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Research Article

Language performance as a prognostic factor for developing Alzheimer's clinical syndrome and mild cognitive impairment: Results from the population-based HELIAD cohort

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Abstract

Objectives: There is limited research on the prognostic value of language tasks regarding mild cognitive impairment (MCI) and Alzheimer's clinical syndrome (ACS) development in the cognitively normal (CN) elderly, as well as MCI to ACS conversion. **Methods:** Participants were drawn from the population-based Hellenic Longitudinal Investigation of Aging and Diet (HELIAD) cohort. Language performance was evaluated via verbal fluency [semantic (SVF) and phonemic (PVF)], confrontation naming [Boston Naming Test short form (BNTsf)], verbal comprehension, and repetition tasks. An additional language index was estimated using both verbal fluency tasks: SVF-PVF discrepancy. Cox proportional hazards analyses adjusted for important sociodemographic parameters (age, sex, education, main occupation, and socioeconomic status) and global cognitive status [Mini Mental State Examination score (MMSE)] were performed. **Results:** A total of 959 CN and 118 MCI older (>64 years) individuals had follow-up investigations after a mean of ∼3 years. Regarding the CN group, each standard deviation increase in the composite language score reduced the risk of ACS and MCI by 49% (8–72%) and 32% (8–50%), respectively; better SVF and BNTsf performance were also independently associated with reduced risk of ACS and MCI. On the other hand, using the smaller MCI participant set, no language measurement was related to the risk of MCI to ACS conversion. **Conclusions:** Impaired language performance is associated with elevated risk of ACS and MCI development. Better SVF and BNTsf performance are associated with reduced risk of ACS and MCI in CN individuals, independent of age, sex, education, main occupation, socioeconomic status, and MMSE scores at baseline.

Key words: verbal fluency; Boston naming test; comprehension; repetition; longitudinal study; risk factor

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Introduction

Language decline is a long-recognized feature of mild cognitive impairment (MCI) and dementia. Heterogeneous patterns of language impairment are often considered characteristic of different neurocognitive pathologies (Klimova & Kuca 2016; Vuorinen et al., 2000). At the same time, different language aspects tend to record dissimilar longitudinal trajectories with normal aging in older adults, with some of them declining, others improving, and several remaining relatively intact over time (Harada et al., 2013; Hartshorne & Germine, 2015; Kemper et al., 2001; Marini et al., 2005; Shafto & Tyler, 2014). For example, word finding during naturalistic speech, visual confrontation naming, grammatical and syntactic complexity, prepositional content, as well as discourse coherence tend to decline over time, "'empty'" pauses appear more frequently while semantic paraphasias and vague terms become more and more common. On the other hand, the proportion of phonologically well-formed words out of all verbalizations and the ratio of nouns to verbs produced remain unaltered, whereas conceptual knowledge generally increases even during senescence. Thus, the pattern of language impairment may provide valuable assistance

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in discriminating pathological neurocognitive entities from each other, as well as in differentiating healthy aging from early MCI and dementia processes (Gomez & White, 2016; Klimova & Kuca, 2016; Maseda et al., 2014; Nutter-Upham et al., 2008).

Apart from the discriminant quality of language performance, a small number of studies have investigated the prognostic value of language performance regarding the development of dementia or MCI. Recently, Sutin and colleagues (2019) investigated the predictive value of semantic verbal fluency (SVF) with respect to the risk of developing dementia and cognitive impairment – not dementia (CIND), capitalizing data from a sample of 18,189 individuals from the Health and Retirement Study (Sutin et al., 2019). Each standard deviation (SD) increase in SVF scores was related to 60% reduced risk of incident dementia and 25% reduced risk of incident CIND in cognitively normal (CN) adults, as well as 25% reduced risk of conversion from CIND to dementia, independently of age, sex, education, race, ethnicity, and APOE risk status. Additional smaller studies have also obtained corroborating evidence suggesting a predictive quality for SVF. SVF performance has been found to predict the development of amnestic MCI (aMCI) in CN individuals (Gustavson et al., 2020) as well as the conversion from aMCI to dementia (Gallucci et al., 2018), independently of episodic memory impairment, the hallmark of aMCI and Alzheimer's disease (AD), termed as Alzheimer's clinical syndrome (ACS) throughout the text (Jack et al., 2018). Of note, an abrupt (within two years) 1-SD decrease in SVF has been even revealed to predict the onset of dementia three years following the SVF drop, with a sensitivity and specificity of 92% and 62%, respectively (Wong et al., 2013). Furthermore, measures combining SVF with phonemic verbal fluency (PVF) scores (e.g., SVF minus PVF scores) have proved to be fair prognostic indices of MCI to dementia conversion (Vaughan et al., 2018). On the other hand, there is limited existing evidence not indicative of a predictive quality for PVF measures alone (Holtzer et al., 2020).

