

Towards the development of a management protocol for Subjective Cognitive Decline: Insights from a cross-sectional and longitudinal analysis of multimodal data from a memory clinic

Salvatore Mazzeo^{1,2,3}, Michael Lassi⁴, Sonia Padiglioni^{5,6}, Alberto Arturo Vergani^{4,7}, Valentina Moschini⁵, Maenia Scarpino⁵, Giulia Giacomucci^{3,5}, Rachele Burali⁸, Carmen Morinelli⁵, Carlo Fabbiani³, Giulia Galdo³, Lorenzo Gaetano Amato⁴, Silvia Bagnoli³, Assunta Ingannato³, Maria Salsone^{1,2}, Massimo Filippi⁹, Benedetta Nacmias^{3,8}, Sandro Sorbi^{3,8}, Antonello Grippo¹⁰, Alberto Mazzoni⁴, Valentina Bessi^{3,5}

BACKGROUND AND AIMS

Subjective cognitive decline (SCD) is the earliest manifestation of Alzheimer's Disease (AD). There is currently no consensus on the optimal clinical management of individuals with SCD, leading to considerable heterogeneity across centers, variability in diagnostic and therapeutic approaches. We aimed to investigate the relationships between features in Subjective Cognitive Decline (SCD) and to assess the importance of these features in the future development of dementia to inform a targeted management protocol.

RESULTS

Cross-Sectional Analysis

Table 1. Description of the sample. Median age at onset and at baseline were 59.0 years and 62.8 years respectively. Most of patients were women (68.9% vs. 31.1%, one-sample t-test for proportion: $p < 0.001$). Women were generally younger at onset and had lower APOE $\epsilon 4$ prevalence compared to men. Family history of AD was reported by about half of patients (56%). Only 6.9% of patients had depressive symptoms. 60% of patients had cerebral small vessel disease (CSVD) at MRI scan. Older patients (age >60) exhibited a higher prevalence of APOE $\epsilon 4$ and CSVD. Patients with depressive symptoms demonstrated lower cognitive performance across multiple domains.

Table 1	Median (IQR)/ n (%)
Age at onset	59.0 (14.0)
Age at onset > 60	207 (47.0)
Age at first visit	62.8 (14.0)
Symptoms duration	2.8 (3.6)
Women	303 (68.9)
Women in menopause	231 (89.2)
Menopause age	50.0 (5.0)
Family history of dementia	241 (56.6)
Women with use of HRT	71 (31.0)
Early menopause	6 (2.6)
Insomnia	224 (54.6)
Depressive symptoms	25 (6.9)
MMSE	27.9 (7.8)
SCD severity	26.0 (4.0)
APOE $\epsilon 4$	57 (29.1)
Confirmation by caregiver	50 (63.3)
Memory complaint	196 (92.0)
Worry about SCD	111 (74.0)
Years of education	13.0 (9.0)
Benzodiazepine use	58 (14.2)
SSRI/SNRI use	69 (16.8)
Anticholinergic drug use	94 (22.9)
Hypertension	142 (38.7)
Dyslipidemia	98 (29.3)
IFG or diabetes	33 (10.1)
Diabetes	14 (4.3)
Smoking habit	161 (42.6)
Current smoking habit	34 (9.0)
CSVD (Fazekas > 1)	135 (60.0)

Fig.1: The estimated MRF network showed an inverse connection between female gender and cognitive reserve. Severity of SCD was directly connected with insomnia, use of BZD, symptom duration, and female gender. Depressive symptoms were directly connected with education, female gender, use of anticholinergics, and sleep disorder. The network did not show connection between depressive symptoms and severity of SCD. MMSE had poor connections. Cognitive reserve, gender and use of BZD had a higher strength compared to depressive symptoms and symptom duration.

