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RESEARCH ARTICLE

# Exploring cognitive progression subtypes in the Framingham Heart Study

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## Abstract

**INTRODUCTION:** Alzheimer's disease (AD) is a heterogeneous disorder characterized by complex underlying neuropathology that is not fully understood. This study aimed to identify cognitive progression subtypes and examine their correlation with clinical outcomes.

**METHODS:** Participants of this study were recruited from the Framingham Heart Study. The Subtype and Stage Inference (SuStaIn) method was used to identify cognitive progression subtypes based on eight cognitive domains.

**RESULTS:** Three cognitive progression subtypes were identified, including verbal learning (Subtype 1), abstract reasoning (Subtype 2), and visual memory (Subtype 3). These subtypes represent different domains of cognitive decline during the progression of AD. Significant differences in age of onset among the different subtypes were also observed. A higher SuStaIn stage was significantly associated with increased mortality risk.

**DISCUSSION:** This study provides a characterization of AD heterogeneity in cognitive progression, emphasizing the importance of developing personalized approaches for risk stratification and intervention.

KEYWORDS
age of onset, Alzheimer's disease, cognitive progression, heterogeneity, machine learning, mortality

**Highlights**

- We used the Subtype and Stage Inference (SuStaIn) method to identify three cognitive progression subtypes.
- Different subtypes have significant variations in age of onset.
- Higher stages of progression are associated with increased mortality risk.

## 1 | BACKGROUND

Alzheimer's disease (AD) is a chronic neurodegenerative disease characterized by progressive cognitive decline, typically starting with subtle symptoms that become evident in later stages.[1] AD, traditionally viewed as a uniform neurodegenerative disorder, is increasingly recognized for its heterogeneity. Broadly, AD subtypes can be categorized based on predominant symptoms (such as memory-focused versus non-memory cognitive impairments),[2] pathophysiological mechanisms (including variations in amyloid beta [A$\beta$] deposition and tau pathology),[3] and genetic predispositions (with certain genotypes associated with specific clinical manifestations).[4] The limited treatment options may partially be attributed to this intricate diversity.[5] Consequently, the recognition of the heterogeneous nature of disease manifestation and progression is acknowledged as a significant challenge in the current strategy of developing novel treatments for AD.[6,7] Therefore, the initial step toward AD personalized medicine could involve the identification of clinically relevant subtypes.

Neuropsychological (NP) tests are widely used to evaluate cognitive performance across various domains, including memory, attention, and language function.[8,9] The cognitive heterogeneity of AD is evident as the optimal combination of NP tests for AD screening may vary depending on specific risk factors.[10] Moreover, while memory impairment is a prominent characteristic of AD, other cognitive functions such as executive function and processing speed can also deteriorate at various rates among individuals.[11] Moreover, studies suggest that the rate of cognitive decline is associated with mortality risk in older adults.[12] These findings underscore the importance to investigate cognitive progression subtypes, crucial for devising efficient cognitive monitoring strategies and more targeted interventions.

Data-driven progression models have emerged as valuable computational approaches for investigating neurodegenerative diseases. These models obviate the need for prior knowledge about underlying progression mechanisms, making them especially suitable for exploring cognitive progression and offering an alternative to methods reliant on predefined disease stages[13] or labeled training databases.[14] However, identifying cognitive progression subtypes poses challenges due to the extensive variability in performance patterns across a wide spectrum of cognitive functions. This variability leads to temporal heterogeneity, in which cognitive function changes over time, and phenotypic heterogeneity, in which distinct groups of participants exhibit different cognitive function patterns at the same stage. Existing methods, such as regression against disease stage,[15] data-driven disease progression modeling,[16] and clustering,[17] have primarily focused on either temporal heterogeneity or phenotypic heterogeneity, often disregarding the simultaneous consideration of both. To address this challenge, the Subtype and Stage and Inference (SuStaIn) method has been introduced, integrating clustering and disease progression modeling to disentangle the disease heterogeneity of subtypes from stages. This method has demonstrated its utility in a wide range of medical research studies, such as identifying disease subtypes,[18,19] characterizing trajectories of tau deposition,[20] identifying A$\beta$ accumulation subtypes,[21] and identifying temporal trajectories of pathological brain changes.[22]

This study aims to leverage the extensive NP test battery in the Framingham Heart Study (FHS) to identify cognitive progression subtypes using the SuStaIn method. We further examined the association between these subtypes and various risk factors to understand the implications of cognitive progression patterns.

