

RESEARCH ARTICLE

Trajectories of cognitive function in community-dwelling older adults: A longitudinal study of population heterogeneity

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Abstract

Introduction: This study aimed to investigate cognitive aging trajectories, the associated sociodemographic characteristics, and the association of these trajectories with dementia.

Methods: Generally healthy older adults ($n = 19,114$) were followed for up to 7 years, with regular cognitive assessments. Group-based trajectory modeling identified distinct cognitive trajectories.

Results: Four to seven trajectories were identified per cognitive domain. Stable trajectories were observed across domains. Improvement in verbal fluency and minor psychomotor slowing were common. Substantial decline in global cognition and episodic memory were observed in a small proportion of individuals. Older, less educated participants and men were more common in lower-functioning trajectories ($p < .001$). The highest proportions of dementia cases were in trajectories with major decline in global cognition (56.9%) and memory (33.2%).

Discussion: Inter-individual variability in cognitive trajectories was observed across all domains. Some individuals appear resilient to cognitive decline even with advancing age. Further research into factors promoting cognitive resilience is needed.

KEYWORDS

cognitive function, dementia, longitudinal, older adults, prospective

1 | INTRODUCTION

Changes in cognitive function are common as individuals age, but there is considerable variability between individuals and across cognitive domains.^{1,2} Cognitive function can be categorized into domains such as learning and memory, processing speed, attention, visuospatial and psychomotor function, language, and executive function. Often, there is some loss in cognitive function, such as memory and processing speed, with aging.¹ However, even minor deficits can affect an individ-

ual's daily functioning, such as their capacity to drive, manage finances, and to understand instructions.³ On the other hand, some cognitive domains, such as vocabulary, may remain stable even with advanced age.¹ Therefore, a better understanding of the natural process and variability of cognitive aging within the general population is needed.

The majority of studies investigating changes in cognitive function in late life have focused on individuals who already exhibit cognitive decline through diagnosis of mild cognitive impairment or incident dementia.⁴ Other studies have examined cognitive change between

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only two timepoints,⁵ investigating the extent of cognitive decline. Longitudinal cognitive data, collected at multiple timepoints, enable the patterns or trajectories of cognitive function over time to be determined within a population sample.

A systematic review of 37 studies found that cognitive aging in late life may involve an extended period of stability, decline, and even slight improvement over time, and there is evidence of significant inter-individual variability.² The majority of studies have been restricted to a global measure of cognitive function, most commonly the Mini-Mental State Examination (MMSE), which has floor and ceiling effects and is insensitive to subtle cognitive change.^{6,7} Furthermore, it remains unclear to what extent sociodemographic characteristics (i.e., age, education) are associated with cognitive trajectories. Meanwhile, although cognitive decline is associated with dementia, it is uncertain how changes in different cognitive domains in late life predict the development of dementia.

Using a large cohort of generally healthy older adults from Australia and the United States, the present study aimed to characterize how cognitive function changes over time using four cognitive tests, and to describe the most common distinct cognitive trajectories. The second aim was to investigate sociodemographic characteristics associated with trajectory classes, and to determine how incidence risk of dementia differs by trajectory.

2 | METHODS

2.1 | Participants

This study used data obtained from the ASPREE (Aspirin in Reducing Events in the Elderly) clinical trial: full details of the study have been published previously.⁸ In brief, 19,114 adults aged 65+ years (Black and Hispanics) or 70+ years (all other ethno-racial groups) were recruited from Australia and the United States. At baseline, participants were without recognized cardiovascular disease, diagnosed dementia, or a modified MMSE (3MS) score < 78. Participants were followed for a median of 4.7 years. All participants provided written informed consent.

2.2 | Cognitive and dementia assessment

The cognitive battery included the 3MS examination for global cognitive function,⁹ single letter Controlled Oral Word Association Test (COWAT-F) for vocabulary and executive function,¹⁰ Hopkins Verbal Learning Test—Revised (HVLTR) delayed recall task for episodic memory,¹¹ and Symbol Digit Modalities Test (SDMT) for attention and psychomotor speed.¹² Seven waves of cognitive data collected at baseline and over follow-up (year 1, 3, 4, 5, 6, 7, or close-out visit) were used. Three composite scores, including a global, an executive function, and a memory composite score, were generated using z-scores of the above cognitive tests (components of the composite scores are shown in the supporting information). Dementia was a secondary endpoint in the ASPREE trial, and was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV).¹³

HIGHLIGHTS

- There is inter-individual heterogeneity of cognitive aging across all domains.
- High-functioning and stable trajectories were observed in most domains.
- Rapid decline in global cognition and episodic memory was associated with dementia.
- Improvement in verbal fluency and minor psychomotor slowing were common at old age.
- Some individuals may be resilient to cognitive decline with advancing age.

RESEARCH IN CONTEXT

1. **Systematic review:** The authors performed a systematic review via MEDLINE and EMBASE. Findings highlighted the need for further studies to investigate population heterogeneity of cognitive trajectories across multiple cognitive domains, in a large representative sample of community-dwelling older individuals.
2. **Interpretation:** Our findings identified considerable inter-individual variability in cognitive aging. However, patterns of cognitive trajectories differed across cognitive domains. Slight improvements in verbal fluency and minor decline in psychomotor speed were common. Substantial decline in global cognition and episodic memory were evident for a small proportion of individuals with significantly increased risk of dementia. The majority of individuals maintained stable cognitive trajectories over time.
3. **Future directions:** A proportion of individuals appeared to maintain their cognitive function at high levels over time, even with advancing age. Further research into the characteristics of these “successful cognitive agers” who appear resilient to cognitive decline, might help identify novel resilient factors.

