Structuring the heterogeneity of Subjective Cognitive Decline: data-driven subtypes reveal distinct cognitive profiles, Alzheimer's disease biomarkers, and clinical trajectories

Salvatore Mazzeo[1,2], Sara Boveri[3], Elisa Bortolin[1,2], Giulia Bruschi[1], Emanuele Girani[3], Alessandro Bombaci[1,2], Federico Emanuele Pozzi[2], Maria Vittoria Corbari[1], Federico Ambrogi[3], Federica Agosta[4], Massimo Filippi[4], Maria Salsone[1,2], for the Alzheimer's Disease Neuroimaging Initiative

1. Vita-Salute San Raffaele University, Via Olgettina 58, 20132, Milan, Italy; 2. Neurology Unit, IRCCS Policlinico San Donato, Piazza Edmondo Malan 2, 20097, San Donato Milanese, Italy; 3. Laboratory of Biostatistics and Data Management, Scientific Directorate, IRCCS Policlinico San Donato, San Donato Milanese, Italy; 4. Vita-Salute San Raffaele University, and Neurology Unit, Neurorehabilitation Unit, and Neurophysiology Service, IRCCS Ospedale San Raffaele, Milan, Italy

BACKGROUND AND AIMS

Subjective Cognitive Decline (SCD) could represent the first manifestation of symptomatic Alzheimer's disease (AD) stages, preceding mild cognitive impairment (MCI). However, SCD constitutes a heterogeneous group, often linked to non-degenerative and potentially treatable conditions. Thus, identifying the underlying causes is essential to guide patients toward the most appropriate care pathway. Building on evidence from MCI research, we hypothesized that **distinct cognitive subtypes may exist within the SCD population**, each associated with specific biomarker profiles and differing clinical outcomes.

METHODS

We analyzed data from the AD Neuroimaging Initiative (ADNI) database, including 346 SCD individuals, 542 cognitively normal controls (CN), and 423 early-MCI (E-MCI) patients. For all participants, demographic variables, cognitive measures, *APOE* genotype, CSF biomarkers, and ^{18}F-FDG-PET data were available. Participants underwent follow-up visits every 6 or 12 months. To reduce dimensionality of cognitive domain scores and functional measures (RAVLT-immediate, RAVLT-learning, RAVLT-forgetting, LDEL, ADASQ4, TMT-B, FAQ and all the ECog dimensions), we applied principal component analysis (PCA). Based on the identified principal components (PCs) a hierarchical cluster analysis was performed by using Ward's method to order SCD group patients. Linear mixed effects models appropriate for repeated measures data were used to assess the effects of time, cluster, and the interaction of cluster and time on cognitive measures. All models were adjusted for age.

RESULTS

Table 1. Cluster analysis identified three clusters among the SCD participants (k1 = 37, k2 = 199, k3 =110). We compared the three SCD clusters between themselves and with the CN and E-MCI groups (Table 1). Regarding demographic features, k2 had the highest proportion of women compared to k3, CN, and E-MCI, and had the lowest mean age compared to k1, CN, and E-MCI. Also, k3 was younger than CN.

Table 1	CN (n=542)	k1 (n=37)	k2 (n=199)	k3 (n=110)	E-MCI (n=423)	p-value
Gender, women	287 (53.0) $ &	21 (56.8)	137 (68.8) $ + ◊	57 (51.8) +	195 (46.1) & ◊	<0.0001
Age, years	73.3±6.3 $ % &	75.2±7.6 * §	69.3±6.09 $ * ◊	71.1±7.0 %	71.2±7.5 & § ◊	<0.0001
Education, years	16.42±2.62 &	16.8±2.4	16.8±2.2 ◊	16.4±2.6	16.00±2.65 & ◊	0.003
Ethnic group						0.52
Hispanic/latino	26 (4.8)	2 (5.4)	18 (9.0)	6 (5.5)	23 (5.4)	
Non-Hispanic White	514 (94.8)	34 (91.9)	181 (90.9)	103 (93.6)	398 (94.1)	
Unknown	2 (0.4)	1 (2.7)	0	1 (0.9)	2 (0.5)	
Married	370 (68.3)	21 (56.8)	145 (72.9)	73 (66.4)	321 (76.1)	0.46
APOE ε4	142 (26.2) &	19 (51.4)	101 (50.8)	61 (55.5)	163 (38.5) &	0.002