## 2 | METHODS

### 2.1 | Study population

The FHS is a community-based prospective cohort study initiated in 1948. A continuous dementia assessment started in 1976.[23] The original sample included 7528 participants from the Original Cohort (Gen 1), Offspring Cohort (Gen 2), Third Generation Cohort (Gen 3), Omni Cohort (Omni 1), Second Generation Omni Cohort (Omni 2), and New Offspring Spouse Cohort (NOS) who completed at least one NP assessment (1982–2021). Exclusion criteria included those with missing education information ($n$ = 35), mild cognitive impairment (MCI; $n$ = 301), non-AD dementia ($n$ = 206), missing earliest documented date of dementia ($n$ = 50), those < 65 years old at the time of examination ($n$ = 3231), and those flagged as potential MCI but who had not undergone dementia review ($n$ = 274). The detailed sample selection flowchart is shown in Figure 1. The diagnosis of dementia in FHS is based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,[24] and AD diagnosis follows the criteria established by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.[2] A review panel, which includes at least one neurologist and one neuropsychologist, is responsible for making the diagnosis.[25] The institutional review board of the Boston University Medical Campus approved the procedures and protocols of the Framingham Heart

**RESEARCH IN CONTEXT**

1. **Systematic review**: We reviewed the literature using databases such as PubMed. Alzheimer's disease (AD) is a heterogeneous disorder characterized by complex underlying neuropathology that is not fully understood. Understanding subtypes of cognitive progression is crucial for gaining insights into disease mechanisms and risk stratification.
2. **Interpretation**: Our study aimed to identify cognitive progression subtypes and examine their correlation with clinical outcomes. Three cognitive progression subtypes were identified. Significant differences in age of onset among the different subtypes were also observed. A higher Subtype and Stage Inference (SuStaIn) stage was significantly associated with increased mortality risk.
3. **Future Directions**: Future studies should include (1) generalizing our findings to other ethnic and racial groups and (2) investigating the synergetic effects of various risk factors on the progression of cognitive function.

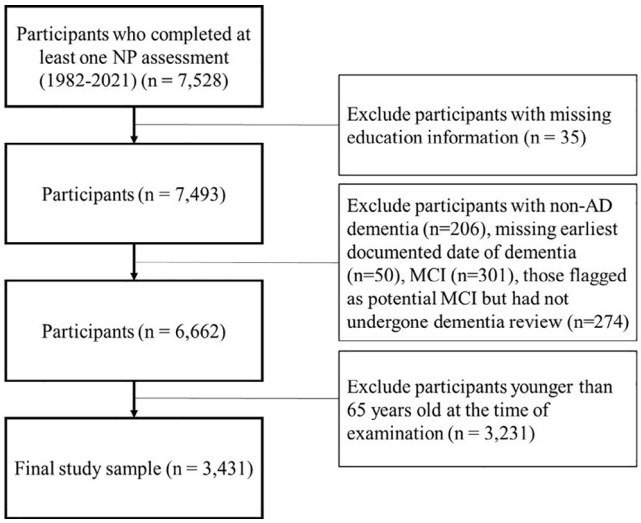


**FIGURE 1** The sample selection diagram of this study. AD, Alzheimer's disease; MCI, mild cognitive impairment; NP, neuropsychological

Study (FHS is H-32132). All participants provided written informed consent.