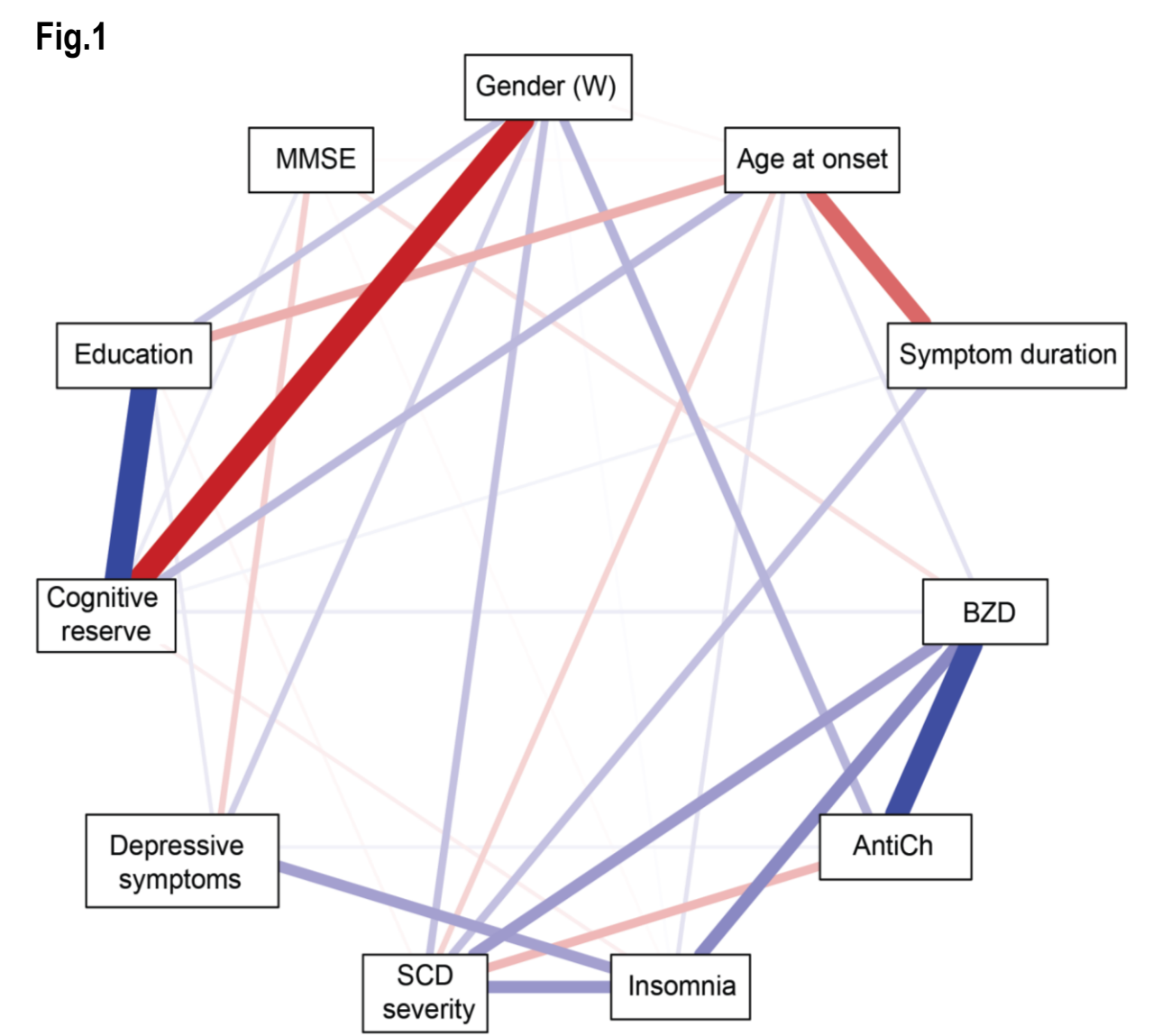


Fig. 2: During follow-up (9.7 years [min:2; max:29.2]) 60.4% of patients (69.1% women and 30.9% men) remained cognitively unimpaired (reversible/stable SCD). 38.6% of patients showed progression to MCI and 12.0% furtherly progressed to dementia (progressing SCD [p-SCD]).