Linguistic components other than verbal fluency have been less extensively explored. A number of writing (e.g., misspelling and number of commas) and syntactic (e.g., dependency labels and determiners) parameters may be useful in the prediction of ACS development in CN individuals (Eyigoz et al., 2020). Measures of semantic degradation and namely lexical impoverishment reflected as increased production of high-frequency words during spontaneous speech appear to be fine predictors of future cognitive testing performance in individuals with normal cognition (Ostrand & Gunstad, 2021). Finally, little and conflicting published data support a potential prognostic value for confrontation naming in the progression of cognitive impairment, while verbal comprehension and repetition have been substantially underinvestigated as potential prognostic markers of cognitive impairment (Albert et al., 2001; Chodosh et al., 2002; Jacobs et al., 2021).

Despite the limited relevant research, language indices possess several qualities that could potentially render them suitable candidates for the prediction of ACS and MCI. SVF (rather than PVF) and confrontation naming deficits are quite prominent in individuals with ACS from an early stage, potentially reflecting a degradation of the semantic store (Henry et al., 2004). Language impairment appears to afflict individuals with MCI as well, with language subtests being more sensitive than other neuropsychological indices (even episodic memory) in revealing the presence of cognitive deficits in the early stages of MCI (McCullough et al., 2019). At the same time, previous research has suggested that episodic memory and category fluency tend to deteriorate sooner than other cognitive functions, even in the preclinical course of MCI-ACS (Mistridis et al., 2015). Moreover, relatively poor semantic fluency performance has been even found to predict incident episodic memory deficits, although episodic memory performance has not been associated with the risk of incident language deficits (Gustavson et al., 2020). Considering the above, SVF might reflect ongoing neurodegenerative processes in the preclinical course of MCI-ACS, sooner than other neuropsychological tasks.

Therefore, the present study was undertaken to investigate the prognostic value of language performance for MCI and ACS development, as well as MCI to ACS progression. Data from the prospective Hellenic Longitudinal Investigation of Aging and Diet (HELIAD) study were used. The prognostic value of composite and individual language measures (specifically SVF, PVF, SVF-PVF discrepancy, confrontation naming, comprehension, and repetition) was explored, while adjusting for global cognitive status (to account for the confounding of concomitant cognitive dysfunctions) and important sociodemographic parameters that might affect language impairment as well as the risk of developing ACS and MCI (Karp et al., 2004; Letenneur et al., 1999). It was hypothesized that relative language deficits could be present from a preclinical stage preceding the development of MCI and ACS (reflecting ongoing neurodegenerative processes) and, therefore, serve as potential clinical markers of MCI or ACS development.

Methods

Study reporting adhered to the STROBE reporting recommendations (Strengthening the Reporting of Observational Studies in Epidemiology) (von Elm et al., 2014). Participants originated from the prospective HELIAD cohort. Extensive details regarding the rationale, objectives, and other key elements of the HELIAD study have been previously reported (Dardiotis et al, 2014; Kosmidis et al., 2018; Liampas et al., 2022). In short, it is a multidisciplinary, population-based study primarily exploring the epidemiology of dementia, cognitive impairment, as well as other neuropsychological entities, among the elderly Greek population. The Institutional Ethics Review Boards of the University of Thessaly and the Kapodistrian University of Athens approved all procedures prior to the initiation of the study and was conducted in accordance with the Declaration of Helsinki. Informed consent was acquired from all participants or surrogates prior to participation.

Participant selection was carried out by random sampling, from the elderly (>64 years) registries of two Greek municipalities, Marousi (city of Athens) and Larissa (province of Thessaly). Participants underwent extensive baseline and follow-up evaluations (ongoing to date), which were intended to take place at approximately 3-year intervals. Study procedures were carried out at participants' homes, day care centers for the elderly, municipal public health clinics, etc., according to participants' wishes and feasibility considerations. Collaborative assessments (2–2.5-hour sessions) designated by a consortium of expert neurologists and neuropsychologists were performed at both visits. Relevant information was collected either from participants or participant carers, when necessary (first-degree relatives, etc). A maximum of two assessments (baseline and second visit) are readily available per individual, so far (3rd visits were recently initiated). A description of the evaluations pertinent to the present article is provided below.

Neuropsychological assessments

A comprehensive neuropsychological assessment was carried out (Bougea et al., 2019). The Mini Mental State Examination (MMSE) was utilized as a measure of orientation and global cognitive status (Folstein et al., 1975). The cognitive domain of language was

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evaluated according to the parameters of verbal fluency (semantic and phonemic), confrontation naming, comprehension, and repetition. Verbal fluency was appraised as previously described in more detail (Kosmidis et al., 2004). In brief, individuals were first asked to generate as many different words as possible, belonging to one semantic category (animals, fruits, or objects), whereas, in the second part, participants were asked to generate as many different words as possible, beginning with one Greek letter ([χ] (chi), [s] (sigma) or [a] (alpha)). Participants were instructed to immediately begin generating items, following the announcement of the category or letter, and each trial lasted for 60 s. Regarding word search and production, no instructions were given, to ensure that any cognitive strategies would be spontaneously employed by the examinees. However, participants were told to abstain from reporting items irrelevant to the designated category or letter and proper nouns (regarding the phonemic test), as well as repetitions and word variations. Finally, for the purposes of the current article, an additional language index calculated using the semantic and PVF scores was devised (SVF – PVF discrepancy).