## 2.2 | Neuropsychological assessment

The methodology for administering NP tests in FHS has been previously documented.[26] Our study comprised 13 commonly used NP tests to assess cognitive decline in eight cognitive functions (Table S1 in supporting information).[27] The NP tests with missing values were imputed by the multiple imputations using the chained equations (MICE) method.[28] The test scores were then normalized to *z* scores with mean 0 and standard deviation of 1. For the computation of cognitive function scores represented by multiple NP tests, such as verbal memory, visual memory, verbal learning, and attention and concentration, the mean of the associated NP test scores was calculated. The remaining NP tests each represented a distinct cognitive function including abstract reasoning, language, and visuoperceptual organization. Moreover, a global cognitive function score was generated by averaging these seven cognitive function scores. To obtain the average, the attention and concentration function score was subtracted from the sum of the scores of the other functions.

## 2.3 | Subtype identification

The SuStaIn algorithm[22,29] was used to identify cognitive progression subtypes from different cognitive domains. Each subtype is characterized by a distinct trajectory of cognitive function changes with a probabilistic assignment of each subject to a subtype and stage along the corresponding trajectory. These trajectories are modeled using a linear *z* score model.[22] The model encompasses distinct stages, wherein each stage corresponds to a cognitive function score reaching a specific *z* score relative to a healthy control group with intact cognition. Cognitive function scores were converted into age-, sex-, and education-adjusted *z* scores, using the cognitive intact participants as a reference. The optimal number of subtypes was determined from a candidate set based on the cross-validation–based information criterion (CVIC) and the out-of-sample log-likelihood.[22] The analysis was performed using pySuStaIn software.[29]

For participants with multiple neuropsychological examinations, we only used the data from the last examination to identify cognitive subtypes. In the sensitivity analysis, we examined the consistency of subtype assignments for those with multiple examinations.

## 2.4 | Statistical analyses

We compared different subtypes based on a variety of factors including demographic characteristics such as age, sex, education; cerebrovascular and metabolic markers including body mass index (BMI) and blood pressure (BP, systolic and diastolic); glycemic variables—fasting blood glucose (FBG); lifestyle factor—smoking status; and lipid profile—total cholesterol (TC), low-density and high-density lipoprotein cholesterol (LDL and HDL). Furthermore, we also evaluated the proportion of participants with cardiovascular disease, including myocardial infarction (MI), congestive heart failure (CHF), stroke, atherosclerotic cardiovascular disease (ASCVD). Chi-square tests for categorical variables and one-way analysis of variance (ANOVA) for continuous variables were used to analyze differences in these clinical factors among the three subtypes.

We used a multivariable Cox proportional hazards regression model to assess the association of subtypes with mortality. The model was adjusted for age and sex. The follow-up time was truncated at the time of death or the end of 2021. We also assessed the association between stages and mortality using a linear regression model adjusted for age and sex. ANOVA was used to examine potential significant differences in the age of onset among the three subtypes. Statistical significance was determined using a significance level of $P < 0.05$ for all analyses.

## 3 | RESULTS

### 3.1 | Cognitive progression subtypes

This study included 3431 FHS participants (mean age 78 ± 9 years old, 58.1% women). Among them, 635 participants were diagnosed with AD. Further details regarding the clinical characterization of both cognitively intact participants and those diagnosed with AD can be found in Table S2 in supporting information. SuStaIn was used to identify distinct cognitive progression subtypes. As shown in Figure S1 in supporting information, the model with three subtypes reached the best performance. Figure 2 displays the positional density maps representing the cognitive progression subtypes, namely verbal learning (Subtype 1; $n = 2180$, 63.5%), abstract reasoning (Subtype 2; $n = 610$, 17.8%), and visual memory (Subtype 3; $n = 641$, 18.7%). These subtypes were classified based on the initial cognitive function that showed evidence of decline. Verbal learning subtype's earliest stages involved a decrease in verbal learning function, followed by verbal memory function. Abstract reasoning subtype's initial stages saw a decline in abstract reasoning function, followed by visuoperceptual organization function. Last, visual memory subtype's early stages included a decrease in visual memory function, followed by visuoperceptual organization function.