2.3 | Statistical analysis

Full details of statistical analysis are presented in supporting information. In brief, trajectories were identified using group-based trajectory modeling (GBTM), which is a semi-parametric technique that identifies the latent subgroups with distinct trajectories of an indicator within a heterogeneous population based on the longitudinal patterns of the indicator. It subsequently assigns each participant into the most likely subgroup that produced the maximum posterior probability. Participants in the same group share homogenous patterns of the trajectory.

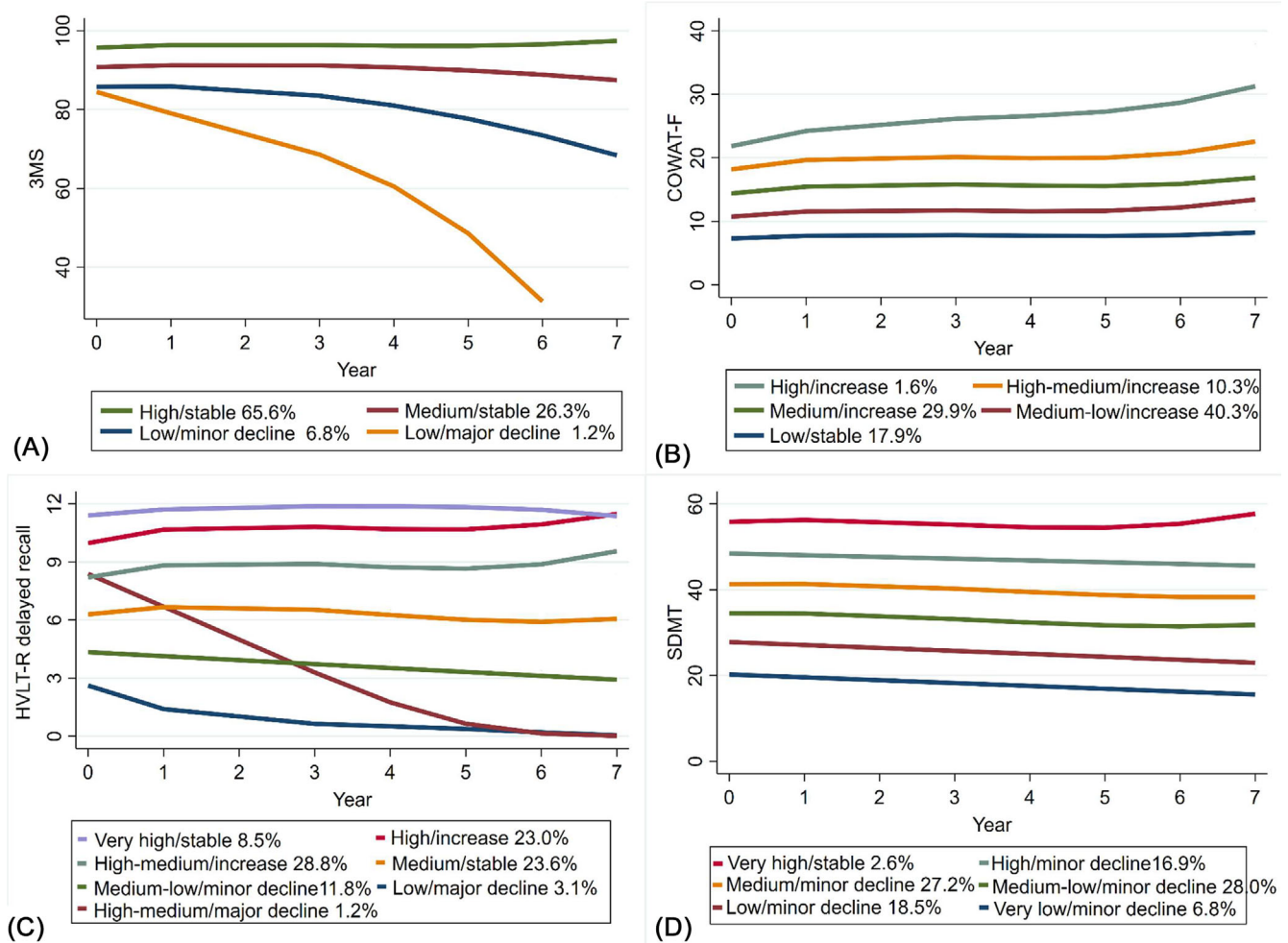


FIGURE 1 Trajectory plots of individual cognitive tests (A) 3MS ($n = 18,016$), (B) COWAT-F ($n = 17,971$), (C) HVLTR delayed recall ($n = 17,837$), (D) SDMT ($n = 17,883$). 3MS, modified Mini-Mental State Examination; COWAT-F, Controlled Oral Word Association Test-F; HVLTR, Hopkins Verbal Learning Test–Revised (delayed recall); SDMT, Symbol Digit Modalities Test. Note: (1) The x-axis denotes the year of cognitive assessments conducted at baseline as well as 1, 3, 4, 5, 6, and 7 years of follow-up. The y-axis denotes the raw scores of the cognitive tests. (2) The percentages refer to the proportions of participants assigned into the corresponding classes

GBTM was conducted separately for the four cognitive tests and three composite scores.

Participants included in the analyses were required to have cognitive data at baseline and at one or more subsequent study visit. Year was used as the time metric. Sociodemographic characteristics (age, sex, ethnicity, education), length of follow-up, and incidence risk of dementia were compared between population subgroups (based on the assigned trajectory class of participants). All statistical analyses were performed using Stata version 16.0 (Stata Corp.).