Values quoted in the table are mean±SD for continuous variables and frequencies (%) for categorical variables. Superscript symbols denote pairwise group comparisons as follows: (!) CN vs k1; ($) CN vs k2; (%) CN vs k3; (&) CN vs E-MCI; (*) k1 vs k2; (?) k1 vs k3; (§) k1 vs E-MCI; (+) k2 vs k3; (◊) k2 vs E-MCI; (#) k3 vs E-MCI. Underlined values denote statistically significant differences between clusters.

Fig 1.A: **Comparisons in cognitive measures**

- **Global cognition**: all SCD clusters performed better on the MMSE compared to the E-MCI group; in the MoCA and ADAS-Cog, k1 and k3 performed worse than CN and k2; in the ADAS-Cog, k2 performed even better than CN.
- **Short-term verbal memory:** in RAVLT, k2 outperformed all other groups (CN, k1, k3, and E-MCI); k3 showed the worst performance compared to k1, k2, and CN; k3 also performed worse than the E-MCI group on the RAVLT-forgetting.
- **Long-term verbal memory:** k2 performed better than all other SCD clusters and the E-MCI group on the LDEL, and even outperformed CN on ADAS-Q4; k3 performed worse than both CN and k2 on ADAS-Q4 and LDEL; k1 performed worse than CN on LDEL.
- **Executive function:** in TMT-B, k1 showed the poorest performance, even compared to the E-MCI group; k2 outperformed all groups (CN, k1, k3, and E-MCI); k3 did not differ significantly from CN.