As shown in Table 1, there is no significant difference between age distribution among the three subtypes. However, we observed that the verbal learning subtype had higher education levels and DBP compared to the other subtypes ($P < 0.05$). The comparison of means of cognitive function scores between subtypes is illustrated in Figure S2 in supporting information. Significant differences were observed in most cognitive functions among the subtypes (Mann–Whitney $U$ test, all $P < 0.05$).

### 3.2 | Cognitive progression stages

For each subtype, participants were further assigned to a progressive stage ranging from 1 to 16. As expected, most of the participants with normal cognition were assigned to early stages within each of the three subtypes (Figure S3 in supporting information). Significant correlations were observed between cognitive function scores and SuStaIn stage, as illustrated in Figure 3. Furthermore, the relationship exhibits variation across subtypes. For example, the correlation between language function scores and stages is most pronounced in verbal learning subtype ($r = -0.86$, $P < 0.001$), followed by visual memory subtype ($r = -0.77$, $P < 0.001$), and finally abstract reasoning subtype ($r = -0.70$, $P < 0.001$; Figure S4 in supporting information).

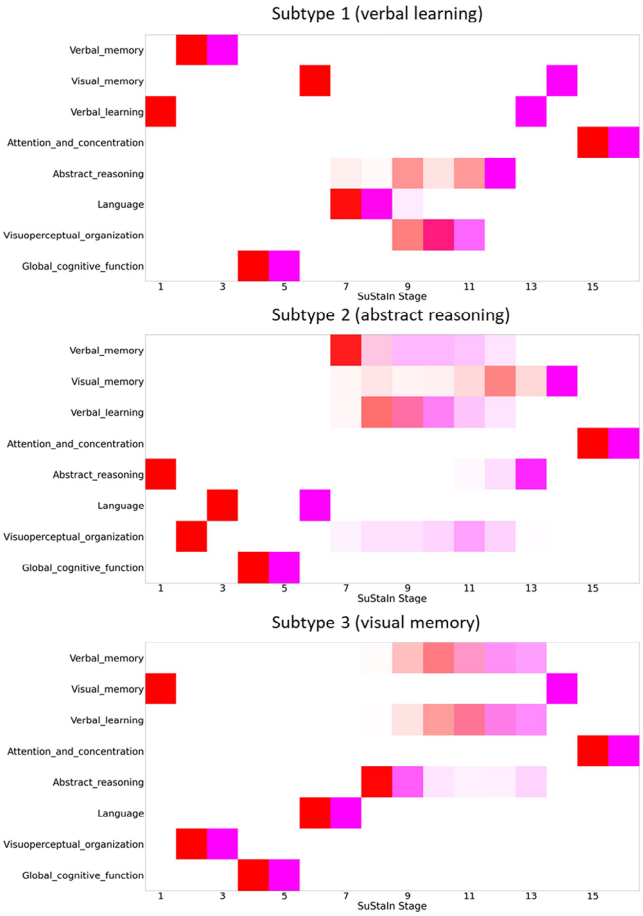


**FIGURE 2** Three cognitive progression subtypes identified in this study. The $x$ axis represents the SuStaIn stages of cognitive decline, while the $y$ axis represents the cognitive functions. At each SuStaIn stage, a new $z$ score event occurs when a cognitive function declines to a new severity level, as indexed by a $z$ score with respect to the participants who are cognitively intact; $z$ scores of $z = 1$ red) and $z = 2$ (magenta). Higher opacity represents a higher confidence in the ordering.

There is also a visible non-linear relationship between BMI and SuStaIn stage in Subtype 3, with a more rapid increase in BMI at later SuStaIn stages (Figure S5 in supporting information). However, we did not observe any significant correlations between other clinical risk factors, such as HDL and FBG, with the SuStaIn stage.

