Received: 19 April 2024 | Revised: 25 October 2024 | Accepted: 6 December 2024

DOI: 10.1002/dad2.70063

Alzheimer's & Dementia
Diagnosis, Assessment & Disease Monitoring

RESEARCH ARTICLE

Amyloid-related changes in fluency in patients with subjective cognitive decline

Rosanne L. van den Berg[1,2,3] | **Elke Butterbrod**[1,2,3,4] | **Casper de Boer**[1,2] | **Lisa-Marie Schlüter**[1,2] | **Argonde C. van Harten**[1,2] | **Charlotte E. Teunissen**[2,5] | **Elsmarieke van de Giessen**[6,7] | **Wiesje M. van der Flier**[1,2,8] | **Sietske A. M. Sikkes**[1,2,3]

[1]Alzheimer Center Amsterdam, Neurology, Amsterdam University Medical Center, Amsterdam, the Netherlands

[2]Amsterdam Neuroscience, Neurodegeneration, Amsterdam, the Netherlands

[3]Department of Clinical, Neuro and Developmental Psychology, Faculty of Movement and Behavioral Sciences, VU University, Amsterdam, the Netherlands

[4]Department of Neurosurgery, Elisabeth-Tweesteden Hospital, Tilburg, the Netherlands

[5]Department of Clinical Chemistry, Neurochemistry Laboratory and Biobank, Amsterdam Neuroscience, Amsterdam University Medical Center, Amsterdam, the Netherlands

[6]Department of Radiology & Nuclear Medicine, Amsterdam University Medical Center, Amsterdam, the Netherlands

[7]Amsterdam Neuroscience, Brain Imaging, Amsterdam, the Netherlands

[8]Department of Epidemiology and Biostatistics, Amsterdam Neuroscience, VU University Medical Center, Amsterdam, the Netherlands

Correspondence
Rosanne L. van den Berg, Alzheimer Center Amsterdam, Neurology, Amsterdam University Medical Center, De Boelelaan 1118, 1081 HZ, Amsterdam, the Netherlands.
Email: r.l.vandenberg@amsterdamumc.nl

Funding information
Health~Holland, Grant/Award Number: #LSHM20084

Abstract

INTRODUCTION: We examined semantic and phonemic fluency in individuals with subjective cognitive decline (SCD) in relation to amyloid status and clinical progression.

METHODS: A total of 490 individuals with SCD (62 ± 8 years, 42% female, 28% amyloid-positive, 17% clinical progression) completed annual fluency assessments (mean ± SD follow-up 4.3 ± 2.9 years). Associations between fluency trajectories, amyloid status, and clinical progression were examined with linear mixed models and joint models.

RESULTS: Amyloid-positive individuals declined faster than amyloid-negative individuals on semantic fluency ($B = -0.35$, $p < 0.001$), but not on phonemic fluency ($B = -0.06$, $p = 0.218$). An annual decline of one word in semantic and phonemic fluency was associated with 22% (hazard ratio [HR] = 1.22, $p < 0.001$) and 28% (HR = 1.28, $p = 0.004$) increased risk of clinical progression.

DISCUSSION: Our results indicate that decline in semantic fluency is an early indicator of cognitive deficits in preclinical Alzheimer's disease.

KEYWORDS
Alzheimer's disease, amyloid positive, language, longitudinal, subjective cognitive decline, verbal fluency

Highlights

- Abnormal amyloid burden is associated with decline in semantic fluency.
- Fluency trajectories are associated with an increased risk of clinical progression.
- More refined measures are needed to detect the earliest language deficits.

1 | INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease characterized by cognitive decline, and biologically defined by amyloid accumulation and neurofibrillary tau tangles.[1] AD has a long preclinical stage that can last for decades, with subtle cognitive decline occurring years before overt impairment leads to a diagnosis of mild cognitive impairment (MCI) or dementia.[2] Early in the AD continuum, individuals may report subjective cognitive decline (SCD), although cognitive testing reveals no objective deficit.[1]

Although memory decline is among the earliest and most prominent features of AD, patients may also experience focal language difficulties, in particular in word finding, naming, and verbal fluency, prior to a diagnosis of AD dementia.[3–6] Suboptimal performance on language tests can reflect underlying semantic problems.[4,5,7] In the memory clinic setting, language is commonly assessed with semantic and phonemic fluency tasks. Of these verbal fluency tasks, semantic fluency is most prominently impaired in individuals with AD dementia.[8] In the MCI stage, semantic fluency performance is reduced, whereas evidence about phonemic fluency is inconclusive.[9–13] Semantic fluency performance and the discrepancy between affected semantic but relatively preserved phonemic verbal fluency performance have more recently been shown to predict progression from MCI to dementia.[14,15]

Research focusing on the preclinical AD stage has demonstrated that generally no impairments on traditional measures of semantic fluency are observed cross-sectionally in individuals with amyloid pathology.[16–19] By contrast, amyloid-positive individuals do show faster decline on longitudinal semantic fluency assessment.[16–19] For single phonemic fluency assessment, previous research is inconclusive, indicating no amyloid-related difference in performance, or higher phonemic fluency scores for amyloid-positive individuals.[16,17] Over time, however, both studies demonstrated that abnormal amyloid burden was related to faster phonemic fluency decline, although this effect disappeared when correcting for semantic fluency in the study by Papp et al.[17] Moreover, research considering progression in cognitively unimpaired individuals, has indicated that those who progressed to AD dementia had lower semantic, but not phonemic, fluency at baseline, and showed faster decline over time in both semantic and phonemic fluency.[20] In addition, the prognostic value of single semantic fluency assessment, but not phonemic fluency, has been demonstrated in cognitively unimpaired individuals.[21–23] To date, however, a knowledge gap remains on the degree to which fluency trajectories are predictive for clinical progression in cognitively unimpaired individuals.

We aimed to investigate the diagnostic and prognostic value of longitudinal verbal fluency in individuals with SCD who visited the memory clinic. First, we examined whether longitudinal trajectories of verbal fluency depended on amyloid status. Second, we investigated verbal fluency trajectories in individuals who progressed to MCI or dementia versus those who did not progress. Third, we examined whether longitudinal change in verbal fluency could predict progression to MCI or dementia.

2 | METHODS

2.1 | Participants

We included 490 participants diagnosed with SCD from the Amsterdam Dementia Cohort (ADC, 2016.061)[24,25] and the embedded Subjective Cognitive Impairment Cohort (SCIENCe, 2014.019).[26] Both studies were approved by the medical ethics review committee of the VU University Medical Center, Amsterdam UMC. All participants provided written informed consent to participate in the study. As part of standard diagnostic workup of the memory clinic of the Alzheimer Center Amsterdam, all participants underwent a neurological and neuropsychological examination. In a multidisciplinary consensus meeting participants were diagnosed with SCD when clinical and cognitive examination was within normal range and diagnostic criteria for MCI, dementia, or other psychiatric or neurological disorders were not fulfilled, based on research criteria for SCD.[27] At annual follow-up visits (mean ± SD follow-up 4.3 ± 2.9 years, range 0.6–17.4, *N* visits = 1974), neurological and neuropsychological examination was repeated, and diagnoses were reevaluated as SCD, or as MCI or dementia, based on established criteria.[28,29] During follow-up, 81 individuals (17%) progressed to MCI (n = 63, 78%) or dementia (n = 18, 22%), with a mean progression time of 3.2 ± 2.5 years (range 0.85–11.4). More information on clinical progression can be found in Table S1.