Confrontation naming, as well as verbal comprehension and repetition of words and phrases, was evaluated using subtests of the Greek version of the Boston Diagnostic Aphasia Examination short form, i.e., the Boston Naming Test short form (BNTsf, 15-item test) and selected items from the Complex Ideational Material Subtest (12-item and 6-item tests for the assessments of comprehension and repetition, respectively) (Tsapkini et al., 2010). Participants' raw scores in each language measure were converted into z scores using mean and standard deviation values of the CN individuals. Subsequently, z scores from individual language tests were averaged to generate an equally weighted composite z score for the domain of language.

The diagnostic assessment of participants' cognitive status took place during expert meetings, involving senior neurologists (E.D., G.M.H., P.S., and N.S) and neuropsychologists (M.H.K.). For a detailed description of the diagnostic procedures, please refer to Kosmidis et al. (2018). In brief, particular focus was placed on identifying potential comorbidities that could affect cognitive performance through screening the participants for depression, anxiety, essential tremor, behavioral symptoms, Parkinson's disease, dementia with Lewy bodies (DLB), as well as personal history of cerebrovascular disease accounting for the onset or deterioration of cognitive decline. The diagnoses of dementia and possible-probable ACS were based on the Diagnostic and Statistical Manual of Mental Disorders-IV-text revision criteria and the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer Disease and Related Disorders Association criteria (American Psychiatric Association, 2000; McKhann et al., 1984), respectively. MCI and its subtypes were diagnosed according to the Petersen criteria (Petersen, 2004).

Statistical analysis and outcome measures

Two discrete primary outcomes were defined a priori: development of ACS and MCI of any type (amnestic or nonamnestic) at follow-up. Both outcomes were investigated using Cox proportional hazards regressions. For the former outcome (ACS diagnosis at follow-up), CN participants at baseline were analyzed, excluding those with any dementia diagnosis other than ACS at follow-up, in view of the competing nature of different dementia entities. For the latter outcome (MCI of any type at follow-up), CN participants at baseline without any dementia diagnosis at follow-up were analyzed (due to the lack of information regarding the transitional MCI development). A secondary analysis investigating the conversion of MCI to ACS was also planned a priori (using a smaller participants' set, those with MCI at baseline). Individuals with any dementia diagnosis other than ACS at follow-up were excluded from the secondary analysis as well.

Time-to-second-visit was employed as the time-to-event variable. In case of not documenting the event of interest, participants were censored at second visit. Cox models were adjusted for age at baseline, sex, years of education, standardized MMSE scores, main occupation, and socioeconomic status. Inclusion of MMSE aimed toward controlling for global cognitive function, i.e., we explored the predictive ability of language function independently of the general cognitive status of the participants. First, composite language scores were analyzed using the conventional $\alpha = 0.05$ threshold of significance. Sequentially, individual language raw scores (6 in total, i.e., SVF, PVF, SVF-PVF discrepancy, confrontation naming, verbal comprehension, and repetition) were inserted into separate Cox proportional hazards models. To correct for multiple comparisons (six per participant set), the significance cutoff was set at $\alpha = 0.008$.

All statistical analyses were performed using the IBM SPSS Statistics Software Version 25 (Chicago, IL, USA). Age at baseline, years of education, and standardized MMSE scores (i.e., MMSE scores of illiterate participants were converted to the literate MMSE scale of 30) were treated as scale variables. Sex, main occupation (manual or mental), and socioeconomic status (low or high) were treated as dichotomous variables (Mourtzi et al., 2018). Baseline differences between groups were tested using independent sample t-test for continuous variables and Pearson's chi-squared test for categorical data. Depression (evaluated according to the 15-item Geriatric Depression Scale with higher values reflecting greater depression levels) and functional status (appraised using the 9-item instrumental activities of daily living – extended scale with higher values reflecting better functional status) assessments were provided for descriptive purposes (Kalligerou et al., 2020).

Results

Baseline characteristics and missing data

The prospective HELIAD cohort consisted of 1984 participants with baseline evaluations. Among them, there were 103 individuals with dementia, 243 with MCI, and 4 with an inconclusive cognitive diagnosis (all excluded from our analysis). From the total of 1607 individuals who were CN at baseline, a subgroup of 959 individuals had available follow-up assessments at the time of the present analysis. The mean duration between the initial and follow-up assessments was 3.09 years (range: 1.16 – 7.26 years). Compared to those without follow-up assessments, those with available follow-up evaluations were younger, more often classified as mental laborers, and had higher MMSE, composite as well as individual language scores (data not shown).

