RESEARCH ARTICLE

Diagnosis, Assessment
& Disease Monitoring

Amyloid beta associations with connected speech in cognitively unimpaired adults

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Abstract

Introduction: Connected speech and language (CSL) decline has been associated with early cognitive decline, but associations between CSL and Alzheimer's disease (AD) biomarkers remain a gap in the literature. Our goal was to examine associations with amyloid beta (Aβ) and longitudinal CSL trajectories in cognitively unimpaired adults at increased AD risk.

Methods: Using data from the Wisconsin Registry for Alzheimer's Prevention, CSL measures were automatically extracted from digitally recorded picture descriptions. Positron emission tomography determined Aβ status. Linear mixed effects models assessed the interaction between age and Aβ on CSL trajectories.

Results: Participants who were Aβ positive experienced more rapid decline on specific word content, when controlling for age, sex, and literacy. There were no differences between groups in lexical diversity measures over time.

Discussion: These results indicate that declines in connected speech may be related to preclinical AD. CSL may be a promising, inexpensive, and easy-to-collect digital cognitive marker for AD studies.

KEYWORDS
Alzheimer's disease, computational linguistics, connected speech, dementia, discourse, language, Mild Cognitive Impairment, PET imaging, picture description, Pittsburgh Compound-B; speech, preclinical Alzheimer's disease

1 | INTRODUCTION

The present research framework for defining Alzheimer's disease (AD) in living persons focuses on biomarkers, specifically measures of brain amyloid beta (Aβ) deposition, pathological tau, and neurodegeneration, as assessed by measures of cerebrospinal fluid (CSF), positron emission tomography (PET) imaging, and structural magnetic resonance imaging (MRI).[1,2] Accruing evidence that AD pathology accumulation begins decades before the onset of clinical symptoms[1,3] has prompted the development of multiple clinical trials investigating both pharmacological and non-pharmacological early interventions. This movement has created an urgent need for sensitive tools that can measure functional and cognitive changes, particularly in the very early or preclinical stages of the AD continuum, and as measures of response to treatment in clinical trials. One such potential tool is the analysis of connected speech and language (CSL).

"Connected speech and language," also referred to as "connected speech," or "discourse," refers to spoken language that is used in a continuous sequence, as in everyday conversations. While episodic memory declines are a hallmark sign of AD, another early clinical symptom includes problems with communication, evidenced by both subjective complaints about word-retrieval problems,[4] as well as by objective differences in semantic verbal fluency (naming items from a category under timed conditions).[5,6] CSL production involves the coordination of multiple cognitive processes, including retrieval from semantic and episodic memory,[7] the ability to sustain and divide attention for error monitoring,[8] and reliance upon working memory for syntax organization.[9] Changes in CSL, consisting of fluency disruptions and limited semantic content, have long been noted in persons with dementia[10–12] moreover, accruing research suggests that subtle, yet detectable, changes in CSL are present even in preclinical stages of cognitive decline.[13–15] Because CSL is an ecologically valid measure of language use (it approximates "everyday talking"), and because it is quick, inexpensive, able to be collected remotely, and presents low burden to participants, it is a potentially valuable digital cognitive marker to explore in the context of AD studies.

Language devoid of content words, or "empty speech," as well as the more subtle deficits in CSL, are presumably the result of underlying lexical/semantic processing deficits.[16] Such deficits have been explained as either the result of a primary semantic selection deficit,[17] or as secondary to working memory problems[18] or as a combination of both.[19] However, there is limited evidence investigating how these neurolinguistic theories relate to the neuropathology of AD, particularly in those individuals without frank clinical cognitive impairment. As noted above, the multiple cognitive processes involved in CSL production stemming from semantic/lexical processing implicate a complex interplay among multiple brain regions, most primarily the left inferior frontal gyrus, the left superior temporal gyrus/angular gyrus, and the medial and superior pre-frontal cortex, all of which are sites of accumulation of AD pathology in pre-symptomatic individuals.[20,21]

Verfaillie et al.[19] investigated the cross-sectional relationship between measures from CSL and amyloid levels in cognitively unimpaired participants with subjective cognitive decline. The study showed

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RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional (e.g., PubMed) sources and meeting abstracts and presentations. There is currently limited evidence investigating the relationship between connected speech and amyloid burden, especially in those individuals without frank cognitive impairment, a critical population for early detection and clinical trial monitoring. Several publications have demonstrated a reduction in content words relative to total words in more advanced stages of AD. These relevant publications are appropriately cited.