Additional inclusion criteria for the present study were: (1) diagnosis of SCD at baseline; (2) age at baseline ≥45 years; (3) availability of at least baseline and one follow-up assessment of semantic or phonemic fluency; and (4) availability of amyloid biomarkers (cerebrospinal fluid [CSF] or positron emission tomography [PET]; see below) within 1 year of baseline assessment.

2.2 | Measures

2.2.1 | Verbal fluency

Participants completed the Dutch version of the semantic fluency task (animal category) and Controlled Oral Word Association Test (COWAT; phonemic fluency).[25,30,31] During annual follow-up,

participants completed 1944 semantic fluency assessments and 1734 phonemic fluency assessments, resulting in 1720 assessments for which discrepancy scores were calculated. In the semantic fluency task, participants produced as many animals as they could in 1 minute. The phonemic fluency task consisted of three trials. In each trial, participants produced as many words with a particular onset letter as they could in 1 minute(alternating versions: D, A, T or K, O, M). The following verbal fluency outcomes were used for statistical analysis:

1. Semantic fluency score: total number of correctly produced items on semantic fluency;
2. Phonemic fluency score: total number of correctly produced items on phonemic verbal fluency, averaged across three trials;
3. Semantic–phonemic discrepancy score: calculated by subtracting the phonemic fluency score from the semantic fluency score, following previous research.[14,15] This score was calculated if both semantic fluency and phonemic fluency were completed.

2.2.2 | Amyloid biomarkers

All included participants had biomarker assessment in CSF and/or an amyloid PET scan. CSF was obtained by lumbar puncture and amyloid beta $(A\beta)_{1\text{-}42}$ concentrations were analyzed by either enzyme-linked immunosorbent assay (ELISA) or electrochemiluminescence immunoassays (Elecsys). PET scans were performed using [^{18}F]flutemetamol, [^{18}F]florbetapir, or [^{18}F]florbetaben radiotracers.[26,32,33] Amyloid burden was dichotomized as positive/negative based on local cutoffs of our center for $A\beta_{1\text{-}42}$ concentrations in CSF,[34,35] or based upon visual reading of amyloid PET by a nuclear radiologist according to company guidelines. In the event that both CSF and PET were available, PET results were used.[19,26]

2.3 | Statistical analyses

All analyses were run in R (version 4.2.1). For all analyses *p*-values < 0.05 were considered statistically significant. Participant characteristics and baseline fluency performance were compared between amyloid-positive and amyloid-negative groups, and between progressors and non-progressors, using chi-square tests (categorical variables) or independent *t*-tests (continuous variables). Assumptions of equality of variance and normality of data distribution were checked and Wilcoxon tests were used if appropriate.

We used linear mixed models (LMMs) to investigate longitudinal changes in fluency measures (semantic and phonemic, and discrepancy), and their associations with amyloid status. As independent variables we used time in years from baseline, and amyloid status. An interaction term was added between time and amyloid status (main variable of interest) to investigate whether slopes were different between amyloid-positive and amyloid-negative groups. Each model included a random intercept for each subject and covariates for age, sex, and education. Random slopes were investigated, but did not improve model fit and were not adopted in the models. If the interaction between amyloid and time was significant, we subsequently stratified the LMMs for amyloid status (positive/negative) in line with our first research question.

Subsequently, we investigated trajectories of fluency measures (semantic and phonemic and discrepancy), and their associations with clinical progression using LMMs. The same model structure was used as for previous LMM analyses, with the main variable of interest being progression status (i.e., clinical progression to MCI or dementia or no clinical progression). If the interaction between clinical progression and time was significant we subsequently stratified the LMMs for progression status (progressors/non-progressors). We repeated these LMMs for progression to MCI and AD dementia, where participants who progressed to non-AD dementia were excluded, as well as for progression to dementia only, where MCI was considered as no progression.

Finally, we used joint models to examine the association between longitudinal changes in fluency measures (i.e., semantic and phonemic and discrepancy) and risk of clinical progression to MCI or dementia. Joint models combine LMMs with Cox proportional hazards models to concurrently estimate longitudinal change and the risk of clinical progression, correcting for baseline score.[36] For each joint model we first specified the LMM for each verbal fluency measure, which included time in years from baseline and progression status as independent variables, and a random intercept for each subject. Then, we specified the Cox proportional hazards model, with baseline verbal fluency measure as predictor, and time in years from baseline to event (progression) or to last follow-up (censoring) as the outcome. The joint models were

RESEARCH IN CONTEXT

1. **Systematic review**: The existing literature was reviewed by searching for relevant publications in PubMed. The literature indicates that especially semantic fluency is associated with Alzheimer's disease (AD) and clinical progression, whereas semantic and phonemic fluency trajectories in relation to clinical progression in preclinical AD have not yet been sufficiently explored. (References are appropriately cited.)
2. **Interpretation**: Our findings indicate that the abnormal presence of amyloid in cognitively normal adults predisposes for semantic decline, and that semantic decline is associated with increased risk of clinical progression. These findings support the importance of measuring semantic decline in the earliest stages of AD.
3. **Future directions**: Further research should include more refined item-level measures of semantic fluency to identify the earliest, subtle signs of semantic decline that are associated with amyloid pathology in individuals with subjective cognitive decline.

TABLE 1 Participant characteristics at baseline.

	Total group (*N* = 490)	Amyloid-negative (*n* = 353)	Amyloid-positive (*n* = 137)	*p*-value	Nonprogressor (*n* = 409)	Progressor (*n* = 81)	*p*-value
Demographics							
Age, years, mean (SD)	61.5 (7.5)	60.2 (7.4)	64.9 (6.9)	<0.001[c]	60.7 (7.5)	65.5 (6.5)	<0.001[c]
Female gender, *n* (%)	205 (41.8)	136 (38.5)	69 (50.4)	0.017[d]	172 (42.1)	33 (40.7)	0.827[d]
Education, years, mean (SD)	12.3 (3.0)	12.1 (3.0)	12.6 (3.1)	0.236[c]	12.3 (3.0)	12.2 (3.3)	0.654[c]
Amyloid status positive, *n* (%)	137 (28.0)	-	-	-	83 (20.3)	54 (66.7)	<0.001[d]
Baseline cognitive measures							
Mini-Mental State Examination, mean (SD)	28.3 (1.6)	28.3 (1.6)	28.2 (1.4)	0.295[c]	28.4 (1.5)	27.8 (1.7)	0.003[c]
Semantic fluency, mean (SD)	22.7 (5.8)	22.8 (5.9)	22.5 (5.4)	0.756[c]	23.1 (5.8)	21.2 (5.1)	0.021[c]
Phonemic fluency (average D, A, T), mean (SD)	12.4 (4.0)	12.3 (4.0)	12.6 (3.9)	0.435[c]	12.4 (4.0)	12.2 (4.0)	0.717[c]
Discrepancy score, mean (SD)	10.4 (5.2)	10.5 (5.2)	10.0 (5.2)	0.234[c]	10.7 (5.1)	8.9 (5.2)	0.010[c]
Follow-up time, years, mean (SD)	4.3 (2.9)	4.3 (3.1)	4.2 (2.6)	0.948[c]	4.2 (3.0)	4.8 (2.6)	0.009[c]
Range follow-up time, years, min–max	0.6–17.4	0.6–17.4	0.9–15.2	-	0.56–17.4	1.0–12.6	-