3 | RESULTS

3.1 | Trajectory modeling

After excluding participants whose cognitive data were missing at baseline or available only at one follow-up timepoint, the number of participants included for analysis was 18,016 for 3MS, 17,971 for

COWAT-F, 17,873 for HVLTR, and 17,883 for SDMT (Figure S1 in supporting information). The sample size available for the three composite scores—the global, executive function, and memory composite score was 17,724, 17,861, and 17,835, respectively. Of the participants included in the analysis, the number with cognitive data at each study visit is summarized in Table S1 in supporting information.

From the trajectory modeling of the four cognitive tests, between four and seven classes were identified, depending on the test. The full process of model selection and the assessment of model adequacy are shown, respectively, in Tables S2 and S3 in supporting information. The trajectory plots of the four cognitive tests are presented in Figure 1, with the parameters of these trajectories summarized in Table S4 in supporting information. Distinct trajectory classes were given subjective labels according to visual features of the mean trajectory, specifically the baseline level and slope of change.

The model for 3MS scores over time identified four classes (Figure 1A), including a high-functioning class with the highest baseline and slight improvement that accounted for the majority of participants

(high/stable: 65.6%), and a medium-functioning class that started at a lower baseline and remained quite stable over time (medium/stable: 26.3%). The two lower-functioning classes had the lowest initial score, of which one had only gradual decline (low/minor decline: 6.8%) while the other dropped substantially (low/major decline: 1.2%).

The five classes detected for the COWAT-F differed from one another on the basis of baseline score, but all remained relatively stable over time with some improvements in performance, and the degree of improvement increased progressively from the class with the lowest baseline to the highest class (Figure 1B). However, most participants fell into the lowest three classes which together accounted for 88.1% of the study sample (medium/increase: 29.9%, medium-low/increase: 40.3%, low/stable: 17.9%).

Seven classes were identified for the HVLTR delayed recall (Figure 1C), including two classes starting at the highest level (very high/stable: 8.5%, high/increase: 23.0%) and another two that had medium baseline scores (high-medium/increase: 28.8%, medium/stable: 23.6%), all either increasing or remaining stable over time. Two classes starting at lower baselines showed decline over time (medium-low/minor decline: 11.8%, low/major decline: 3.1%), and one class was seen with a relatively high baseline score that declined substantially (high-medium/major decline: 1.2%).

For SDMT (Figure 1D), the six classes identified were roughly parallel and remained relatively stable from baseline across follow-up with minor decline, except for the highest and smallest class (very high/stable, 2.6%).

Trajectories of the three composite scores are presented in Figure S2 in supporting information and their parameters are presented in Table S4. There were seven classes observed in the global composite score; these followed a pattern such that trajectories with lower baselines tended to have higher rates of decline (Figure S2a). Five classes (class 1–5), accounted for 91.3% of the study sample and were all stable over time, but in the lowest two classes at baseline there was minor to substantial decline (class 6: 6.8%, class 7: 2.1%). For the executive function composite score (Figure S2b), the model identified seven classes which were similar in their change over time, with slight decline observed only in the lowest two classes (class 6: 10.2%, class 7: 2.8%). There was a total of eight classes for the memory composite score (Figure S2c), with a number of different patterns. The two most frequent classes were high performing and stable over time (class 1: 43.8%, class 2: 31.9%). Four classes declined over time, with different patterns and to varying degrees. For example, class 3 (5.2%) and class 8 (2.2%) both displayed minor declines, but class 8 had the lowest baseline among the eight classes. Class 6 (4.4%) and class 7 (2.2%) both had medium baseline and rapid decline as well as similar endpoints, but the shapes of these two trajectories were different, with class 6 being more curvilinear. There was improvement observed in class 4 (7.0%) and class 5 (3.3%), with class 5 starting from a lower baseline than class 4.

The observed trajectories of cognitive scores for each individual within the classes were also plotted along with the class-specific mean trajectories, with the results shown in Figure 2 for the four cognitive tests and Figure S3 in supporting information for the three composite

scores. The sensitivity analysis using the dropout model did not materially change the results of the basic models (Table S5, Figures S4 and S5 in supporting information).

3.2 | Baseline characteristics

Table S6 in supporting information shows the baseline sociodemographic and cognitive scores of the individuals who participated in ASPREE. The majority of the participants were aged 70 to 74 years (55.5%), were female (56.4%), and White Australian (85.6%), and received >12 years of education (54.8%).

3.3 | Sociodemographic characteristics and incident dementia according to trajectory classes

Tables 1–4 show the sociodemographic characteristics, randomization group, the number/proportion of incident dementia cases, and the length of follow-up, according to trajectory classes of the four cognitive tests. Results of three composite scores are shown in Tables S7–S9 in supporting information.

Generally, participants in the lower-functioning classes with either lower baseline level or greater decline were more likely to be older, male, and with a lower education level. We did not observe any between-class difference in the randomization to aspirin versus placebo, for any of the cognitive tests, which aligns with the main findings of the trial.¹⁴

For all tests, there was a significant difference in incident dementia cases across the classes. This was most noticeable for the 3MS, where more than half of the participants in the low/major decline class developed dementia during follow-up. For HVLTR delayed recall, the two classes with major decline (starting at medium and low, respectively) also had a substantial proportion of individuals with incident dementia (31.4% and 33.2%, respectively). Similar patterns were seen for the global and memory composite scores. On the other hand, the differences in the proportion of individuals with incident dementia were less marked for COWAT (1.8% to 6.7%), SDMT (0% to 15.5%), and the executive function composite score (0% to 18.1%).

