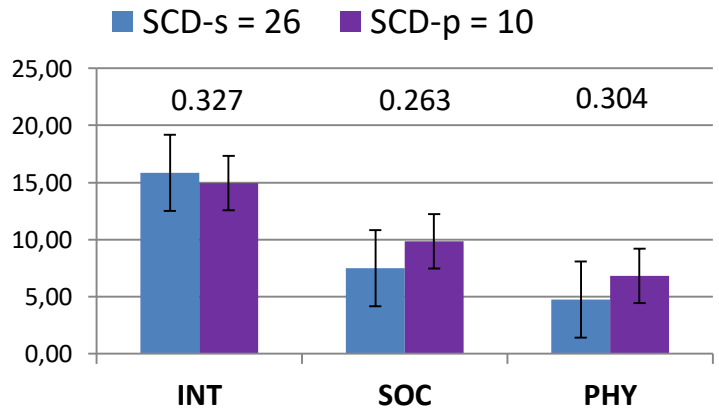


SCD to MCI	*B*	Wald	*p*	HR	[95% CI]
E.S.	0.086	5.442	0.013	1.089	(1.019;1.165)

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

Cognitive reserve - SCD





SCD to MCI	*B*	Wald	*p*	HR	95% CI	
INT	-0.357	5.093	0.007	0.700	0.540	0.907

Cox regression model controlled for age and schooling. (χ^2= 12.122 , *p* = 0.007)

Conclusions

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.

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Thank you for the attention