Abbreviation: SD, standard deviation.
[a]Independent *t*-test.
[b]Welch *t*-test.
[c]Wilcoxon test.
[d]Chi-square test.

adjusted for age as the progressor, and non-progressor groups differed in age. We additionally performed the joint models for conversion to MCI and AD dementia, excluding participants who progressed to non-AD dementia, and for progression to dementia only, where MCI was considered as no progression.

3 | RESULTS

3.1 | Participant characteristics and baseline verbal fluency

We included 490 individuals with SCD. Of the participants, 205 (42%) were female and 137 (28%) were amyloid- positive. The mean age ± SD at baseline was 61.5 ± 7.5 years, and the mean Mini-Mental State Examination (MMSE) was 28.3 ± 1.6. Table 1 shows demographics and baseline cognitive measures for the total sample, as well as for amyloid-positive and amyloid-negative groups and clinical progressor and non-progressor groups. At baseline, mean semantic fluency was 22.7 ± 5.8 words, phonemic fluency was 12.4 ± 4.0 words, and semantic–phonemic discrepancy was 10.4 ± 5.2 words.

Compared to the amyloid-negative group, the amyloid-positive group was older at baseline ($p < 0.001$), and relatively more individuals were female ($p = 0.017$). No amyloid group differences were observed for years of education, baseline cognitive measures, or follow-up time. The group that progressed to MCI or dementia was older at baseline ($p < 0.001$), had lower baseline MMSE scores ($p = 0.003$), and longer follow-up time ($p = 0.009$) than the group that did not progress. In addition, progressors had lower baseline semantic fluency scores ($p = 0.021$) and lower baseline discrepancy scores ($p = 0.010$).

3.2 | Fluency performance over time in relation to amyloid status

Figure 1 shows the longitudinal trajectories on semantic fluency, phonemic fluency, and discrepancy scores for amyloid-positive and amyloid-negative individuals. On semantic fluency, amyloid-positive individuals declined faster than amyloid-negative individuals ($p_{interaction} < .001$). Stratified analyses showed that the former group declined with 0.43 words per year (95% confidence interval [CI] = −0.57 to −0.28, $p < 0.001$), whereas amyloid-negative individuals showed no significant change ($B = -0.08$, 95% CI = −0.16 to 0.01, $p = 0.069$). For phonemic fluency, the main effect of time was significant, showing an improvement over time independent of amyloid status ($B = 0.08$, 95% CI = 0.03 to 0.13, $p = 0.003$). The main effect of amyloid was not significant for phonemic fluency ($B = 0.03$, 95% CI = −0.71 to 0.77], $p = 0.929$); nor was the interaction effect between amyloid status and time ($p_{interaction} = 0.218$). On the discrepancy score, the amyloid-positive group declined faster ($p_{interaction} < 0.001$). Stratified analyses showed that amyloid-positive individuals declined with 0.47 per year (95% CI = −0.63 to −0.31, $p < 0.001$), whereas amyloid-negative individuals declined with 0.13 per year (95% CI = −0.23 to −0.04, $p = 0.005$). Results of the LMMs are displayed in Table S2.