4 | DISCUSSION

In this study, we explored the trajectories of cognitive function in late life and the underlying heterogeneity at a population level, using a sample of initially healthy older adults. We identified substantial heterogeneity in cognitive change across individuals, with multiple subgroups displaying hierarchically distinct trajectories, and these varied across the domains assessed. Our findings also suggest that for a large proportion of individuals, the process of cognitive aging is relatively stable over the maximum 7 years of follow-up. However, in a small proportion of individuals cognitive change was dynamic. In general, moderate to substantial decline in global cognition and delayed recall was

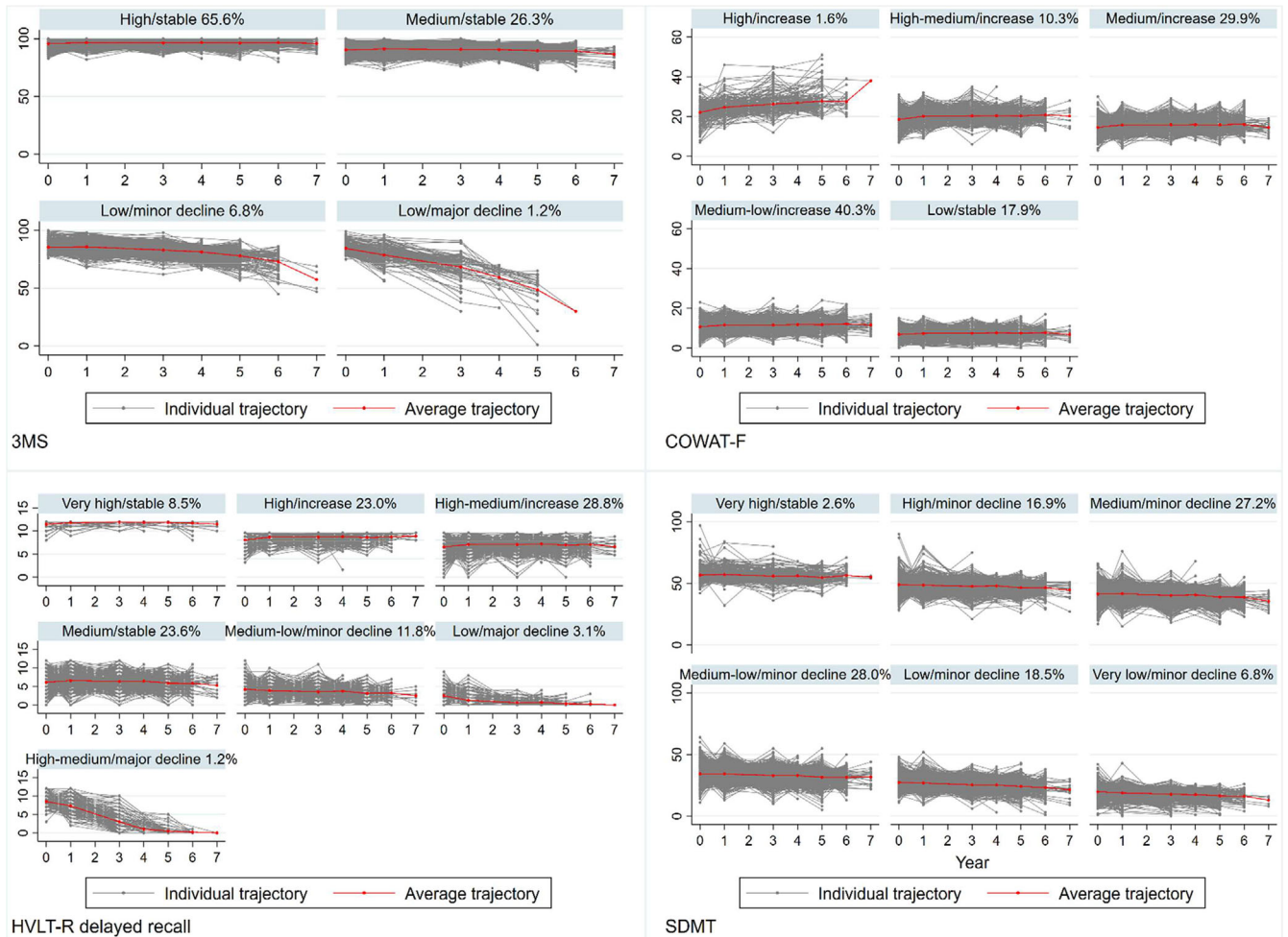


FIGURE 2 Individual trajectories of individual cognitive tests by class: 3MS ($n = 18,016$), COWAT-F ($n = 17,971$), HVLt-R delayed recall ($n = 17,837$), SDMT ($n = 17,883$). 3MS, modified Mini-Mental State Examination; COWAT-F, Controlled Oral Word Association Test-F; HVLt-R, Hopkins Verbal Learning Test–Revised (delayed recall); SDMT, Symbol Digit Modalities Test. Note: (1) The x-axis denotes the year of cognitive assessments conducted at baseline as well as 1, 3, 4, 5, 6, and 7 years of follow-up. The y-axis denotes the raw scores of the cognitive tests. (2) The percentages refer to the proportions of participants assigned into the corresponding classes. (3) Trajectories were generated by connecting the observed cognitive data at each timepoint

observed in a small proportion of participants, and this corresponded to a high proportion of individuals with incident dementia. On the other hand, the majority of participants had only slight decline in SDMT and small improvements of varying degrees in COWAT-F over time. Overall, a pattern of increasing age, lower education, and a lower proportion of women was observed from the highest to lowest trajectory class, but this was not consistent across all domains.