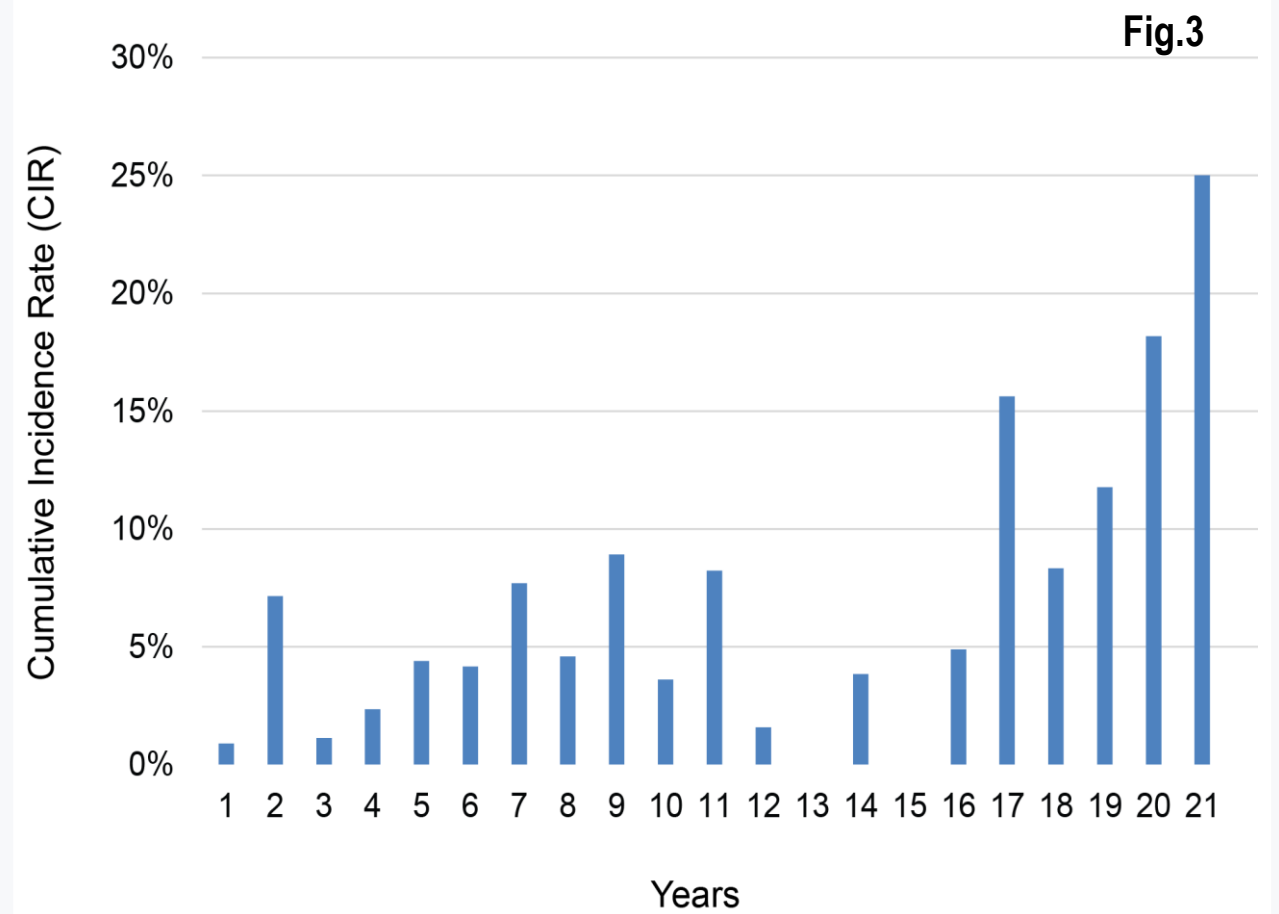


Fig. 3: The median progression time from SCD to MCI was 7.2 (IQR = 5.2) years (range: 1.0 – 20.0). Median progression time from SCD to dementia was 10.8 (IQR = 8.7) years (range: 3.4 – 22.1). We identified a first peak of incidence of progression at two years (11%) a second peak at 8 years (16%) and the highest incidence after 17 years.