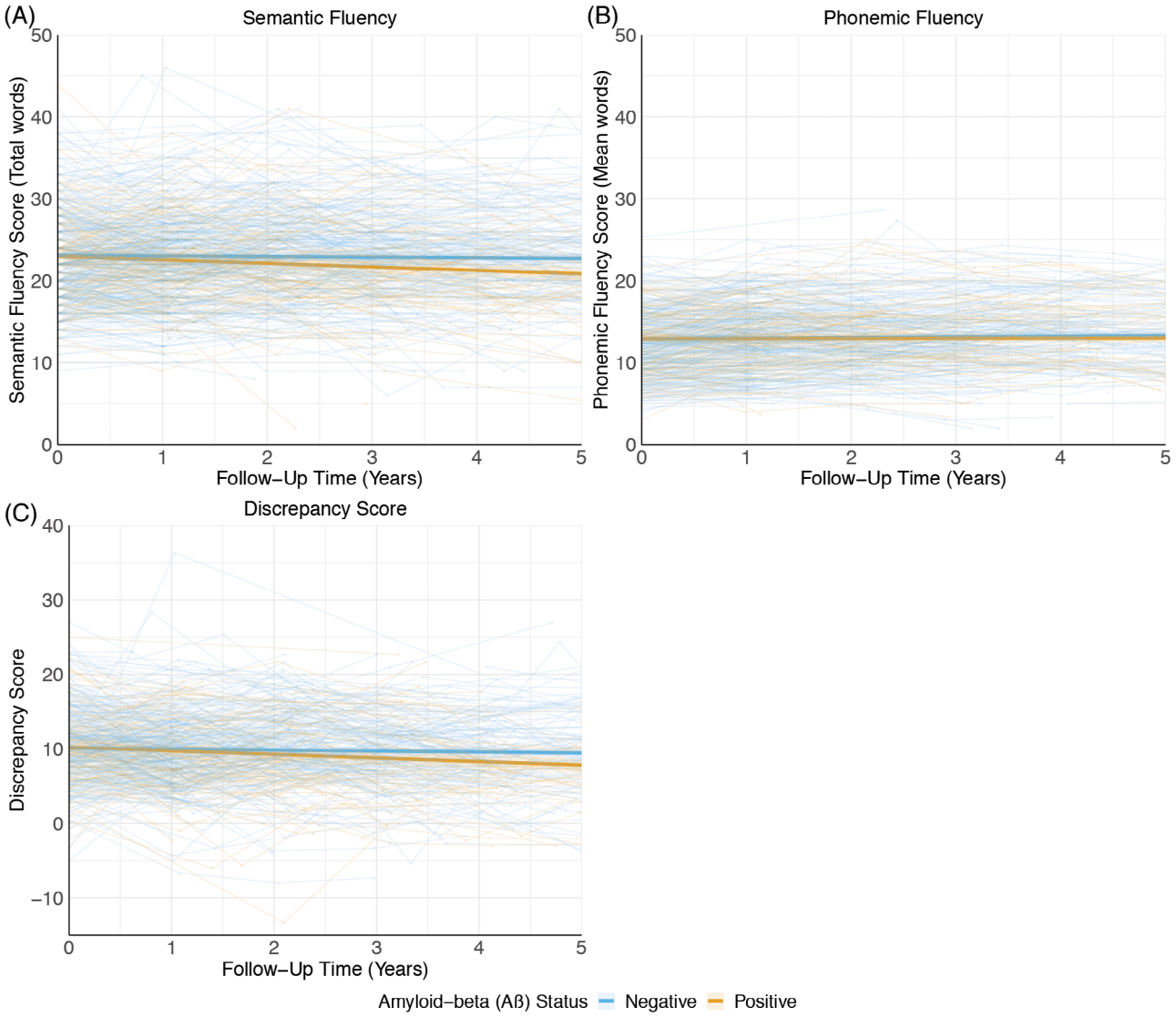

FIGURE 1 Longitudinal trajectories of (A) semantic fluency, (B) phonemic fluency, and (C) discrepancy scores in amyloid-positive and amyloid-negative individuals with SCD. Bold lines with 95% confidence intervals represent the LMMs to predict verbal fluency, adjusted for age, sex, and education. Dots and lines represent raw data points. Figures are scaled to a range of 5 years of follow-up for visibility purposes. Significant interaction effects were demonstrated between time and amyloid status for semantic fluency ($p < 0.001$), and the discrepancy score ($p < 0.001$), but not for phonemic fluency ($p = 0.218$). LMMs, linear mixed models; SCD, subjective cognitive decline.

3.3 | Fluency performance over time in relation to clinical progression

Figure 2 shows the longitudinal trajectories of semantic fluency, phonemic fluency, and discrepancy scores for individuals who progressed to MCI or dementia, and for individuals who did not progress. On semantic fluency, progressors declined faster than non-progressors ($p_{interaction} < 0.001$). Progressors declined with 0.79 words per year (95% CI = −0.96 to −0.62, $p < 0.001$), whereas non-progressors showed no significant change over time ($B = -0.02$, 95% CI = −0.10 to 0.05, $p = 0.532$). Similarly, progressors declined faster on phonemic fluency ($p_{interaction} < 0.001$). Progressors declined with 0.23 words per year (95% CI = [−0.34 to −0.13, $p < 0.001$), whereas non-progressors improved with 0.13 words per year (95% CI = 0.09 to 0.18, $p < 0.001$). Regarding the discrepancy score, for the progressor group the discrepancy between semantic and phonemic fluency was reduced more rapidly ($p_{interaction} = 0.002$). In the progressor group this score was reduced with 0.46 per year (95% CI = −0.65 to −0.28, $p < 0.001$), and in the non-progressor group with 0.15 per year (95% CI = −0.24 to −0.06, $p = 0.001$). Results of the LMMs, as well as results of sensitivity analyses for progression to MCI and AD dementia, and for progression to dementia only, are displayed in Table S3. Results were not substantially different for the sensitivity analyses.

Subsequently, we used joint models to examine the association between change over time in verbal fluency and risk of progression to MCI or dementia. These models showed that a decline in semantic fluency over time was associated with risk of clinical progression (hazard ratio [HR] = 0.82, 95% CI = 0.73 to 0.92, $p < 0.001$).

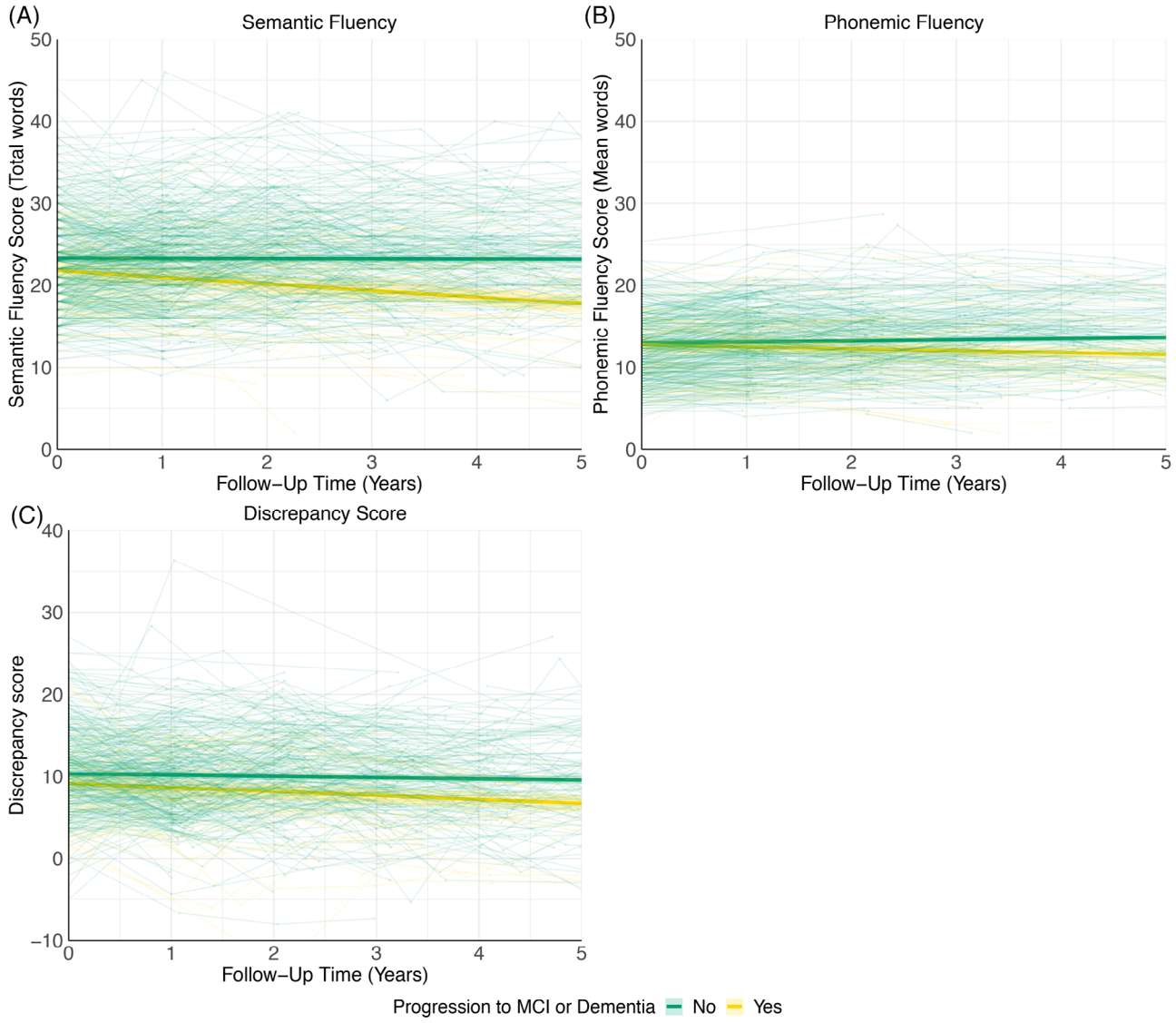

FIGURE 2 Longitudinal trajectories of (A) semantic fluency, (B) phonemic fluency, and (C) discrepancy scores in progressors and nonprogressors. Bold lines with 95% confidence intervals represent the LMMs to predict verbal fluency, adjusted for age, sex, and education. Dots and lines represent raw data points. Figures are scaled to a range of 5 years follow-up for visibility purposes. Significant interaction effects were demonstrated between time and progressor status for semantic fluency ($p < 0.001$), phonemic fluency ($p < 0.001$), and the discrepancy score ($p = 0.002$). LMMs, linear mixed models.