Four CN participants at baseline were missing a follow-up cognitive diagnosis. Among the remaining 955 individuals, 34 developed dementia, 29 of whom developed ACS, and 5 of whom converted to other dementia entities (excluded from our analysis). The baseline characteristics of the CN sample according to the development of ACS or not at follow-up are provided in Table 1. Those who developed ACS were older at baseline, less educated, and had worse functional status and lower MMSE and language scores.

Among the 921 nondemented participants at follow-up, 761 remained CN and 160 developed MCI of any type (amnestic or

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Table 1. Baseline characteristics of cognitively normal participants (CN) according to the follow-up diagnosis of Alzheimer's clinical syndrome (ACS) or not. Those with any other dementia diagnosis at follow-up were excluded. The number of participants with available data per parameter is provided

Baseline parameter	Without ACS at follow-up ($n = 921$)	With ACS at follow-up ($n = 29$)	p-value for differences between groups
Age in years at baseline (N = 950)	72.75 ± 4.86	77.04 ± 5.05	< **.001**
Years of Education (N = 950)	8.39 ± 4.86	6.59 ± 4.76	**.049**
Sex (M/F) (N = 950)	363/558 (39.4%/60.6%)	15/19 (44.1%/55.9%)	.582
Main Occupation (Manual/Mental) (N = 855)	520/307 (62.9%/37.1%)	24/9 (72.7%/27.3%)	.250
Socioeconomic Status (Low/High) (N = 950)	395/526 (42.9%/57.1%)	18/16 (52.9%/47.1%)	.245
Geriatric Depression Scale scores (N = 949)	1.83 ± 3.03	3.55 ± 4.63	.056
Instrumental activities of daily living – extended scale (N = 949)	4.75 ± 1.26	4.00 ± 1.51	**.002**
MMSE (N = 933)	27.66 ± 2.16	25.32 ± 2.91	< **.001**
Composite language score (N = 937)	0.08 ± 0.75	−0.77 ± 1.05	< **.001**
SVF performance (N = 932)	16.55 ± 4.88	11.67 ± 3.40	< **.001**
PVF performance (N = 911)	7.80 ± 4.64	5.85 ± 4.39	**.032**
BNTsf (N = 935)	11.21 ± 2.75	8.89 ± 3.39	< **.001**
Comprehension (N = 918)	11.04 ± 1.38	9.89 ± 1.88	< **.001**
Repetition (N = 933)	4.92 ± 1.22	3.96 ± 1.53	< **.001**
SVF-PVF discrepancy (911)	8.89 ± 5.50	5.81 ± 4.31	**.004**

N, total number of participants; *n*, number of participants with available data per variable; M/F, male/female; MMSE, Mini Mental State Examination; SVF, semantic verbal fluency; PVF, phonemic verbal fluency; BNTsf, Boston Naming Test short form; **bold** denotes statistical significance.

Table 2. Baseline characteristics of cognitively normal participants (CN) based on the follow-up diagnosis of mild cognitive impairment (MCI) of any type (amnestic or nonamnestic) or not. Those with dementia diagnosis at follow-up were excluded. The number of participants with available data per parameter is provided

Baseline parameter	Without ACS or MCI at follow-up ($n = 761$)	With MCI at follow-up ($n = 160$)	P value for differences between groups
Age in years at baseline (N = 921)	72.46 ± 4.70	74.13 ± 5.36	< **.001**
Years of Education (N = 921)	8.74 ± 4.86	6.72 ± 4.52	< **.001**
Sex (M/F) (N = 921)	297/464 (39.0%/61.0%)	66/94 (41.3%/58.7%)	.601
Main Occupation (Manual/Mental) (N = 827)	414/269 (60.6%/39.4%)	106/38 (73.6%/26.4%)	**.003**
Socioeconomic Status (Low/High) (N = 921)	313/448 (41.1%/58.9%)	82/78 (51.3%/48.7%)	**.019**
Geriatric Depression Scale scores (N = 920)	1.77 ± 2.97	2.13 ± 3.30	.173
Instrumental activities of daily living – extended scale (N = 920)	1.27 ± 0.05	1.22 ± 0.10	.232
MMSE (N = 905)	27.78 ± 2.00	27.09 ± 2.50	< **.001**
Composite language score (N = 910)	0.16 ± 0.72	−0.27 ± 0.80	< **.001**
SVF performance (N = 905)	17.07 ± 4.69	14.05 ± 5.01	< **.001**
PVF performance (N = 884)	8.02 ± 4.68	6.68 ± 4.26	**.001**
BNTsf (N = 908)	11.46 ± 2.66	10.00 ± 2.84	< **.001**
Comprehension (N = 891)	11.15 ± 1.26	10.54 ± 1.74	< **.001**
Repetition (N = 906)	4.97 ± 1.205	4.66 ± 1.26	**.003**
SVF-PVF discrepancy (884)	9.12 ± 5.45	7.70 ± 5.59	**.004**