We further examined the consistency of subtype assignment among participants with multiple NP examinations. As expected, when using data from the previous NP exam compared to the latest NP exam, the majority of AD cases were assigned to earlier SuStaIn stages. Among them, 186 participants (79.8%) remained in the verbal learning subtype, 18 participants (36.7%) in the abstract reasoning subtype, and 20 participants (45.5%) in the visual memory subtype.

**TABLE 1** Clinical characterization of cognitive progression subtypes.

| Variable | Cognitively intact ($n = 2796$) | Subtype 1 ($n = 443$) | Subtype 2 ($n = 97$) | Subtype 3 ($n = 95$) | *P* value |
|---|---|---|---|---|---|
| Age, years | 76 ± 8 | 86 ± 7 | 88 ± 7 | 86 ± 7 | 0.06 |
| Women, *n* (%) | 1533 (54.8) | 329 (74.3) | 66 (68.0) | 67 (70.5) | 0.40 |
| Education, *n* (%) | | | | | **<0.001** |
| No high school | 282 (10.1) | 134 (30.2) | 64 (66.0) | 23 (24.2) | |
| High school | 683 (24.4) | 149 (33.6) | 25 (25.8) | 38 (40.0) | |
| Some college | 701 (25.1) | 88 (19.9) | 4 (4.1) | 23 (24.2) | |
| College and higher | 1130 (40.4) | 72 (16.3) | 4 (4.1) | 11 (11.6) | |
| SBP, mmHg | 135 ± 20 | 133 ± 21 | 135 ± 20 | 129 ± 17 | 0.14 |
| DBP, mmHg | 71 ± 10 | 69 ± 11 | 67 ± 12 | 65 ± 11 | **0.04** |
| BMI, kg/m$^2$ | 27.8 ± 5.1 | 25.5 ± 4.5 | 25.0 ± 3.3 | 25.9 ± 4.4 | 0.67 |
| TC, mg/dL | 184 ± 38 | 185 ± 34 | 185 ± 43 | 178 ± 37 | 0.70 |
| LDL, mg/dL | 102 ± 32 | 103 ± 27 | 108 ± 35 | 97 ± 30 | 0.48 |
| HDL, mg/dL | 58 ± 18 | 54 ± 15 | 50 ± 15 | 56 ± 15 | 0.61 |
| FBG, mg/dL | 107 ± 25 | 110 ± 21 | 109 ± 21 | 97 ± 19 | 0.05 |
| Current smoker | 83 (3.0) | 4 (1.0) | 1 (1.0) | 2 (2.1) | 0.84 |
| Diabetes | 246 (8.8) | 36 (8.1) | 7 (7.2) | 10 (10.5) | 0.53 |
| CVD | 767 (27.4) | 206 (46.5) | 47 (48.5) | 36 (37.9) | 0.26 |
| MI | 247 (8.8) | 61 (13.8) | 17 (17.5) | 8 (8.4) | 0.18 |
| CHF | 147 (5.3) | 56 (12.6) | 17 (17.5) | 9 (9.5) | 0.24 |
| Stroke | 279 (10.0) | 82 (18.5) | 14 (14.4) | 21 (22.1) | 0.39 |
| Ischemic stroke | 261 (9.3) | 69 (15.6) | 14 (14.4) | 18 (18.9) | 0.65 |
| ASCVD | 381 (13.6) | 105 (23.7) | 26 (26.8) | 20 (21.1) | 0.64 |

*Note*: Values are reported as mean ± standard deviation for continuous variables and *n* (%) for categorical variables.
*P* values less than 0.05 were bolded.
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CHF, congestive heart failure; CVD, cardiovascular disease; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; SBP, systolic blood pressure; TC, total cholesterol.

### 3.3 | Association of subtypes and stages with mortality and age of onset

As shown in Table S3 in supporting information, there is no significant difference in terms of morality among the three subtypes ($P > 0.05$). However, a higher SuStaIn stage was significantly associated with mortality risk in all participants as well as within each subtype (Table 2). We also found there were significant differences in age of onset among the different subtypes ($P = 0.01$).