In particular, a decrease of one word per year in semantic fluency was associated with a 22% increase for risk of progression (HR for decline = 1/0.82 = 1.22). Likewise, phonemic fluency (HR = 0.78, 95% CI = 0.66 to 0.92, $p = 0.004$) was associated with risk of clinical progression, where a one-word decrease per year was associated with a 28% increased risk of progression (HR = 1/0.78 = 1.28). Change in discrepancy score was not associated with risk of progression (HR = 0.94, 95% CI = 0.83 to 1.07, $P = 0.345$). Results of the joint models and of sensitivity analyses for progression to MCI and AD dementia, and for progression to dementia only, are provided in Table S4. Sensitivity analyses did not substantially change the results, except for the finding that a decline in phonemic fluency over time was not significantly associated with the risk of progression to MCI and AD dementia only (HR = 0.83, 95% CI = 0.69 to 1.01, $p = 0.057$).

4 | DISCUSSION

This study showed that amyloid-positive individuals with SCD declined faster on semantic fluency and the semantic–phonemic fluency discrepancy than amyloid-negative individuals. Compared to nonprogressors, individuals who progressed to MCI or dementia declined faster on semantic fluency, phonemic fluency, and the discrepancy score. An annual one-word decline in semantic and phonemic fluency at any point in time was associated with an 18%–22% increased risk of clinical progression. These results suggest that AD biomarker–positive individuals diagnosed with SCD are likely to experience semantic decline, in particular, and that even a subtle decrease in semantic and phonemic fluency provides prognostic value for future clinical progression.

A meta-analysis across nondemented populations (i.e., no MCI or dementia diagnosis) has recently demonstrated a cross-sectional association between lower semantic fluency performance and amyloid positivity, although the weighted effect size was small (Cohens $d = 0.19$).[37] In the present study, however, we found no cross-sectional differences between amyloid-positive and amyloid-negative SCD patients in any of the baseline verbal fluency measures. This difference in results may be explained by differences in the investigated study samples; whereas the meta-analysis included populations from different settings (i.e., community based, memory-clinic based samples), the current study used a memory-clinic based sample in which patients were diagnosed with SCD in the absence of objective cognitive decline based on extensive neuropsychological assessment. Previous studies assessing the association between amyloid burden and semantic fluency in patients with SCD also demonstrated no cross-sectional differences between amyloid-positive and amyloid-negative individuals. However, similar to our study, amyloid-related differences on performance over time were demonstrated.[16,19]

Upon repeated testing, otherwise cognitively unimpaired individuals are expected to show improved performance on verbal fluency tests, and the absence of such a learning effect may be an early indication of cognitive decline.[31,38–40] In phonemic fluency we indeed found a small learning effect independent of amyloid status. In contrast, in research by Papp et al., a decline in phonemic fluency was reported that was steeper for amyloid-positive than for amyloid-negative individuals. This difference in results is notable, given that they included a sample of clinically normal adults recruited from the community, who had more years of education and a slightly higher MMSE score than our memory-clinic sample. For semantic fluency we demonstrated stable performance for amyloid-negative individuals, whereas amyloid-positive individuals declined over time. These findings indicate that amyloid positivity is associated with a semantic loss, even in adults with no objective cognitive deficits, extending previous research.[17,18]

Previous research is inconclusive about whether decreased semantic–phonemic discrepancy, that is, more similar scores, is characteristic for early AD.[41,42] We found that the discrepancy between tasks reduced more rapidly in amyloid-positive than in amyloid-negative individuals. This faster discrepancy reduction in the former group seems to be driven primarily by decreased semantic fluency. The less-rapid discrepancy reduction in the amyloid-negative group was driven by their slight improvement in phonemic fluency, and stable semantic fluency. The observed discrepancy reduction in amyloid-positive individuals might reflect that the semantic-to-phonemic-fluency advantage, which has been shown to be preserved in normal aging,[43] is decreasing in the preclinical AD stage, possibly as a result of semantic loss.

Another finding was that progressors declined on all three verbal fluency measures, whereas non-progressors remained stable on semantic fluency, improved on phonemic fluency, and declined on the discrepancy, albeit less pronounced than progressors. The faster decline for progressors in semantic and phonemic fluency is consistent with previous work in progressors with initially unimpaired cognition.[20] However, progressors with MCI have been reported not to differ from nonprogressors in semantic fluency trajectories,[13] suggesting that fluency trajectories may differ across disease stages. Furthermore, we found that declines in both semantic and phonemic fluency were associated with a proportional increased risk of clinical progression, whereas the decline in discrepancy between tasks was not. Previous research has indicated that a single semantic fluency assessment differs between progressors and non-progressors, and could predict future decline, although the literature is not conclusive.[13,15,21–23,44] Our finding that semantic fluency trajectories predicted progression in initially cognitively unimpaired individuals adds to this body of literature, suggesting that fluency trajectories might provide additional information about performance development (i.e., decline rather than stable performance), thereby holding prognostic value.

Single phonemic fluency assessment has been shown previously to hold no prognostic value for progression in individuals with unimpaired cognition and MCI.[14,15,23] Possibly, as indicated by our results, it might rather be its trajectory that is indicative for progression, which might not be captured cross-sectionally. However, in additional analyses for progression to MCI and AD dementia, phonemic fluency decline was no longer associated with progression risk, whereas the decline in semantic fluency still was, aligning our finding that semantic, but not phonemic, fluency trajectories were associated with abnormal amyloid burden at baseline. Semantic and phonemic fluency have been shown to tap into both distinct and overlapping cognitive processes. Whereas both tasks seem to depend on executive functioning, semantic fluency seems to rely more heavily on intact semantic memory.[45,46] Hence, our findings may support that semantic processes are most prominently impaired in AD.[5]

Regarding the semantic–phonemic discrepancy, previous research has shown that cross-sectionally the discrepancy predicted progression in individuals with MCI.[14,15] An explanation for why the discrepancy trajectory did not predict progression in our study, could be that the difference in the discrepancy trajectories between groups was too subtle (i.e., both groups declined). Hence, these findings suggest that rather than combining fluency scores into a discrepancy score, individual verbal fluency trajectories are more promising to predict clinical conversion in initially cognitively normal adults with SCD.

This study has several limitations. First, we did not consider amyloid biomarkers at follow-up, and thus did not take into account that some individuals might have had positive amyloid biomarkers at later time points. Second, our sample was highly educated, meaning that results may not be representative of the general population. Third, because fluency scores were part of the overall neuropsychological evaluation at follow-up, there is a potential incorporation bias regarding diagnostic progression. However, a decline in fluency alone did not suffice for progression to a new diagnostic category. At the same time, this study included a large and unique study sample of cognitively unimpaired adults who were well characterized by the presence of amyloid biomarkers.