There are several strengths in our study. With more than 17,000 participants, this is so far the largest study investigating the inter-individual variability in late-life cognitive trajectories. In addition, we used four cognitive tests in this study, enabling an investigation into the variability of the trajectories across multiple domains comparably in the same population, which has seldom been investigated previously.^{15–18} Further, we set minimum inclusion criteria related to cognitive data availability to reduce the risk of selection bias, while also performing sensitivity analyses to ensure that the results were not significantly affected by non-random dropouts.

The trajectories of 3MS score followed a typical pattern—the lower the baseline, the greater the rate of decline, and therefore the trajectories did not intersect. This pattern is consistent with previous studies of the trajectories of global cognition,² suggesting that the level of cognitive function, in the absence of disease, remains relatively stable over adulthood and into later life. The 3MS is a global cognitive measure that covers a variety of cognitive domains. It is considered to be superior to the MMSE with a refined scoring scale that means it is less susceptible to ceiling effects and has improved validity and reliability.^{9,19} The 3MS has been widely used to screen for dementia,¹⁹ and this is supported by our findings showing that baseline 3MS, even though all participants had a score above 77, had the best performance of all tests in distinguishing incident dementia. Our results suggest that the two higher classes with 3MS scores > 90 at baseline did not have substantial decline over follow-up, while the two classes with lower baseline scores (around 85) experienced decline. This decline reached what could be considered clinically significant (< 78)⁴⁵ by the second

TABLE 1 Characteristics by cognitive trajectory class of modified Mini-Mental State Examination (3MS; n = 18,016)

Baseline characteristics	Class, N (%)				P-value*
	High/stable 11,824 (65.6)	Medium/stable 4744 (26.3)	Low/minor decline 1232 (6.8)	Low/major decline 216 (1.2)	
Age, years					<.001
65–69 ^a	299 (2.5)	153 (3.2)	29 (2.4)	7 (3.2)	
65–74	7275 (61.5)	2297 (48.4)	482 (39.1)	57 (26.4)	
75–84	4001 (33.8)	2053 (43.3)	595 (48.3)	115 (53.2)	
≥85	249 (2.1)	241 (5.1)	126 (10.2)	37 (17.1)	
Sex					<.001
Male	4690 (39.7)	2423 (51.1)	672 (54.6)	106 (49.1)	
Female	7134 (60.3)	2321 (48.9)	560 (45.4)	110 (50.9)	
Ethnicity					<.001
Australian White	10,245 (86.7)	4068 (85.8)	1028 (83.4)	174 (80.6)	
US White	833 (7.0)	148 (3.1)	39 (3.2)	12 (5.6)	
Black	394 (3.3)	275 (5.8)	85 (6.9)	18 (8.3)	
Hispanic/Latino	229 (1.9)	154 (3.3)	45 (3.7)	8 (3.7)	
Other	123 (1.0)	99 (2.1)	35 (2.8)	4 (1.9)	
Education, years					<.001
< 12	4559 (38.6)	2692 (56.8)	745 (60.5)	123 (56.9)	
12–15	3540 (29.9)	1275 (26.9)	349 (28.3)	59 (27.3)	
≥16	3725 (31.5)	777 (16.4)	138 (11.2)	34 (15.7)	
Randomization group					.443
Aspirin group	5853 (49.5)	2374 (50.0)	626 (50.8)	117 (54.2)	
Placebo group	5971 (50.5)	2370 (50.0)	606 (49.2)	99 (45.8)	
Incident dementia					<.001
Yes	31 (0.3)	129 (2.7)	264 (21.4)	123 (56.9)	
No	11,793 (99.7)	4615 (97.3)	968 (78.6)	93 (43.1)	
	Median (inter-quartile range)				
Length of follow-up, years	4 (3-5)	3 (3-5)	3 (3-5)	3 (1-3)	<.001
Number of cognitive assessments	4 (3-4)	3 (3-4)	3 (3-4)	3 (2-3)	<.001

^aOnly includes U.S. Black or Hispanic/Latino individuals, who were eligible to enroll from 65 years and over (all other individuals needed to be aged at least 70 years to be eligible).

*P-values were based on chi-squared tests or Fisher's exact tests for categorical variables, and Kruskal-Wallis H-tests for length of follow-up.

Note: The labels of the trajectory classes correspond to those shown in Figure 1A.

and sixth annual visit for the major and minor decliners, respectively. They were also at an increased likelihood of having dementia compared to the general population of older adults in Australia and the United States, according to nationally representative data from these two countries.^{20,21} Our results looking at the global composite score largely align with findings from the 3MS, although a greater number of classes were identified, probably reflecting the greater variability of the data using z-scores.²²

In terms of HVLT-R delayed recall, the classes were largely distinguished by their baseline level. The four classes with a score of 6 or above at baseline remained relatively constant during follow-up, while the two lower classes with baseline scores at around 3 to 4 experienced

some decline. However, there was one class starting at relatively high initial function with a baseline score of 8.4 that showed a sharp decline (≈ 1.7 annually) during follow-up. Given that a 5-point drop on the HVLT-R is equivalent to a 1.5 standard deviation decline,¹¹ this level of decline is substantial and would be highly clinically significant. A similar finding was also reported in one study that investigated the trajectories of delayed recall using a sample of 219 subjects who were cognitively normal and aged 60+ years at baseline.²³ Unsurprisingly, individuals in this class in our study were most likely to reach the dementia endpoint during the trial, followed by those in the lowest class with moderate decline. The memory composite score partitioned the study sample to a larger extent, identifying more distinct trajectories and less

TABLE 2 Characteristics by cognitive trajectory class of Controlled Oral Word Association Test-F (COWAT-F; n = 17,971)