## 4 | DISCUSSION

The identification of distinctive subtypes defined by individual cognitive progression patterns has significant implications for advancing our understanding of AD and tailoring clinical interventions. This study applied the SuStaIn method and identified three cognitive progression subtypes in the FHS. These subtypes exhibit significant differences in cognitive function profiles and age of onset. Participants in later stages have a significantly increased risk of mortality.

AD neuropathology is not yet fully understood. The absence of a definitive cure for AD may be partially attributed to its heterogeneity. It is possible that different biological pathways could result in similar final clinical symptoms. Therefore, a single universal treatment for all AD patients may not be feasible, and instead, different therapeutic agents may be more effective for specific subgroups of individuals. Therefore, identification of AD subtypes is crucial to advance personalized medicine in this field. One approach to identifying subtypes of AD involves grouping individuals based on neurobiological characteristics such as age, apolipoprotein E status, imaging-based volumetric measurements, and cerebrospinal fluid biomarkers,[22] and then exploring the relationships with cognitive profiles. Our previous research has revealed hierarchical interactions and interdependencies among NP tests, uncovering specific risk factors that influence these relationships.[30] Prior research has shown that although episodic memory loss typically stands out as the most notable symptom in AD,[2] there are clinical variations of AD that exhibit relative preservation of memory, such as logogenic progressive aphasia[31] and posterior cortical atrophy.[32] These findings suggest that cognitive heterogeneity extends beyond the atypical cases and is also discernible among