Our findings underscore that language, especially semantic-related, processes are affected early in the disease course of AD. We therefore argue for a stronger emphasis on language in the diagnostic workup of cognitively normal adults with SCD at the memory clinic. This

is particularly important as these patients may report word-finding difficulties,[3] which cannot be captured by a single verbal fluency assessment. We speculate that these reported language problems may be reflected in the semantic fluency declines over time. Possibly, more refined analysis of item-level verbal fluency characteristics may be more sensitive to detect language deficits in patients with SCD, such as semantic clustering,[13,47] which should be examined in future research. Still, it may be debated whether verbal fluency is the optimal task to measure language. For instance, this task eliciting single words rather than connected sentences may not provide an ecologically valid representation of daily language use, which comprises a wide range of language domains (i.e., phonology, morphology, syntax, semantics, and pragmatics).[48] Digital language tasks may overcome these challenges. Such digital speech assessments enable automated analysis of spontaneous language recordings, thereby offering a more sensitive and ecologically valid measure of language, which has been indicated to hold promise for detecting subtle language related changes in an early AD stage, such as more pauses, more pronouns, and fewer specific words.[48–50] Our observation that especially semantic fluency trajectories were associated with abnormal amyloid burden and clinical progression highlight the importance of such refined language assessments for detecting language deficits as an early symptom in preclinical AD.

ACKNOWLEDGMENTS

This project was funded by the public-private partnership (PPP) Allowance made available by Health~Holland, Top Sector Life Sciences & Health, to stimulate public-private partnerships (#LSHM20084). Research of Alzheimer Center Amsterdam is part of the neurodegeneration research program of Amsterdam Neuroscience. Alzheimer Center Amsterdam is supported by Stichting Alzheimer Nederland and Stichting Steun Alzheimercentrum Amsterdam. The chair of W.F. is supported by the Pasman stichting. The SCIENCe project receives funding from stichting Dioraphte and the Noaber foundation. The funders of this study had no involvement in study design, data collection, data interpretation, or writing of the report.

CONFLICT OF INTEREST STATEMENT

C.B. is a recipient of funds from Health~Holland, Topsector Life Sciences & Health (public-private partnership (PPP) allowance: LSHM20084), and the Alzheimer's Association; all funds are paid to his institution. The research of A.H. is supported by Alzheimer Nederland, Alzheimer's Drug Discovery Foundation (ADDF), and ZonMw. A.H. provides consultancy services to Lilly and was a speaker at Eisai. All payments are made to her institution. The research of C.T. is supported by the European Commission (Marie Curie International Training Network, #860197 (MIRIADE), Innovative Medicines Initiatives 3TR (Horizon 2020, #831434) EPND (IMI 2 Joint Undertaking (JU), #101034344) and JPND (bPRIDE), National MS Society (Progressive MS alliance), Alzheimer's Association, Health~Holland, the Dutch Research Council (ZonMW), Alzheimer Drug Discovery Foundation, The Selfridges Group Foundation, and Alzheimer Netherlands. C.T. is a recipient of ABOARD, which is a public–private partnership receiving funding from ZonMW (#73305095007) and Health~Holland, Topsector Life Sciences & Health (PPP-allowance; #LSHM20106). C.T. has research contracts with Acumen, ADx Neurosciences, AC-Immune, Alamar, Aribio, Axon Neurosciences, Beckman-Coulter, BioConnect, Bioorchestra, Brainstorm Therapeutics, Celgene, Cognition Therapeutics, EIP Pharma, Eisai, Eli Lilly, Fujirebio, Instant Nano Biosensors, Novo Nordisk, Olink, PeopleBio, Quanterix, Roche, Toyama, and Vivoryon. C.T. provides consultancy services to Aribio, Eli Lilly, Merck, Novo Nordisk, Poxel, and Roche. C.T. serves on editorial boards of *Medidact Neurologie/Springer*, *Alzheimer Research and Therapy*, *Neurology: Neuroimmunology & Neuroinflammation*. All payments are made to her institution. The research of E.G. has been funded by Alzheimer Nederland (Cross border grant), Health~Holland Top Consortium Knowledge and Innovation - Top Sector Life Sciences and Health (TKI-LSH), ZonMw, Hersenstichting, KWF, Heuron Inc., and Roche. E.G. provides consultancy services to Roche, Ixico, and Life Molecular Imaging. All payments are made to her institution. The research programs of W.F. have been funded by ZonMW, The Dutch Research Council (NWO), EU Joint Programming Initiative Neurodegenerative Diseases (JPND), EU Innovative Health Initiative (IHI), Alzheimer Nederland, Hersenstichting CardioVascular Onderzoek Nederland, Health~Holland, Topsector Life Sciences & Health, stichting Dioraphte, Gieskes-Strijbis fonds, stichting Equilibrio, Edwin Bouw fonds, Pasman stichting, stichting Alzheimer & Neuropsychiatrie Foundation, Philips, Biogen MA Inc, Novartis-NL, Life-MI, AVID, Roche BV, Fujifilm, Eisai, and Combinostics. W.F. holds the Pasman chair. W.F. is a recipient of ABOARD, which is a public-private partnership receiving funding from ZonMW (#73305095007) and Health~Holland, Topsector Life Sciences & Health (PPP-allowance; #LSHM20106). W.F. is a recipient of TAP-dementia (www.tap-dementia.nl), receiving funding from ZonMw (#10510032120003). TAP-dementia receives co-financing from Avid Radiopharmaceuticals and Amprion. W.F. has been an invited speaker at Biogen MA Inc, Danone, Eisai, WebMD Neurology (Medscape), NovoNordisk, Springer Healthcare, European Brain Council. W.F. is consultant to Oxford Health Policy Forum CIC, Roche, Biogen MA Inc, and Eisai. W.F. participated in advisory boards of Biogen MA Inc, Roche, and Eli Lilly. W.F. is a member of the steering committee of EVOKE/EVOKE+ (NovoNordisk). W.F. is a member of the steering committee of PAVE, and Think Brain Health. W.F. was associate editor of *Alzheimer, Research & Therapy* in 2020/2021, and is associate editor at *Brain*. All payments are made to her institution. W.F. and S.S. are recipients of IHI-AD-RIDDLE (#101132933), a project supported by the Innovative Health Initiative Joint Undertaking (IHI JU). The JU receives support from the European Union's Horizon Europe research and innovation programme and COCIR, EFPIA, EuropaBio, MedTech Europe, and Vaccines Europe, with Davos Alzheimer's Collaborative, Combinostics OY., Cambridge Cognition Ltd., C2N Diagnostics LLC, and neotiv GmbH. All funding is paid to the institution. S.S. is a recipient of funds from Health~Holland, Topsector Life Sciences & Health (PPP allowance: DEFEAT-AD, LSHM20084; REMONIT-AD, LSHM22026), Alzheimer Nederland (SPREAD+) and Ministry of Health, Welfare and Sports (#90001586), ZonMw in the context of Onderzoeksprogramma Dementie, part of the Dutch