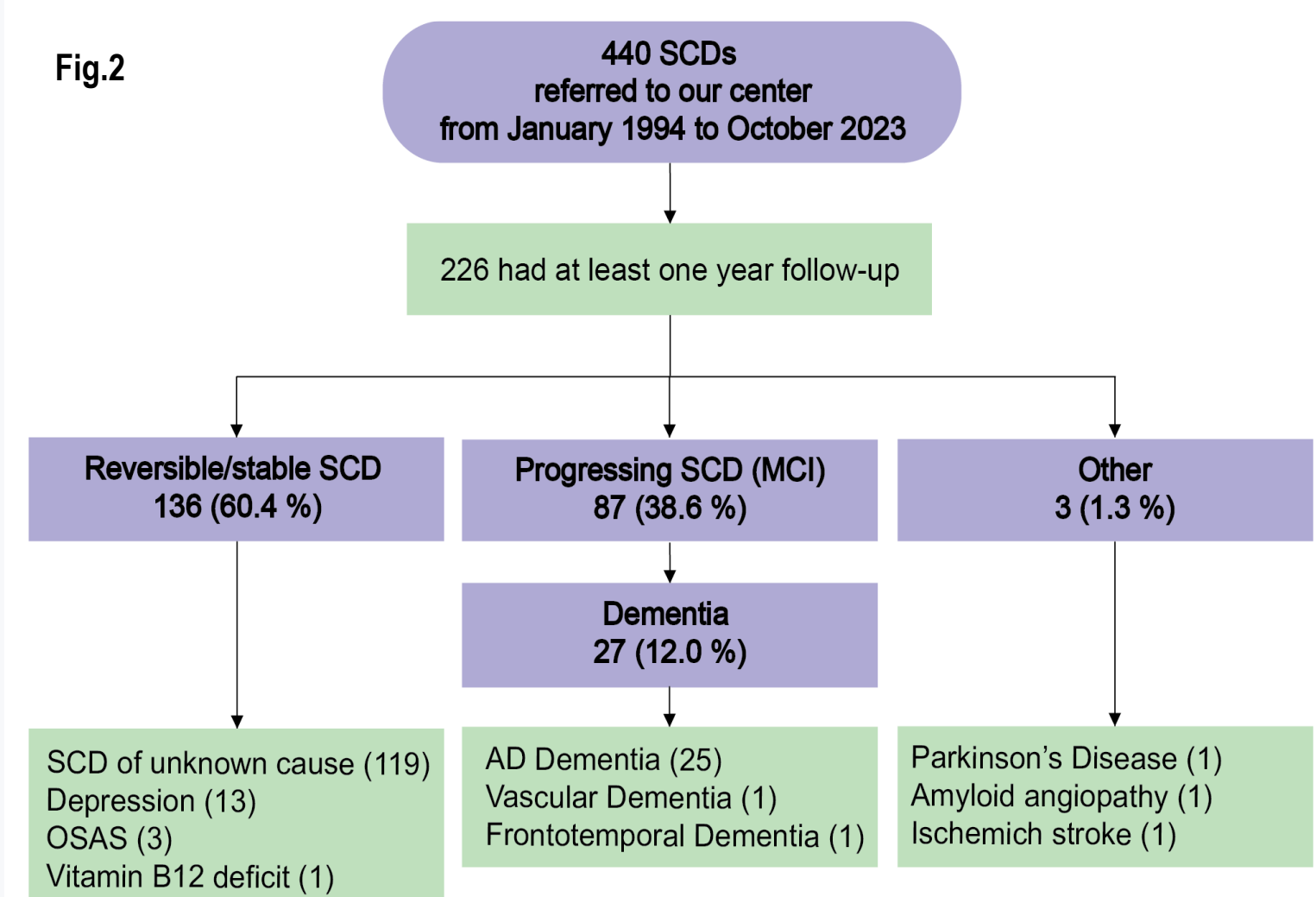