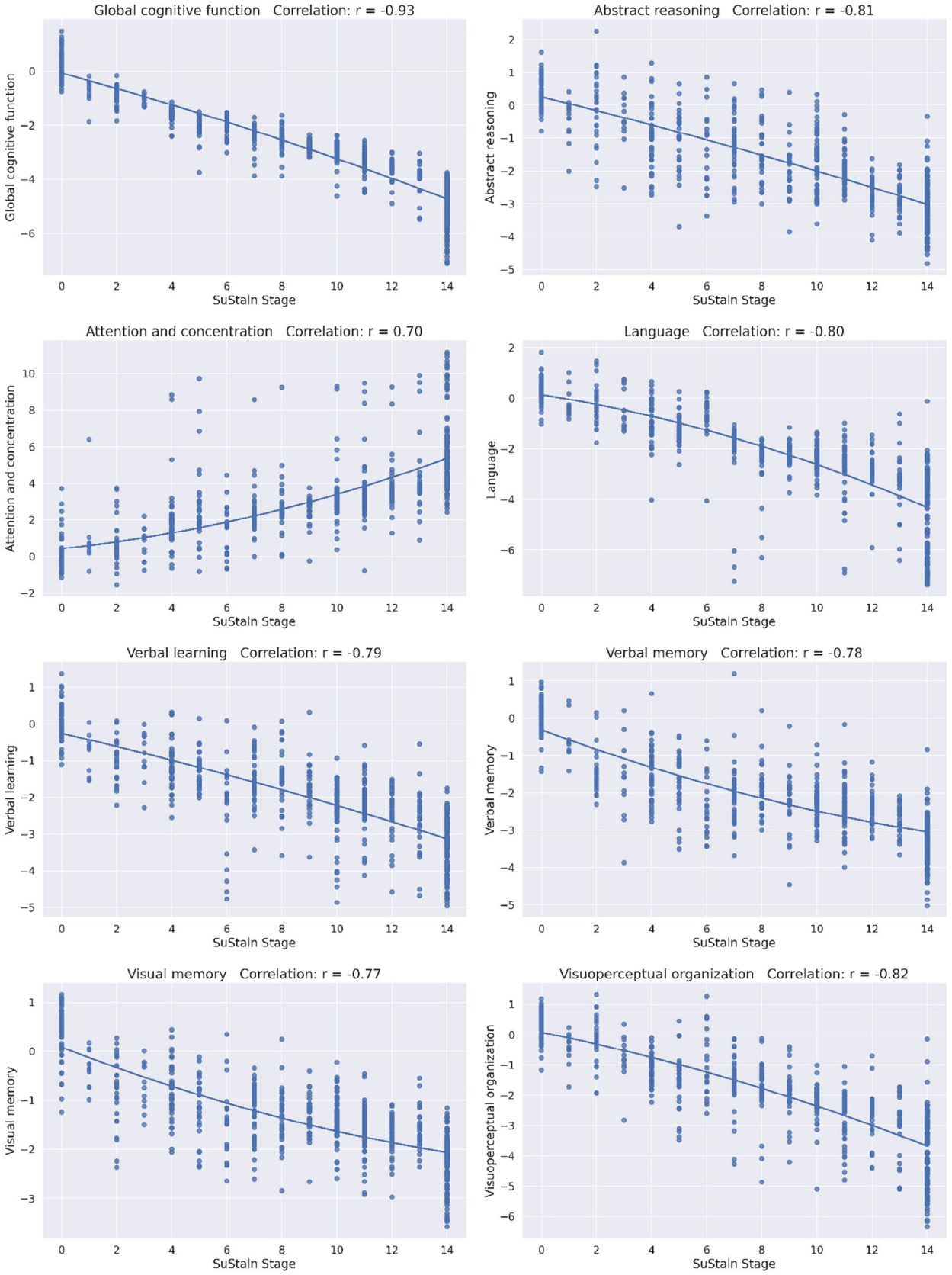


**FIGURE 3** Correlation between SuStaIn stage and different cognitive function scores. SuStaIn, Subtype and Stage Inference method

**TABLE 2** Association between SuStaIn stage and mortality.

| SustaIn stage | HR | 95% CI | *P* value |
|---|---|---|---|
| All | 1.08 | 1.07–1.09 | <.001 |
| Subtype 1 | 1.08 | 1.07–1.10 | <.001 |
| Subtype 2 | 1.05 | 1.02–1.08 | <.001 |
| Subtype 3 | 1.07 | 1.05–1.10 | <.001 |

*Note*: All models were adjusted for age and sex.
Abbreviations: CI, confidence interval; HR, hazard ratio; SuStaIn, Subtype and Stage Inference method.

participants within the conventional spectrum of AD. Therefore, alternative approaches are to use statistical clustering methods on neuropsychological data to capture the cognitive heterogeneity in neurodegenerative diseases, leading to the identification of distinct cognitive subtypes.[33,34] For example, a prior study identified four distinct subgroups within the population studied: a subgroup experiencing mild and another facing severe global cognitive impairments, a subgroup primarily challenged in attention and constructional abilities, and a final subgroup predominantly showing deficits in memory and orientation.[33] Another investigation reveals diverse clinical manifestations of AD, identifying that ≈ 25% of the individuals exhibit significantly uneven deficits within a specific cognitive area.[34] However, these studies are often limited by small sample sizes or the use of restricted neuropsychological test protocols. Additionally, these studies have predominantly focused on either temporal heterogeneity or phenotypic heterogeneity, rarely considering both simultaneously. In this study, we identified three cognitive progression subtypes across eight cognitive functions. Notably, each of these subtypes exhibits distinct initial declines in cognitive functions, highlighting the diverse trajectories of cognitive function across individuals. The assignment of subtypes can be most useful during the predementia stages of AD, as the significant differences in trajectories are often evident early in the disease process. This implies that identifying subtypes at this stage may have the greatest utility in terms of understanding the disease progression and informing personalized interventions.