National Dementia Strategy (TAP-dementia, #10510032120003), and ZonMW (Verspreidings- en Implementatie Impuls (VIMP)The Dutch Research Council, #7330502051 and #73305095008, NWO (YOD-MOLECULAR, #KICH1.GZ02.20.004) as part of the NWO Research Program KIC 2020-2023 MISSION—Living with dementia. YOD-MOLECULAR receives co-financing from Winterlight Labs, ALLEO Labs, and Hersenstichting. Team Alzheimer also contributes to YOD-MOLECULAR. S.S. is a scientific advisory board member of Prothena Biosciences and Cogstate, provides consultancy services to Aribio Co LTD and Biogen, and receives license fees from Brain Research Center, Green Valley, VtV Therapeutics, Alzheon, Vivoryon and Roche, and the developer of the Amsterdam IADL. All payments are made to her institution. The other authors report no financial disclosures or conflicts of interest. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

This study complies with the Helsinki Declaration of 1975, as revised in 2008. All participants provided written informed consent.

ORCID

Rosanne L. van den Berg https://orcid.org/0009-0008-0685-9074

REFERENCES

1. Jack CR, Jr., Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimers Dement*. 2024;20(8):5143-5169. doi:10.1002/alz.13859
2. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):280-292. doi:10.1016/j.jalz.2011.03.003
3. Montembeault M, Stijelja S, Brambati SM, Alzheimer's Disease Neuroimaging I. Self-reported word-finding complaints are associated with cerebrospinal fluid amyloid beta and atrophy in cognitively normal older adults. *Alzheimers Dement*. 2022;14(1):e12274. doi:10.1002/dad2.12274
4. Verma M, Howard RJ. Semantic memory and language dysfunction in early Alzheimer's disease: a review. *Int J Geriatr Psychiatry*. 2012;27(12):1209-1217. doi:10.1002/gps.3766
5. Wright LM, De Marco M, Venneri A. Current understanding of verbal fluency in Alzheimer's disease: evidence to date. *Psychol Res Behav Manag*. 2023;16:1691-1705. doi:10.2147/PRBM.S284645
6. Kim J, Kim M, Yoon JH. The tip-of-the-tongue phenomenon in older adults with subjective memory complaints. *PLoS One*. 2020;15(9):e0239327. doi:10.1371/journal.pone.0239327
7. Taler V, Phillips NA. Language performance in Alzheimer's disease and mild cognitive impairment: a comparative review. *J Clin Exp Neuropsychol*. 2008;30(5):501-556. doi:10.1080/13803390701550128
8. Henry JD, Crawford JR, Phillips LH. Verbal fluency performance in dementia of the Alzheimer's type: a meta-analysis. *Neuropsychologia*. 2004;42(9):1212-1222. doi:10.1016/j.neuropsychologia.2004.02.001
9. Mueller KD, Koscik RL, LaRue A, et al. Verbal fluency and early memory decline: results from the Wisconsin registry for Alzheimer's prevention. *Arch Clin Neuropsychol*. 2015;30(5):448-457. doi:10.1093/arclin/acv030
10. Nutter-Upham KE, Saykin AJ, Rabin LA, et al. Verbal fluency performance in amnestic MCI and older adults with cognitive complaints. *Arch Clin Neuropsychol*. 2008;23(3):229-241. doi:10.1016/j.acn.2008.01.005
11. Chasles MJ, Tremblay A, Escudier F, et al. An examination of semantic impairment in amnestic MCI and AD: what can we learn from verbal fluency? *Arch Clin Neuropsychol*. 2019;35(1):22-30. doi:10.1093/arclin/acz018
12. Murphy KJ, Rich JB, Troyer AK. Verbal fluency patterns in amnestic mild cognitive impairment are characteristic of Alzheimer's type dementia. *J Int Neuropsychol Soc*. 2006;12(4):570-574. doi:10.1017/s1355617706060590
13. Delage E, Rouleau I, Akzam-Ouellette MA, Roy-Cote F, Joubert S, Cima Q. An examination of semantic performance in mild cognitive impairment progressors and nonprogressors. *Neuropsychology*. 2024;38(4):309-321. doi:10.1037/neu0000947
14. Marra C, Piccininni C, Masone Iacobucci G, et al. Semantic memory as an early cognitive marker of Alzheimer's disease: role of category and phonological verbal fluency tasks. *J Alzheimers Dis*. 2021;81(2):619-627. doi:10.3233/JAD-201452
15. Vaughan RM, Coen RF, Kenny R, Lawlor BA. Semantic and phonemic verbal fluency discrepancy in mild cognitive impairment: potential predictor of progression to Alzheimer's disease. *J Am Geriatr Soc*. 2018;66(4):755-759. doi:10.1111/jgs.15294
16. Verberk IMW, Hendriksen HMA, van Harten AC, et al. Plasma amyloid is associated with the rate of cognitive decline in cognitively normal elderly: the SCIENCe project. *Neurobiol Aging*. 2020;89:99-107. doi:10.1016/j.neurobiolaging.2020.01.007
17. Papp KV, Mormino EC, Amariglio RE, et al. Biomarker validation of a decline in semantic processing in preclinical Alzheimer's disease. *Neuropsychology*. 2016;30(5):624-630. doi:10.1037/neu0000246
18. Ho JK, Nation DA, Alzheimer's Disease Neuroimaging I. neuropsychological profiles and trajectories in preclinical Alzheimer's disease. *J Int Neuropsychol Soc*. 2018;24(7):693-702. doi:10.1017/S135561771800022X
19. Ebenau JL, Timmers T, Wesselman LMP, et al. ATN classification and clinical progression in subjective cognitive decline: the SCIENCe project. *Neurology*. 2020;95(1):e46-e58. doi:10.1212/WNL.0000000000009724
20. Clark LJ, Gatz M, Zheng L, Chen YL, McCleary C, Mack WJ. Longitudinal verbal fluency in normal aging, preclinical, and prevalent Alzheimer's disease. *Am J Alzheimers Dis Other Demen*. 2009;24(6):461-468. doi:10.1177/1533317509345154
21. Pakhomov SV, Hemmy LS. A computational linguistic measure of clustering behavior on semantic verbal fluency task predicts risk of future dementia in the nun study. *Cortex*. 2014;55:97-106. doi:10.1016/j.cortex.2013.05.009
22. Ayers MR, Bushnell J, Gao S, et al. Verbal fluency response times predict incident cognitive impairment. *Alzheimers Dement*. 2022;14(1):e12277. doi:10.1002/dad2.12277
23. Folia V, Liampas I, Siokas V, et al. Language performance as a prognostic factor for developing Alzheimer's clinical syndrome and mild cognitive impairment: results from the population-based HELIAD cohort. *J Int Neuropsychol Soc*. 2023;29(5):450-458. doi:10.1017/S1355617722000376
24. van der Flier WM, Scheltens P. Amsterdam Dementia Cohort: performing research to optimize care. *J Alzheimers Dis*. 2018;62(3):1091-1111. doi:10.3233/JAD-170850
25. van der Flier WM, Pijnenburg YA, Prins N, et al. Optimizing patient care and research: the Amsterdam Dementia Cohort. *J Alzheimers Dis*. 2014;41(1):313-327. doi:10.3233/JAD-132306
26. Slot RER, Verfaillie SCJ, Overbeek JM, et al. Subjective Cognitive Impairment Cohort (SCIENCe): study design and first results. *Alzheimers Res Ther*. 2018;10(1):76. doi:10.1186/s13195-018-0390-y