N, total number of participants; *n*, number of participants with available data per variable; M/F, male/female; MMSE, Mini Mental State Examination; SVF, semantic verbal fluency; PVF, phonemic verbal fluency; BNTsf, Boston Naming Test short form; **bold** denotes statistical significance.

nonamnestic). The baseline characteristics of the CN sample based on the development of MCI or not at follow-up are provided in Table 2. Similar to those with dementia at second visit, those with MCI were older at baseline, less educated, and achieved lower MMSE and language scores during the initial evaluation. However, in addition to the above, a greater portion of these individuals was of low socioeconomic status and had a manual occupation.

Finally, regarding those with MCI at baseline (N = 243), 118 participants had available follow-up assessments at the time of the present analysis (secondary set). Twenty-nine individuals with MCI developed dementia at second visit, 25 of whom were diagnosed with ACS. The mean duration between the initial and follow-up assessments was 2.92 years (range: 1.29 – 6.21 years). Those with dementia at second visit were more often of lower socioeconomic status and had worse functional status, while recorded lower MMSE, SVF, verbal comprehension and SVF-PVF discrepancy scores (Table 3).

The prognostic value of language measurements regarding the development of dementia or mild cognitive impairment

Tables 4 and 5 summarize the prognostic value of baseline language scores regarding the risk of developing ACS and MCI of any type (amnestic or nonamnestic). With respect to CN individuals, each SD increase in the composite language score reduced the risk of incident ACS by about 49% (Figure 1).

Among the individual language parameters, only two were found to have significant predictive value regarding the development of ACS at second visit. In particular, each additional response in the SVF task was associated with approximately 16% lower hazard of developing ACS. On the other hand, for each additional item positively scored in the BNTsf, participants presented about 22% lower risk of presenting with ACS at follow-up.

Finally, no significant predictors were revealed in the MCI group, i.e., no language measurement was related to the risk of

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Table 3. Baseline characteristics of participants with mild cognitive impairment (MCI) of any type (amnestic or nonamnestic) based on the follow-up diagnosis of Alzheimer's clinical syndrome (ACS) or not. Those with any other dementia diagnosis at follow-up were excluded. The number of participants with available data per parameter is provided

Baseline parameter	Without ACS at follow-up ($n = 89$)	With ACS at follow-up ($n = 25$)	P-value for differences between groups
Age in years at baseline (N = 114)	74.68 ± 4.98	76.81 ± 4.10	.053
Years of Education (N = 114)	7.25 ± 5.13	5.68 ± 4.84	.175
Sex (M/F) (N = 114)	44/45 (49.4%/51.6%)	9/16 (36%/64%)	.234
Main Occupation (Manual/Mental) (N = 102)	52/26 (66.7%/33.3%)	18/6 (75%/25%)	.442
Socioeconomic Status (Low/High) (N = 114)	43/46 (48.3%/51.7%)	19/6 (76%/24%)	**.014**
Geriatric Depression Scale scores (N = 114)	2.55 ± 3.84	2.68 ± 3.56	.880
Instrumental activities of daily living – extended scale (N = 114)	4.29 ± 1.18	3.72 ± 1.43	**.043**
MMSE (N = 110)	25.03 ± 2.98	22.89 ± 3.54	**.004**
Composite language score (N = 113)	−0.68 ± 1.04	−1.05 ± 1.01	.110
SVF performance (N = 113)	12.95 ± 5.42	8.84 ± 4.57	**.001**
PVF performance (N = 108)	5.34 ± 3.90	4.57 ± 3.57	.391
BNTsf (N = 110)	9.12 ± 2.97	8.88 ± 3.13	.728
Comprehension (N = 103)	10.09 ± 1.77	8.92 ± 2.13	**.008**
Repetition (N = 111)	3.88 ± 1.63	3.60 ± 1.78	.455
SVF-PVF discrepancy (AN = 108)	7.84 ± 5.90	4.52 ± 4.10	**.013**

n, total number of participants per group; N, number of participants with available data per variable; M/F, male/female; MMSE, Mini Mental State Examination; SVF, semantic verbal fluency; PVF, phonemic verbal fluency; BNTsf, Boston Naming Test short form; **bold** denotes statistical significance.