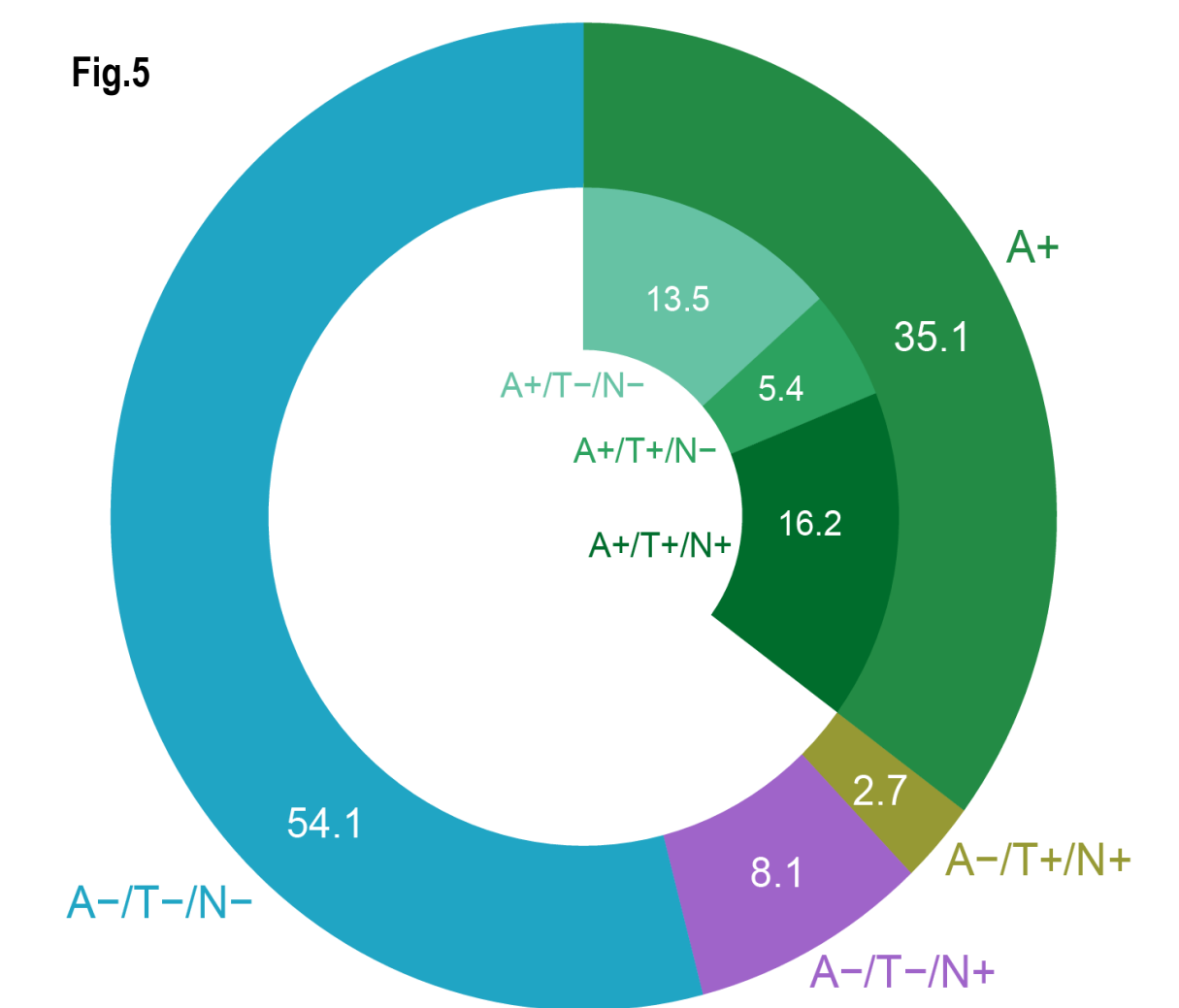