27. Jessen F, Amariglio RE, van Boxtel M, et al. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimers Dement*. 2014;10(6):844-852. doi:10.1016/j.jalz.2014.01.001
28. Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med*. 2004;256(3):183-194. doi:10.1111/j.1365-2796.2004.01388.x
29. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):263-269. doi:10.1016/j.jalz.2011.03.005
30. Snijders J, Luteijn F, van der Ploeg F, Verhage F. Groninger intelligentie test. Lisse, Swets & Zeitlinger; 1983.
31. Schmand B, Groenink SC, van den Dungen M. [Letter fluency: psychometric properties and Dutch normative data]. *Tijdschr Gerontol Geriatr*. 2008;39(2):64-76. Letterfluency: psychometrische eigenschappen en Nederlandse normen. doi:10.1007/BF03078128
32. de Wilde A, van Maurik IS, Kunneman M, et al. Alzheimer's biomarkers in daily practice (ABIDE) project: rationale and design. *Alzheimers Dement (Amst)*. 2017;6:143-151. doi:10.1016/j.dadm.2017.01.003
33. Zwan MD, Bouwman FH, Konijnenberg E, et al. Diagnostic impact of [(18)F]flutemetamol PET in early-onset dementia. *Alzheimers Res Ther*. 2017;9(1):2. doi:10.1186/s13195-016-0228-4
34. Tijms BM, Willemse EAJ, Zwan MD, et al. Unbiased approach to counteract upward drift in cerebrospinal fluid amyloid-beta 1-42 analysis results. *Clin Chem*. 2018;64(3):576-585. doi:10.1373/clinchem.2017.281055
35. Willemse EAJ, van Maurik IS, Tijms BM, et al. Diagnostic performance of Elecsys immunoassays for cerebrospinal fluid Alzheimer's disease biomarkers in a nonacademic, multicenter memory clinic cohort: The ABIDE project. *Alzheimers Dement*. 2018;10:563-572. doi:10.1016/j.dadm.2018.08.006
36. Rizopoulos D. JM: an R package for the joint modelling of longitudinal and time-to-event data. *J Stat Softw*. 2010;35:1-33.
37. Vonk JMJ, Twait EL, Scholten R, Geerlings MI. Cross-sectional associations of amyloid burden with semantic cognition in older adults without dementia: a systematic review and meta-analysis. *Mech Ageing Dev*. 2020;192:111386. doi:10.1016/j.mad.2020.111386
38. Cooper DB, Lacritz LH, Weiner MF, Rosenberg RN, Cullum CM. Category fluency in mild cognitive impairment: reduced effect of practice in test-retest conditions. *Alzheimer Dis Assoc Disord*. 2004;18(3):120-122. doi:10.1097/01.wad.0000127442.15689.92
39. Jutten RJ, Grandoit E, Foldi NS, et al. Lower practice effects as a marker of cognitive performance and dementia risk: a literature review. *Alzheimers Dement*. 2020;12(1):e12055. doi:10.1002/dad2.12055
40. Ebenau JL, Verfaillie SCJ, van den Bosch KA, et al. Grey zone amyloid burden affects memory function: the SCIENCe project. *Eur J Nucl Med Mol Imaging*. 2021;48(3):747-756. doi:10.1007/s00259-020-05012-5
41. Laws KR, Duncan A, Gale TM. 'Normal' semantic-phonemic fluency discrepancy in Alzheimer's disease? A meta-analytic study. *Cortex*. 2010;46(5):595-601. doi:10.1016/j.cortex.2009.04.009
42. Gordon JK, Chen H. How well does the discrepancy between semantic and letter verbal fluency performance distinguish Alzheimer's dementia from typical aging? *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn*. 2023;30(5):729-758. doi:10.1080/13825585.2022.2079602
43. Vaughan RM, Coen RF, Kenny R, Lawlor BA. Preservation of the semantic verbal fluency advantage in a large population-based sample: normative Data from the TILDA Study. *J Int Neuropsychol Soc*. 2016;22(5):570-576. doi:10.1017/S1355617716000291
44. Belleville S, Fouquet C, Hudon C, Zomahoun HTV, Croteau J, Consortium for the early identification of Alzheimer's d-Q. neuropsychological measures that predict progression from mild cognitive impairment to alzheimer's type dementia in older adults: a systematic review and meta-analysis. *Neuropsychol Rev*. 2017;27(4):328-353. doi:10.1007/s11065-017-9361-5
45. Henry JD, Crawford JR. A meta-analytic review of verbal fluency performance following focal cortical lesions. *Neuropsychology*. 2004;18(2):284-295. doi:10.1037/0894-4105.18.2.284
46. Schmidt CSM, Schumacher LV, Romer P, et al. Are semantic and phonological fluency based on the same or distinct sets of cognitive processes? Insights from factor analyses in healthy adults and stroke patients. *Neuropsychologia*. 2017;99:148-155. doi:10.1016/j.neuropsychologia.2017.02.019
47. Cintoli S, Favilli L, Morganti R, Siciliano G, Ceravolo R, Tognoni G. Verbal fluency patterns associated with the amnestic conversion from mild cognitive impairment to dementia. *Sci Rep*. 2024;14(1):2029. doi:10.1038/s41598-024-52562-x
48. Slegers A, Filiou RP, Montembeault M, Brambati SM. Connected speech features from picture description in Alzheimer's disease: a systematic review. *J Alzheimers Dis*. 2018;65(2):519-542. doi:10.3233/JAD-170881
49. Verfaillie SCJ, Witteman J, Slot RER, et al. High amyloid burden is associated with fewer specific words during spontaneous speech in individuals with subjective cognitive decline. *Neuropsychologia*. 2019;131:184-192. doi:10.1016/j.neuropsychologia.2019.05.006
50. Ivanova O, Martinez-Nicolas I, Meilan JJG. Speech changes in old age: methodological considerations for speech-based discrimination of healthy ageing and Alzheimer's disease. *Int J Lang Commun Disord*. 2024;59(1):13-37. doi:10.1111/1460-6984.12888

SUPPORTING INFORMATION

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

How to cite this article: van den Berg RL, Butterbrod E, de Boer C, et al. Amyloid-related changes in fluency in patients with subjective cognitive decline. *Alzheimer's Dement*. 2025;17:e70063. https://doi.org/10.1002/dad2.70063