Baseline characteristics	Class, N (%)					P-value*
	High/increase 285 (1.6)	High- medium/increase 1844 (10.3)	Medium/increase 5371 (29.9)	Medium- low/increase 7250 (40.3)	Low/stable 3221 (17.9)	
Age, years						<.001
65–69 ^a	0 (0.0)	30 (1.6)	118 (2.2)	231 (3.2)	109 (3.4)	
65–74	180 (63.2)	1146 (62.2)	3087 (57.5)	4035 (55.7)	1636 (50.8)	
75–84	99 (34.7)	608 (33.0)	1986 (37.0)	2720 (37.5)	1333 (41.4)	
≥85	6 (2.1)	60 (3.3)	180 (3.4)	264 (3.6)	143 (4.4)	
Sex						<.001
Male	81 (28.4)	621 (33.7)	2080 (38.7)	3312 (45.7)	1778 (55.2)	
Female	204 (71.6)	1223 (66.3)	3291 (61.3)	3938 (54.3)	1443 (44.8)	
Ethnicity						<.001
Australian White	269 (94.4)	1657 (89.9)	4637 (86.3)	6187 (85.3)	2722 (84.5)	
US White	10 (3.5)	105 (5.7)	377 (7.0)	396 (5.5)	142 (4.4)	
Black	0 (0.0)	41 (2.2)	177 (3.3)	365 (5.0)	189 (5.9)	
Hispanic/Latino	2 (0.7)	22 (1.2)	102 (1.9)	197 (2.7)	113 (3.5)	
Other	4 (1.4)	19 (1.0)	78 (1.5)	105 (1.5)	55 (1.7)	
Education, years						<.001
< 12	63 (22.1)	510 (27.7)	1995 (37.1)	3565 (49.2)	1964 (61.0)	
12–15	88 (30.9)	533 (28.9)	1645 (30.6)	2098 (28.9)	845 (26.2)	
≥16	134 (47.0)	801 (43.4)	1731 (32.2)	1587 (21.9)	412 (12.8)	
Randomization group						.487
Aspirin group	138 (48.4)	934 (50.7)	2624 (48.9)	3621 (49.9)	1628 (50.5)	
Placebo group	147 (51.6)	910 (49.3)	2747 (51.1)	3629 (50.1)	1593 (49.5)	
Incident dementia						<.001
Yes	5 (1.8)	21 (1.1)	98 (1.8)	205 (2.8)	216 (6.7)	
No	280 (98.2)	1823 (98.9)	5273 (98.2)	7045 (97.2)	3005 (93.3)	
	Median (inter-quartile range)					
Length of follow-up, years	4 (3-5)	4 (3-5)	3 (3-5)	3 (3-5)	3 (3-5)	<.001
Number of cognitive assessments	4 (3-4)	4 (3-4)	3 (3-4)	3 (3-4)	3 (3-4)	<.001

^aOnly includes U.S. Black or Hispanic/Latino individuals, who were eligible to enroll from 65 years and over (all other individuals needed to be aged at least 70 years to be eligible).

*P-values were based on chi-squared tests or Fisher's exact tests for categorical variables, and Kruskal-Wallis H-tests for length of follow-up.

Note: The labels of the trajectory classes correspond to those shown in Figure 1B.

within-class variation. This might be a reason the incidence risk of dementia was more stratified by the memory composite score than HVLTR delayed recall. Memory deficit is a central diagnostic criterion of DSM-IV dementia.²⁴ Indeed, impairment of episodic memory—including verbal learning and memory—has been consistently observed in patients of Alzheimer's disease (AD), and is the most pronounced symptom in many studies.^{25–27} The findings of our study further indicate that memory loss might be one of the earliest signs of severe cognitive impairment at the pre-symptomatic stage, because the delayed recall trajectories of those who are most susceptible to dementia in this study have already deviated from others a few years prior to diagnosis.

Language ability, especially vocabulary, is known to remain generally intact or even improve in late life, being less influenced by aging.¹ However, verbal fluency incorporates both vocabulary (an aspect of semantic memory) and executive function, and the two subtypes—semantic fluency and phonemic fluency—differ in task demands and clinical implications.²⁸ Compared to semantic fluency, phonemic fluency has been reported to be more preserved in aging and less impaired in individuals with dementia.^{29,30} This is consistent with our findings, as all COWAT-F trajectories appeared to be relatively stable over time, with even some evidence of improvement, particularly for individuals with high baseline scores. This improvement probably reflects practice effects.³¹ Executive function is largely reflected by phone-

TABLE 3 Characteristics by cognitive trajectory class of Hopkins Verbal Learning Test–Revised (HVLTR) delayed recall (n = 17,873)