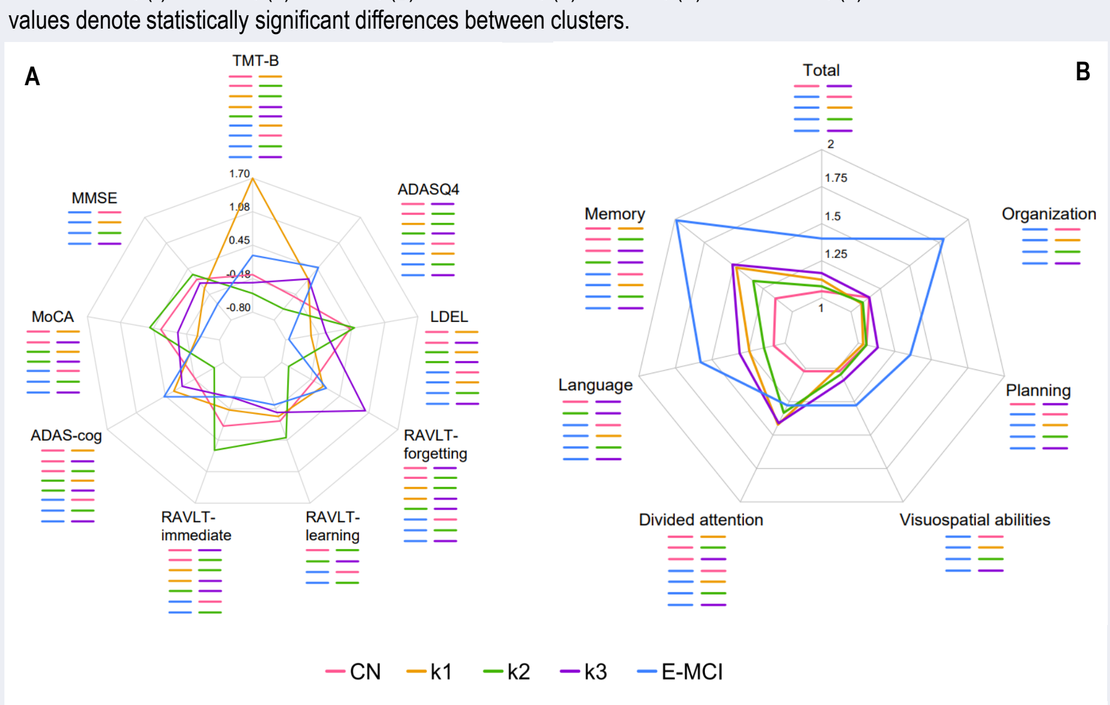


Figure 1. Colored lines under each domain indicate statistically significant pairwise differences between groups for that specific domain CDR-SB (Clinical Dementia Rating–Sum of Boxes), MMSE (Mini-Mental State Examination), MoCA (Montreal Cognitive Assessment), ADAS-cog (Alzheimer's Disease Assessment Scale–Cognitive Subscale), RAVLT (Rey Auditory Verbal Learning Test), ADASQ4 (ADAS-Cog Question 4), LDEL (Logical Delayed Recall).

Fig 1.B: **Everyday cognition**

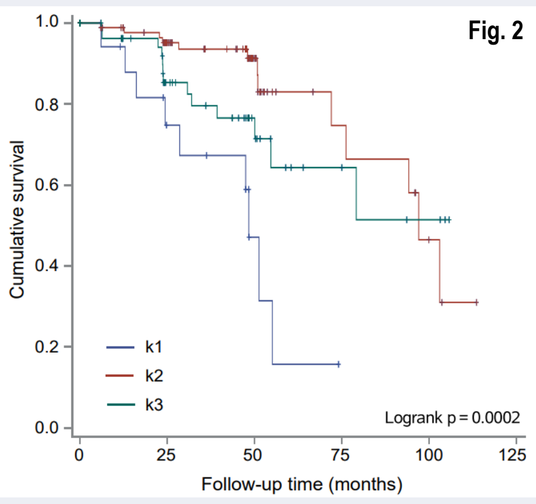
- **Memory:** k2 had better scores than k3; no significant differences were found between k1 and k3 or between k1 and k2; all SCD clusters had worse scores than CN but better than E-MCI.
- **Language**: k3 scored lower than both CN and k2; all the SCD clusters performed better than E-MCI.
- **Divided attention**: all the SCD clusters (k1, k2, k3) had poorer scores compared to both CN and E-MCI, with no differences among the clusters.
- **Visuospatial abilities:** CN and all SCD clusters had better scores than E-MCI, with no significant differences among the SCD clusters.
- **Planning:** k3 scored lower than CN; no significant differences were found among the SCD clusters, and all performed better than E-MCI.
- **Organization**: No significant differences among the clusters.

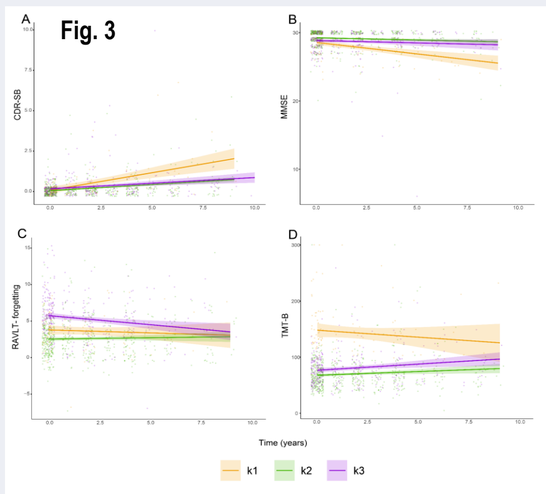
Table 2. AD biomarker comparisons

- **CSF biomarkers**: compared to E-MCI, k2 had lower p-tau concentration and k3 had a higher concentration of $A\beta_{42}$; there were no significant differences between the SCD clusters.
- **FDG-PET SUVRs**: k1 had the lowest values compared to CN, k2, and k3, with no differences observed with E-MCI; CN, k2, and k3 had higher values than E-MCI.
- **Structural MRI:** k2 and k3 exhibited higher trophism in the hippocampus and entorhinal cortex compared to E-MCI; k2 had smaller ventricle volume; there were no significant differences between the SCD clusters.