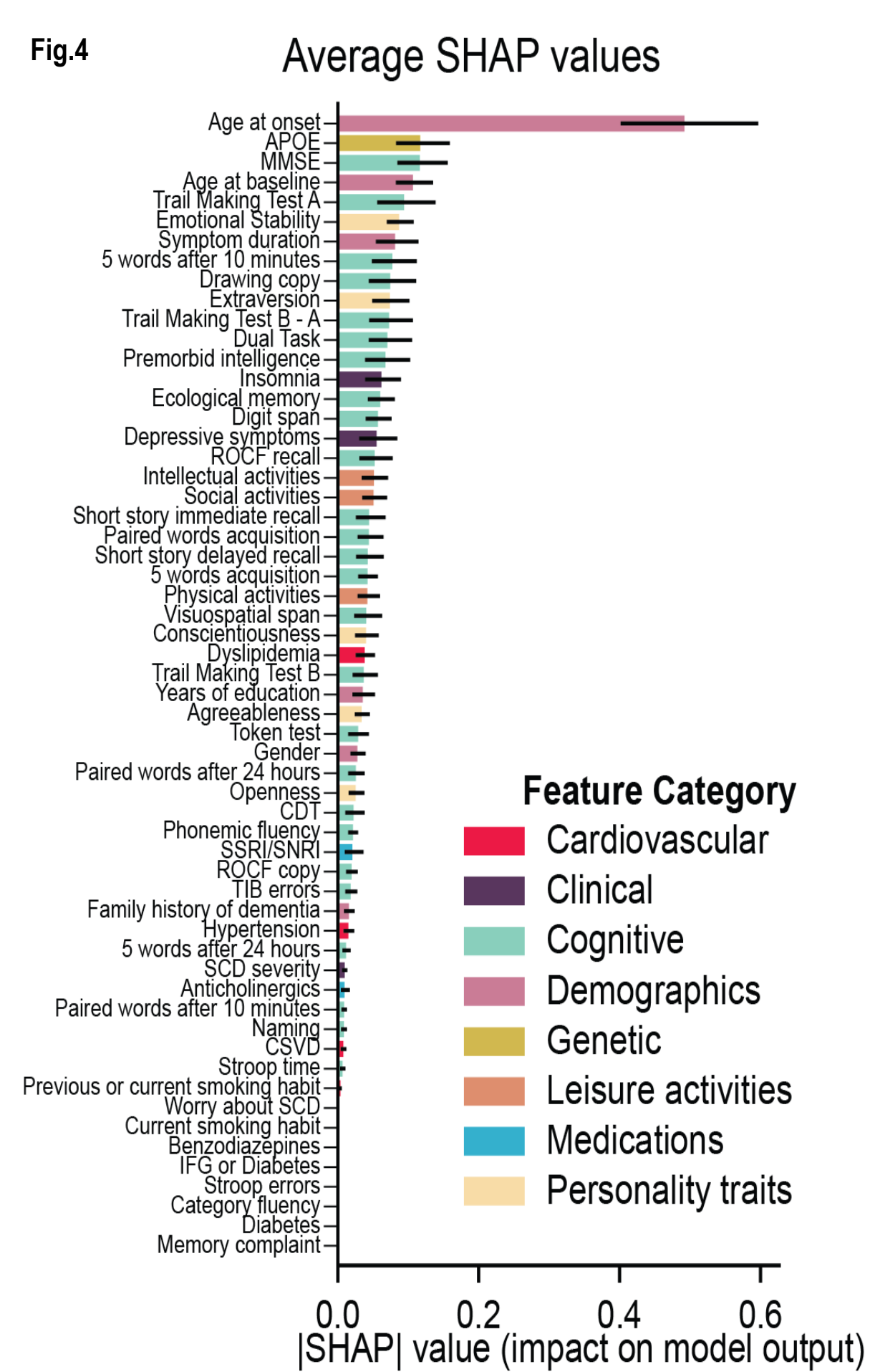