Baseline characteristics	Class, N (%)							P-value*
	Very high/stable 1518 (8.5)	High/increase 4095 (23.0)	High-medium/increase 5139 (28.8)	Medium/stable 4211 (23.6)	Medium-low/minor decline 2112 (11.8)	Low/minor decline 554 (3.1)	High-medium/major decline 208 (1.2)	
Age, years								<.001
65–69 ^a	33 (2.2)	101 (2.5)	175 (3.4)	124 (2.9)	41 (1.9)	10 (1.8)	4 (1.9)	
65–74	1060 (69.8)	2693 (65.8)	2975 (57.9)	2131 (50.6)	897 (42.5)	173 (31.2)	67 (32.2)	
75–84	407 (26.8)	1244 (30.4)	1873 (36.5)	1751 (41.6)	1,017 (48.2)	297 (53.6)	118 (56.7)	
≥85	18 (1.2)	57 (1.4)	116 (2.3)	205 (4.9)	157 (7.4)	74 (13.4)	19 (9.1)	
Sex								<.001
Male	462 (30.4)	1445 (35.3)	2127 (41.4)	2159 (51.3)	1,231 (58.3)	317 (57.2)	75 (36.1)	
Female	1,056 (69.6)	2,650 (64.7)	3012 (58.6)	2052 (48.7)	881 (41.7)	237 (42.8)	133 (63.9)	
Ethnicity								<.001
Australian White	1354 (89.2)	3511 (85.7)	4376 (85.2)	3592 (85.3)	1862 (88.2)	486 (87.7)	165 (79.3)	
US White	92 (6.1)	320 (7.8)	304 (5.9)	192 (4.6)	69 (3.3)	29 (5.2)	20 (9.6)	
Black	27 (1.8)	131 (3.2)	231 (4.5)	221 (5.3)	111 (5.3)	32 (5.8)	18 (8.7)	
Hispanic/Latino	24 (1.6)	73 (1.8)	159 (3.1)	131 (3.1)	41 (1.9)	5 (0.9)	3 (1.4)	
Other	21 (1.4)	60 (1.5)	69 (1.3)	75 (1.8)	29 (1.4)	2 (0.4)	2 (1.0)	
Education, years								<.001
< 12	450 (29.6)	1501 (36.7)	2353 (45.8)	2177 (51.7)	1,155 (54.7)	307 (55.4)	95 (45.7)	
12–15	456 (30.0)	1205 (29.4)	1502 (29.2)	1194 (28.4)	602 (28.5)	151 (27.3)	68 (32.7)	
≥16	612 (40.3)	1389 (33.9)	1284 (25.0)	840 (19.9)	355 (16.8)	96 (17.3)	45 (21.6)	
Randomization group								.435
Aspirin group	777 (51.2)	2029 (49.6)	2519 (49.0)	2082 (49.4)	1090 (51.6)	271 (48.9)	107 (51.4)	
Placebo group	741 (48.8)	2066 (50.4)	2620 (51.0)	2129 (50.6)	1022 (48.4)	283 (51.1)	101 (48.6)	
Incident dementia								<.001
Yes	0 (0.0)	5 (0.1)	35 (0.7)	90 (2.1)	160 (7.6)	174 (31.4)	69 (33.2)	
No	1518 (100.0)	4090 (99.9)	5104 (99.3)	4121 (97.9)	1952 (92.4)	380 (68.6)	139 (66.8)	
	Median (inter-quartile range)							
Length of follow-up, years	5 (3–5)	4 (3–5)	3 (3–5)	3 (3–5)	3 (3–5)	3 (1–5)	4 (3–5)	<.001
Number of cognitive assessments	4 (3–4)	4 (3–4)	3 (3–4)	3 (3–4)	3 (2–4)	3 (2–4)	4 (3–4)	<.001

^aOnly includes U.S. Black or Hispanic/Latino individuals, who were eligible to enroll from 65 years and over (all other individuals needed to be aged at least 70 years to be eligible).

*P-values were based on chi-squared tests or Fisher's exact tests for categorical variables, and Kruskal-Wallis H-tests for length of follow-up.

Note: The labels of the trajectory classes correspond to those shown in Figure 1C.

mic fluency, especially in letter-based tasks, because examinees must retrieve words from their phonetic storage that can be difficult to associate with personal experiences.^{28,32} Therefore, the improvement might be a result of certain word-retrieval strategies proactively generated by high-functioning individuals. A deficit of phonemic fluency was reported to be less prominent than that of semantic fluency or other domains in AD,²⁷ and less evident as well when converted into standard scores.³³ This aligns with our finding that the lower-functioning classes

of COWAT-F could not remarkably distinguish the incident dementia cases.

In terms of psychomotor speed, most SDMT trajectories in this study showed moderate decline to a similar degree, which is partially in line with most previous findings from the general population. A number of cross-sectional studies reported slower speed of information processing in older age groups compared to younger counterparts across countries and ethnicities.^{34–37} In contrast, some other studies

TABLE 4 Characteristics by cognitive trajectory class of Symbol Digit Modalities Test (SDMT; n = 17,883)