Both cognitive ability and cognitive decline have demonstrated associations with mortality in older adults. Previous research has predominantly used global measures of cognitive function, such as the Mini-Mental State Examination, to investigate the link between cognition and mortality. However, only a few studies have used tests that evaluate specific cognitive functions, such as learning, memory, and information processing.[35–37] It is important to recognize that different cognitive domains are interconnected and work together in the brain.[38] Examining them separately may not provide a comprehensive understanding of neurodegenerative mechanisms. Therefore, it is crucial to comprehensively consider multiple cognitive functions simultaneously to gain a deeper insight into this relationship. Despite several studies demonstrating an independent and inverse association between cognition and mortality,[39,40] the nature of this association remains to be explored from a progression standpoint. In this study, we observed a significant association between higher SuStaIn stage and an increased risk of mortality. Furthermore, we found significant differences of age of onset across subtypes. Although this relationship is complex and likely influenced by multiple factors, comprehending the distinct pathological processes underlying different forms of cognitive decline could aid in developing targeted interventions to slow cognitive decline and improve health outcomes in older adults. The identification of distinct cognitive subtypes in AD can serve as an initial step toward such differentiated diagnoses. The rate of change in various cognitive functions also varies across different subtypes. Our findings indicate that while participants of subtype 3 tend to exhibit poorer cognitive outcomes eventually, the rate of change within the two *z* score threshold is comparable to that of the other subtypes. This observation suggests that despite their eventual lower cognitive performance, the progression pace for individuals in subtype 3, within the examined range, aligns with the progression observed in other subtypes. Moreover, the presence of unique neurobiological characteristics in each subtype supports the idea that different pathological pathways contribute to these subtypes, providing valuable insights that can guide the search for new therapies.

Our study benefits from several notable strengths. First, we conducted our research on a well-characterized community-based cohort with meticulous diagnostic assessments by experts. Additionally, we used multiple validated NP tests that were administered simultaneously to derive cognitive function scores, ensuring accurate and reliable measurements. Moreover, we used the SuStaIn method to disentangle the temporal and phenotypic heterogeneity that often complicates neurodegenerative progresses. It can capture the gradual linear accumulation of cognitive decline rather than relying on abrupt transitions from normal to abnormal.

However, this study has several limitations. We included only NP tests to characterize cognitive function, whereas other biomarkers, such as blood biomarkers, neuroimaging biomarkers, and genetic profiles could help to further characterize disease progression. Our findings point toward subtypes that may encompass both AD and CVD characteristics, rather than purely typical AD manifestations. Future work should aim to develop a classification framework that more thoroughly accounts for the interrelation between cognitive decline and cardiovascular health, offering a more holistic understanding of AD heterogeneity. In addition, the selection of NP tests and their subsequent classification into distinct cognitive domains play a critical role in defining AD subtypes. Our study primarily uses NP tests focused on memory functions, which could influence the subtype characterization toward memory-related impairments. This variability underscores the necessity for a more standardized approach to cognitive assessment in AD research, which would facilitate more consistent identification and comparison of subtypes across studies. It is also crucial to investigate the synergetic effects of various risk factors on the progression of cognitive function. For instance, understanding the influence of amyloid and tau pathology, as well as vascular risk factors, on the trajectories of cognitive functions could provide valuable insights into the underlying mechanisms of cognitive decline. Last, the FHS participants in our study were primarily of European ancestry. Therefore, caution should be exercised when generalizing our findings to other ethnic and racial groups. Future studies are warranted

to investigate the consistency of our findings on another independent cohort.

In summary, we identified three cognitive progression subtypes that account for both temporal and phenotypic heterogeneity. These subtypes demonstrated different progression patterns of cognitive functions as well as clinical characterizations. Our findings are expected to improve our understanding of AD risk assessment and intervention.

## ACKNOWLEDGMENTS

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## CONFLICT OF INTEREST STATEMENT

R.A. is a scientific advisor to Signant Health and NovoNordisk, and a consultant to the Davos Alzheimer's Collaborative. The other authors declare no conflicts of interest. Author disclosures are available in the supporting information.

## CONSENT STATEMENT

All participants provided written informed consent.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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