Fig. 4. The XGBoost model achieved a balanced accuracy of 74.37% [66.97 : 80.90]. Average absolute SHAP values showed the rank of importance of the features in the predictive model.



AD biomarker analysis

Fig. 5: Among patients who underwent CSF and/or Amyloid PET, 33.3% were A+. Most of them (16.2%) had a A+/T+/N+ profile and 13.5% had a A+/T-/N- profile. Three patients (8.1%) had a A-/T-/N+ profile. Only one patient had a A-/T+/N+ profile. There were no differences regarding any considered (demographic, clinical or cognitive) feature between A- and A+ patients. Patients who underwent AD biomarker assessment had a median follow-up time of 2 years (min:max = 0.2 : 9.6). During this period, ten patients progressed to MCI. 57.5% of patients who were A+ progressed to MCI. 93.1 % of A- patients, did not progress to MCI.

METHODS

The PREVIEW project is a longitudinal study funded by the Tuscany Region, Italy [1]. 440 patients with SCD were consecutively recruited among patients referred to Careggi Hospital in Florence between January 1994 and November 2023. Participants underwent neurological and neuropsychological assessments, MRI scans and APOE genotyping. Forty-three patients had AD biomarker assessment (CSF and/or amyloid-PET). Patients were followed for a median of 10 years. Relationships among features were first assessed univariately, focusing on differences across stratified subgroups. To capture multivariate associations, we applied network analysis using a Markov Random Field (MRF) [2]. Baseline features were related to dementia progression using an XGboost machine learning model [3].

Proposal for a management protocol for SCD

We suggest distinguishing between clinical and research settings and define three time points: baseline, short-term follow-up, and long-term follow-up. We recommend short-term follow-up intervals of two to five years. Long-term follow-up is the phase where, depending on the patient's trajectory, decisions can be made to either discharge the patient or conduct further evaluations. We identify three trajectories: **Reverted SCD**, **Stable SCD** and **Progressing SCD (p-SCD)**. In clinical setting, we suggest AD biomarker testing only in the p-SCD group. In all other cases, AD biomarkers should be assessed solely for research purposes. For patients undergoing AD biomarkers, we recommend classifying SCD patients with positive biomarkers as "AD with SCD" and patients with negative biomarkers as "SCD not due to AD".

Clinical setting			For research purpose or p-SCD
Baseline assesement	Short-term follow-up	Long-term follow-up	Biomarker assessment
Family history CV risk factors Sleep (insomnia, OSAS) Depressive symptoms Medications Cognitive reserve Neuropsychological examination Brain MRI	Follow-up visits and treatment according to first assesement results	Reverted SCD New evaluation only if cognitive complaint reoccurs	CSF-based AD biomarkers Imaging-based biomarkers Blood-based biomarkers
Cognitive reserve Polysomnography (if sleep disorder suspected) Tyroid function, lipid panel, vitamine B12 and folate APOE genotyping	SCD of unknown cause 1 st follow-up NPS after 1-2 years Subsequent follow-up NPS: Low risk: age at onset < 60 years Every ~5 years High risk: age at onset > 60 years or APOE $\epsilon 4$ Every ~2 years	Stable SCD Repeat MRI scan or brain FDG-PET Reconsider other causes	SCD not due to AD [A-T₁-] AD with SCD [A+ or T₁+] Yearly follow-up visits Psychological counseling Inclusion in clinical trials

REFERENCES

- Mazzeo S, et al. PRedicting the EVolution of SubjectivE Cognitive Decline to Alzheimer's Disease With machine learning: the PREVIEW study protocol. BMC Neurol. 2023 Aug 12;23(1):300. doi: 10.1186/s12883-023-03347-8.
- Epskamp S, Cramer AOJ, Waldorp LJ, et al. Ograph: network visualizations of relationships in psychometric data. J Stat Softw 2012; 48: 1–18.
- Chen T, Guestrin C. XGBoost: A Scalable Tree Boosting System. In: Proceedings of the 22nd ACM SIGKDD International Conference on Knowledge Discovery and Data Mining, pp. 785–794.

ACKNOWLEDGMENTS



1. Vita-Salute San Raffaele University, Milan, Italy; 2. IRCCS Policlinico San Donato, San Donato Milanese, Italy; 3. University of Florence, Florence, Italy; 4. The BioRobotics Institute and Department of Excellence in Robotics and AI, Scuola Superiore Sant'Anna, Pisa, Italy; 5. SOD Neurologia, Dipartimento Neuromuscolo-Scheletrico e degli Organi di Senso, AOU Careggi, Florence, Italy; 6. Regional Referral Centre for Relational Criticalities - Tuscany Region, Florence, Italy; 7. Department of Brain and Behavioural Sciences, University of Pavia, Pavia, Italy; 8. IRCCS Fondazione Don Carlo Gnocchi, Florence, Italy; 9. Vita-Salute San Raffaele University, and Neurology Unit, Neurorehabilitation Unit, and Neurophysiology Service, IRCCS Ospedale San Raffaele, Milan, Italy; 10. SOD Neurofisiopatologia, Azienda Ospedaliero-universitaria Careggi, Florence, Italy