Table 4. Adjusted cox proportional hazards regressions with follow-up diagnosis of Alzheimer's clinical syndrome (ACS) and mild cognitive impairment (MCI) of any type (amnestic or nonamnestic) as the dichotomous outcomes. Individuals with normal cognition (CN) at baseline were analyzed

NC at baseline	ACS at follow-up	MCI of any type at follow-up
Test	Adjusted HR (95%CI), P-value	Adjusted HR (95%CI), P-value
Composite language score	**0.510 (0.283, 0.917), .025**	**0.677 (0.497, 0.921), 0.013**
SVF performance	**0.837 (0.749, 0.935), .002**	**0.920 (0.881, 0.960), <0.001**
PVF performance	0.913 (0.804, 1.036), .158	0.970 (0.920, 1.022), .249
BNTsf	**0.780 (0.652, 0.933), .007**	**0.837 (0.767, 0.914), <0.001**
Comprehension	0.774 (0.615, .974), .029	0.875 (0.784, 0.977), 0.018
Repetition	0.912 (0.657, 1.267), .584	1.043 (0.895, 1.216), .590
SVF-PVF discrepancy	0.921 (0.843, 1.006), .068	0.963 (0.929, 0.998), .037

N/A, not applicable; HR, hazard ratio; CI, confidence interval; SVF, semantic verbal fluency; PVF, phonemic verbal fluency; BNTsf, Boston Naming Test short form; **bold** denotes statistical significance

Table 5. Adjusted cox proportional hazards regressions with follow-up diagnosis of Alzheimer's clinical syndrome (ACS) as the dichotomous outcome. Individuals with mild cognitive impairment (MCI) of any type (amnestic or non-amnestic) at baseline were analyzed

MCI at baseline	ACS at follow-up
Test	Adjusted HR (95%CI), *p*-value
Composite language score	0.966 (0.489, 1.908), .921
SVF performance	0.914 (0.822, 1.017), .098
PVF performance	1.009 (0.873, 1.165), .905
BNTsf	1.214 (0.992, 1.486)
Comprehension	0.809 (0.583, 1.124), .207
Repetition	1.146 (0.798, 1.647), .460
SVF-PVF discrepancy	0.907 (0.811, 1.016), .091

N/A not applicable; HR, hazard ratio; CI, confidence interval; SVF, semantic verbal fluency; PVF, phonemic verbal fluency; BNTsf, Boston Naming Test short form; **bold** denotes statistical significance.

conversion from MCI of any type (amnestic or amnestic) to ACS (secondary analysis).

With respect to the prognostic value of baseline language scores regarding the risk of developing MCI, each additional SD unit in the composite language score reduced the risk of incident MCI of any type by 32% (Figure 2). The predictive value of SVF performance and naming was once again significant. Specifically, each additionally reported object in the SVF task was associated with approximately 8% lower hazard of developing MCI at follow-up, while each additional positively scored item in the BNT was related to about 16% inferior risk of presenting with MCI at follow-up (Table 4).

Discussion

The present study demonstrated that impaired language performance among CN individuals is related to an increased risk of developing ACS and MCI. Among individual neuropsychological tests, better SVF and naming performance was specifically associated with reduced risk of incident ACS and MCI, independently of age, sex, education, main occupation, socioeconomic status, and MMSE scores. On the other hand, language measures were not associated with the risk of MCI to ACS conversion. It is important to stress, however, that in view of the small MCI sample (along with the small number of total events), our analysis may have been relatively underpowered to reveal any potential associations. Finally, comprehension, repetition, and PVF in isolation, as well as SVF-PVF discrepancy scores, were not associated with the risk of developing MCI or ACS, as well as the risk of MCI to ACS progression.

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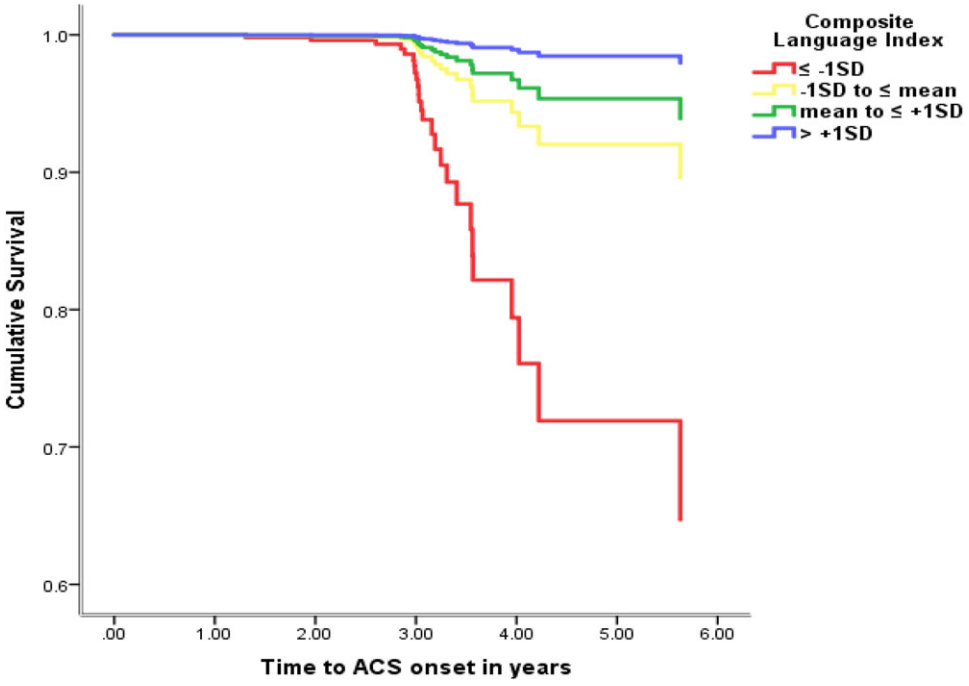