Baseline characteristics	Class, N (%)						P-value*
	Very high/stable 456 (2.6)	High/minor decline 3025 (16.9)	Medium/minor decline 4869 (27.2)	Medium-low/minor decline 5002 (28.0)	Low/minor decline 3314 (18.5)	Very low/minor decline 1217 (6.8)	
Age, years							<.001
65–69 ^a	13 (2.9)	106 (3.5)	133 (2.7)	119 (2.4)	83 (2.5)	29 (2.4)	
65–74	371 (81.4)	2166 (71.6)	3096 (63.6)	2718 (54.3)	1363 (41.1)	328 (27.0)	
75–84	71 (15.6)	739 (24.4)	1567 (32.2)	1998 (39.9)	1650 (49.8)	689 (56.6)	
≥85	1 (0.2)	14 (0.5)	73 (1.5)	167 (3.3)	218 (6.6)	171 (14.1)	
Sex							<.001
Male	130 (28.5)	1034 (34.2)	1971 (40.5)	2370 (47.4)	1673 (50.5)	652 (53.6)	
Female	326 (71.5)	1991 (65.8)	2898 (59.5)	2632 (52.6)	1641 (49.5)	565 (46.4)	
Ethnicity							<.001
Australian White	372 (81.6)	2532 (83.7)	4198 (86.2)	4386 (87.7)	2887 (87.1)	1,022 (84.0)	
US White	59 (12.9)	280 (9.3)	324 (6.7)	217 (4.3)	118 (3.6)	27 (2.2)	
Black	12 (2.6)	120 (4.0)	166 (3.4)	204 (4.1)	167 (5.0)	97 (8.0)	
Hispanic/Latino	5 (1.1)	50 (1.7)	104 (2.1)	125 (2.5)	98 (3.0)	52 (4.3)	
Other	8 (1.8)	43 (1.4)	77 (1.6)	70 (1.4)	44 (1.3)	19 (1.6)	
Education, years							<.001
< 12	110 (24.1)	896 (29.6)	1849 (38.0)	2418 (48.3)	1916 (57.8)	856 (70.3)	
12–15	134 (29.4)	943 (31.2)	1478 (30.4)	1468 (29.4)	906 (27.3)	254 (20.9)	
≥16	212 (46.5)	1186 (39.2)	1542 (31.7)	1116 (22.3)	492 (14.9)	107 (8.8)	
Randomization group							<.001
Aspirin group	214 (46.9)	1513 (50.0)	2391 (49.1)	2506 (50.1)	1681 (50.7)	603 (49.6)	
Placebo group	242 (53.1)	1512 (50.0)	2478 (50.9)	2496 (49.9)	1633 (49.3)	614 (50.4)	
Incident dementia							<.001
Yes	0 (0.0)	9 (0.3)	39 (0.8)	101 (2.0)	201 (6.1)	188 (15.5)	
No	456 (100.0)	3016 (99.7)	4830 (99.2)	4901 (98.0)	3113 (93.9)	1029 (84.5)	
	Median (inter-quartile range)						
Length of follow-up, years	4 (3-5)	4 (3-5)	3 (3-5)	3 (3-5)	3 (3-5)	3 (1-5)	<.001
Number of cognitive assessments	4 (3-4)	3 (3-4)	3 (3-4)	3 (3-4)	3 (3-4)	3 (2-4)	<.001

^aOnly includes U.S. Black or Hispanic/Latino individuals, who were eligible to enroll from 65 years and over (all other individuals needed to be aged at least 70 years to be eligible).

*P-values were based on chi-squared tests or Fisher's exact tests for categorical variables, and Kruskal-Wallis H-tests for length of follow-up.

Note: The labels of the trajectory classes correspond to those shown in Figure 1D.

failed to observe an association between age and SDMT performance in young and middle-aged adults,^{12,38} which potentially indicates that psychomotor slowing might only present in late life. Indeed, linear decline in psychomotor speed was observed in longitudinal studies when the participants were followed-up into their late adulthood.^{39,40} Our findings further suggest that gradual psychomotor slowing might be considerably prevalent or even inevitable after the age of 70, regardless of the level of functioning at an early stage, which is possibly in part due to age-related changes in white matter.⁴¹ Slowed psychomotor speed has also been found to be associated with dementia in

previous studies, and used as a marker for cognitive impairment.^{42,43}

In the current study, the SDMT trajectories with differences mainly at baseline stratified the incidence risk of dementia to a moderate degree, with those starting lower being more likely to reach this endpoint. Because there was not substantial variance across the SDMT trajectories in the changes over follow-up, it is worth investigating the potential role of psychomotor speed in dementia screening, especially the thresholds that can be used cross-sectionally for specific age groups.

Generally, individuals in the lower-functioning classes across all of the cognitive domains were more likely to be older, male, and with

lower levels of education. This is largely consistent with previous studies⁴⁴ as well as the findings regarding the baseline cognitive data from this sample.^{11,45,46} Among cognitively healthy individuals, women generally outperform men in episodic memory at old age, especially in verbal-based recall.^{47,48} However, women are found to be at a higher risk of AD than men^{20,49} and once diagnosed, usually have greater impairment in memory function.⁴⁷ This might help explain why women were in the majority in both the highest performing and in the most rapidly declining classes of episodic memory (HVLt-R delayed recall). This also aligns with the findings that the lowest class in 3MS and the global composite score showed a slightly higher proportion of women. However, we cannot rule out the possibility that some other factors, such as lifestyles and socioeconomic factors, might have been associated with the sharp decline in cognitive function.

There are some limitations to this study that need to be acknowledged. The study sample is comprised of generally healthy older adults, as the eligibility criteria excluded individuals with dementia or other severe comorbidities. However, the recruitment of the participants was mainly through primary care physicians in Australia or clinical trial centers in the United States, and therefore, the participants should be broadly representative of individuals who have reached older age in relatively good health. Another limitation is that the data only concern the cognitive change during a specific period, with participants aged 65 years or above, and the majority between 70 and 75 years, who were followed for an average of almost 5 years. Thus, it is not possible to infer how these trajectories will evolve over a longer time frame. Two trajectories with sharp decline were identified for the 3MS and HVLt-R delayed recall, both with the highest proportion of incident dementia cases. However, it remains unknown why several participants were also in these classes who did not reach the dementia endpoint during the follow-up. Possible explanations include the continuation of pre-existing neurodegenerative diseases other than dementia, and the terminal cognitive decline prior to death.⁵⁰ However, future studies are needed to investigate and validate the cause of such rapid decline.

5 | CONCLUSION

The results of this study indicate that, in relatively healthy older adults, the variability of cognitive change was observed across individuals in all cognitive domains assessed. Most individuals were able to maintain their cognitive function at a relatively stable level over the follow-up period. Slight improvement in phonemic fluency and moderate decline in psychomotor speed were common. Accelerated decline was observed in only a small proportion of individuals in delayed recall and global cognitive function, and this was most common in individuals that developed incident dementia. Therefore, although gradual cognitive decline is often thought to be an expected component of aging in many individuals,¹ normal cognitive aging can also be characterized as the maintenance of cognitive function over time, with some individuals continuing to perform at very high levels, even with advancing age.

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CONFLICTS OF INTEREST

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SUPPORTING INFORMATION

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

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