Table 2						
CSF biomarkers						
$A\beta_{42}$	1015.32±385.99 &	1002.6±351.1	1092.2±379.3	1131.3±379.8 #	942.87±355.28 & #	0.01
t-tau	238.45±88.96 &	250.0±110.5	226.0±89.7	255.6±91.4	256.41±121.74 &	0.03
p-tau	22.00±9.08 &	22.4±9.8	20.6±9.2 ◊	23.4±10.0	24.25±13.69 & ◊	0.03
Brain metabolism						
FDG-PET SUVRs	1.28±0.12 ! &	1.19±0.50 ! * ?	1.33±0.45 * ◊	1.31±0.47 ? #	1.25±0.13 & ◊ #	<0.001
Structural brain MRI						
Hippocampus	4.98±0.65 %	4.83±0.51 ?	5.35±0.49 +	5.10±0.69 % ? + #	4.90±0.72 #	<0.001
Entorhinal cortex	2.63±0.45 % &	2.70±0.43 ?	2.84±0.44	2.72±0.42 ? %	2.58±0.47 &	<0.001
Ventricles	21.76±10.70 %	26.32±13.64	20.36±10.51	22.28±9.70 %	23.44±12.54	0.02
MTL	13.74±1.61 %	13.98±1.50 ? §	14.54±1.58	14.24±1.6 % ?	13.85±1.55 §	<0.001

Table 2. Values quoted in the table are mean±SD for continuous variables and frequencies (%) for categorical variables. Superscript symbols denote pairwise group comparisons as follows: (!) CN vs k1; ($) CN vs k2; (%) CN vs k3; (&) CN vs E-MCI; (*) k1 vs k2; (?) k1 vs k3; (§) k1 vs E-MCI; (+) k2 vs k3; (◊) k2 vs E-MCI; (#) k3 vs E-MCI. Underlined values denote statistically significant differences between clusters. FDG-PET SUVRs (Global Standardized uptake value ratios of [18F]fluorodeoxyglucose positron emission tomography); MTL (medial temporal lobe).





Read the full text here

Mazzeo S, Boveri S, Bortolin E, et al. Data-driven subtypes of subjective cognitive decline: neuropsychological profiles, Alzheimer's disease biomarkers, and clinical trajectories. J Neurol. 2025;272(10):669. doi:10.1007/s00415-025-13418-0

Longitudinal analysis: During the follow-up, there have been 35 events of progression from SCD to MCI or dementia.

Figure 3. A Kaplan-Meier survival analysis revealed significant differences in progression to MCI or dementia across the three cognitive subtypes. Individuals in k1 had the highest rate of progression (24.3 %) over the follow-up period compared to k2 (6.5 %) and k3 (11. 8%).

Figure 4. Individuals in k1 exhibited significantly greater cognitive decline compared to those in other clusters. Specifically, participants in k1 showed a significantly steeper increase in CDR-SB scores compared to k2, and more rapid decline in MMSE and RAVLT-forgetting.

CONCLUSIONS

We proposed a three-subgroup system for SCD, reflecting different cognitive profiles and longitudinal trajectories: (1) a "dysexecutive" cluster with poorer executive functioning, showing brain hypometabolism on FDG-PET, and levels of both p-tau and $A\beta_{42}$ resembling those of the MCI group; (2) a "worried-well" cluster, with individuals reporting subjective memory and attentional complaints in the absence of objective cognitive impairment; (3) an "amnesic" cluster, marked primarily by memory deficits. Longitudinal analysis showed that cluster 1 exhibited the greatest clinical decline. Classifying individuals with SCD may enhance diagnostic pathways and inform personalized interventions.

REFERENCES

Jessen F, et al (2014) A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. Alzheimer's & Dementia 10:844–852.

Mazzeo S, et al (2020) Assessing the effectiveness of subjective cognitive decline plus criteria in predicting the progression to Alzheimer's disease: an 11-year follow-up study. Eur J Neurol 27:894–899.

Mazzeo S, et al (2024) Towards the development of a management protocol for Subjective Cognitive Decline: insights from a cross-sectional and longitudinal analyses of multimodal data from a memory clinic. 2024.

mazzeo.salvatore@hsr.it