Figure 1. Survival curves for incident Alzheimer's clinical syndrome (ACS) according to the baseline composite language performance of the participants. Individuals were clustered using mean composite language values and standard deviation (SD) units to form four baseline strata: ≤−1SD unit, >−1SD unit and ≤ mean, > mean and ≤ +1SD unit, >+1SD unit.

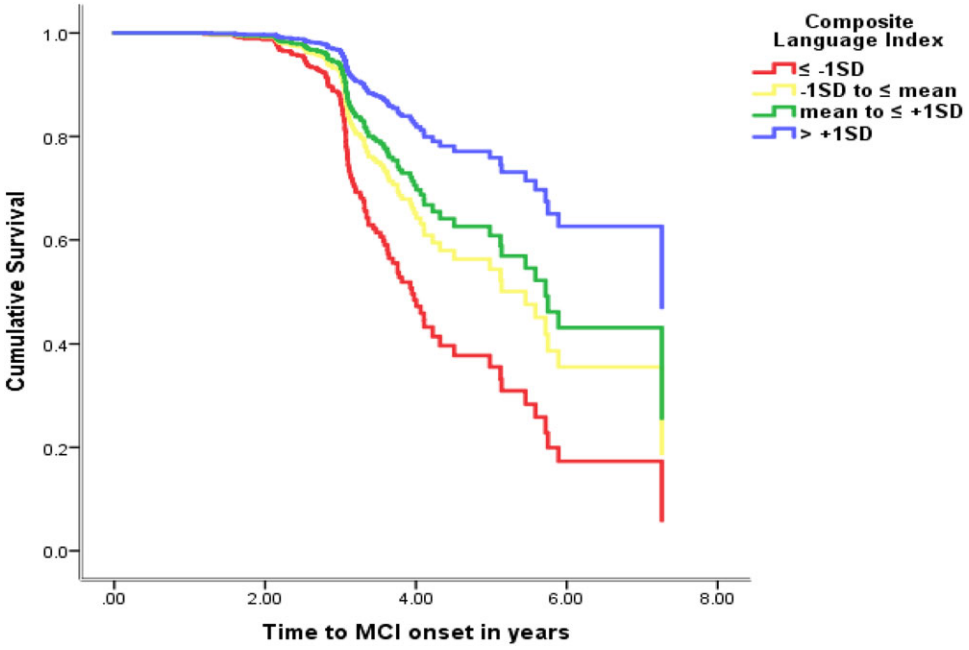

Figure 2. Survival curves for incident mild cognitive impairment (MCI) according to the baseline composite language performance of the participants. Individuals were clustered using mean composite language values and standard deviation (SD) units to form four baseline strata: ≤ −1SD unit, >−1SD unit and ≤ mean, > mean and ≤ +1SD unit, >+1SD unit.

Our findings are consistent with those of previous articles suggesting the prognostic quality for SVF performance (Gallucci et al., 2018; Gustavson et al., 2020; Sutin et al., 2019; Wong et al., 2013). Similar to former studies, we adjusted for important sociodemographic parameters that could confound the relationship between language performance and ACS or MCI development (Letenneur et al., 1999; Karp et al., 2004; Kempler et al., 1998). Unlike previous research, however, our analyses additionally accounted for the potential confounding effect of general cognitive status (as reflected by MMSE scores, which provide a general estimate of cognitive impairment), suggesting that language performance is a prognostic factor of cognitive decline, independently of global cognitive status.

BNTsf was also revealed to have a predictive value regarding the development of MCI and ACS. BNTsf is shorter than the traditional 60-item BNT; thus, it may be less taxing given the frequently observed limited attention span, which can be introduced by multiple common conditions (depression, anxiety, sleep disorders, and so on). Regarding its predictive utility, previous research has provided conflicting evidence using relatively small sample sizes

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(Albert et al., 2001; Chen et al., 2000; Griffith et al., 2006; Jacobs et al., 1995; Tabert et al., 2006). The present study is the largest relevant longitudinal study to date, providing robust evidence (by addressing important sociodemographic confounders and global cognitive status) for the prognostic quality of BNTsf performance in ACS and MCI development.

It is well established that the neuropathological alterations of neurodegenerative disorders such as dementia (with ACS being the most extensively investigated) precede the clinical onset of the disease (DeTure & Dickson 2019; Solomon et al., 2014). Considering the temporal association of our findings (the mean follow-up was about 3 years), language decline (namely semantic fluency and confrontation naming impairment) might as well represent the clinical equivalent of early pathological processes of cognitive impairment in nondemented individuals. Therefore, language impairment may constitute an early clinical marker of the disease. In this context, language decline would also represent a clinical marker of MCI to ACS progression. Despite our findings, previous research has suggested that language performance (SVF in particular) is a fair prognostic factor regarding MCI to all-type dementia or ACS conversion, strengthening the hypothesis that language decline may reflect early neuropathological dementia processes. In support of this theory, SVF impairment was recently correlated to early ACS-specific neurodegenerative alterations in nondemented adults (MEMENTO Cohort Study Group, 2020).

Of note, language impairment appears to be more sensitive than other neuropsychological indices (even episodic memory) to reveal the presence of cognitive deficits in the early stages of MCI (McCullough et al., 2019). Previous research has also suggested that episodic memory and language (namely category fluency) tend to deteriorate sooner than other cognitive functions, even in the preclinical course of MCI-ACS (Mistridis et al., 2015). Intriguingly, relatively poor semantic fluency performance has been found to predict incident episodic memory deficits (but not vice versa) (Gustavson et al., 2020). Considering the above, SVF might potentially reflect ongoing neurodegenerative processes in the preclinical course of MCI-ACS, sooner than other neuropsychological tasks and potentially even sooner than episodic memory. The clinical and anatomical dissociability between semantic and episodic memory are pivotal in the understanding of the true potential of these two neuropsychological measures in the early identification of ACS. Despite the traditional teachings regarding the earlier involvement of episodic memory in aMCI and ACS, ACS neuropathology has been suggested to affect the sub-hippocampal regions including the entorhinal and perirhinal cortices (which are implicated in context-free memory processing, i.e., semantic memory) earlier than the hippocampus in the preclinical course of aMCI-ACS (Didic et al., 2011; Venneri et al., 2018). Therefore, semantic memory has been proposed to allow the earlier clinical detection of ACS-related pathological alterations, at the preclinical point of sub-hippocampal confined neurodegeneration (Didic et al., 2011; Venneri et al., 2018).

Although SVF may be useful as an early clinical marker of dementia, it clearly lacks specificity. Verbal fluency is quite complex in terms of the number of cognitive functions needed to perform it. Consequently, it is not possible to distinguish the specific cognitive domain that is impaired when verbal fluency performance is poor. SVF tasks are specifically regarded to be sensitive to deficits in executive skills, working and semantic memory (Amunts et al., 2020; Kavé and Sapir-Yogev 2020; Rende et al., 2002). As such, SVF performance is implicated in a number of neurodegenerative diseases, including several types of dementia and Parkinson's disease (Suhr & Jones, 1998). Therefore, although SVF may be an early clinical marker of ACS and MCI, the lack of specificity introduces important limitations with respect to its clinical applicability. Similarly, BNTsf, although generally considered a more specific index of verbal naming, might also reflect semantic memory skills (Brouillette et al., 2011; Hodges et al., 1990). Therefore, much alike SVF, BNTsf presents the substantial limitation of low specificity. These limitations should be investigated in future research assessing the prognostic value of language measurements with respect to the development of other dementia entities (a very small number of non-ACS dementia cases were documented in our study) as well as other neurodegenerative disorders, such as Parkinson's disease.

Strengths and limitations

The HELIAD study is a population-based prospective cohort involving a randomly selected sample from the elderly rosters of two Greek communities (both a provincial and a metropolitan community), making it a representative sample of the entire elderly Greek population. Our study included a comprehensive neuropsychological evaluation, as well as a collaborative expert-established clinical diagnosis of dementia based on standard criteria. All analyses were adjusted for important sociodemographic confounders as well as MMSE scores, to account for the potential confounding effect of globally impaired cognition.

However, our study had a number of important limitations as well. First, nonresponse bias and residual confounding cannot be ruled out. Furthermore, although the diagnosis of dementia was clinically established by a consortium of senior experts, it was not supported by imaging and biological biomarkers (potential misclassification bias) (Horgan et al., 2020). Moreover, apart from ACS, the remaining dementia entities were not investigated due to the small number of events per entity (as expected, considering the small prevalence of other dementia entities and the prospective design of the HELIAD study). In addition to the above, language performance was assessed on its own and was not compared to the rest of the cognitive domains in terms of prognostic quality. Finally, the moderate follow-up duration of approximately 3 years, as well as the relatively small MCI set of participants, might have underpowered several analyses.

Conclusions

Impaired language performance was related to an increased risk of incident ACS and MCI. Better SVF and BNTsf performances were specifically associated with reduced risk of incident ACS and MCI in cognitively healthy elderly individuals, independently of their age, sex, education, main occupation, socioeconomic status, and MMSE scores at baseline. However, no language measure was related to the risk of MCI to ACS conversion.

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