2. **Interpretation**: The results indicate that connected speech measures are associated with amyloid beta at preclinical stages of disease.

3. **Future directions**: The article proposes the need for replication in other, larger samples with additional time points in addition to investigation of the relationship between speech and other known AD biomarkers, such as tau and neurodegeneration. Finally, crucial next steps include determining modifiable factors that may moderate effects of AD biomarkers on measures of cognition, including speech and language.

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that individuals with higher levels of amyloid tended to produce fewer specific words in connected speech than those with lower amyloid levels.[19] Because CSL is highly variable and dependent upon multiple social, cultural, and personal factors, a longitudinal design is necessary to confirm these associations. Therefore, the primary objective of this study was to examine whether prospective age-related trajectories of lexical diversity and semantic content from CSL differed by Aβ status ascertained from [C-11]Pittsburgh compound B (PiB) amyloid PET imaging. Specifically, we hypothesized that cognitively unimpaired late-middle-aged adults who were classified as amyloid positive ("A+") would show greater longitudinal declines in lexical diversity and semantic content than those who were classified as amyloid negative ("A−").

2 | MATERIALS AND METHODS

2.1 | Participants

Participants (N = 255) were drawn from the Wisconsin Registry for Alzheimer's Prevention (WRAP), an ongoing, longitudinal natural history study of a late-onset AD–risk-enriched cohort of late-middle-aged adults, with 73% having a parental history of probable AD. WRAP participants are cognitively unimpaired at baseline, and undergo

comprehensive medical, neuropsychological, and lifestyle evaluation and questionnaires biennially, which have been previously described.[22] Participants were selected for this study if they had provided at least two longitudinal speech samples (see below for more information), had English as their first language, had no known neurological impairments including stroke or a diagnosis of dementia, and had at least one amyloid PiB PET scan. All study procedures were approved by the University of Wisconsin–Madison Institutional Review Board and are in accordance with the Declaration of Helsinki.

2.2 | Aβ positivity

Participants underwent structural MRI (3T GE Signa 750) and dynamic [C-11]PiB PET (Siemens EXACT HR +) imaging from 0 to 70 minutes post-injection at the University of Wisconsin–Madison Waisman Center brain imaging lab. Detailed imaging methods including radiopharmaceutical production, acquisition, and image reconstruction, and processing and quantification of MRI and PiB data have been previously described.[23] SPM12 unified segmentation was performed on the T1-weighted MRI for tissue class segmentation and to define nonlinear registration between subject and MNI152 template space (https://www.fil.ion.ucl.ac.uk/spm/software/spm12). Regions of interest for the PET analysis were generated by inverse warping MNI152 template regions of interest[24] to subject space and restricting to gray matter probabilities > .3. The reference region volume of interest for PiB quantification was generated by smoothing a bilateral, binary cerebellar gray matter mask with a 6 mm Gaussian kernel (to simulate PET spatial resolution) and keeping voxels > 0.7.

Reconstructed PiB time series were smoothed (3 mm isotropic Gaussian kernel), interframe realigned (SPM12), dynamically denoised (HYPR-LR),[25] and registered to T1-weighted MRI. PiB distribution volume ratio (DVR) was estimated from a 70-minute dynamic acquisition using reference Logan graphical analysis (t* = 35 minutes, k^2 = 0.149/minute, cerebellum gray matter reference region). Amyloid status ("A+/−") was determined by visual inspection of native space parametric DVR images overlaid on T1-weighted MRI (inter-rater reliability = 0.95, intra-rater reliability = 0.96).[24] Participants with multiple PiB PET scans (n = 100) were coded A+ if any scan indicated amyloid positivity. PET imaging took place on average 2.6 years prior to baseline CSL sample (standard deviation [SD] = 2.6, range –7.3 to 2.6). For amyloid positive individuals, the first positive PET image preceded baseline CSL by 2.8 years on average (SD = 2.9, range –7.1 to 2.9).

2.3 | Discourse collection procedure

Participants who met study criteria provided 679 speech samples that were collected during biennial neuropsychological testing visits beginning in 2013. Participants provide informed consent to have their speech recorded while describing the "cookie theft" picture from the Boston Diagnostic Aphasia Examination.[26] The majority of participants (63%) provided three language samples over time. Examiners

instructed participants, "Tell me everything you see going on in this picture." Evaluators provided no feedback during participants' descriptions; however, if responses were unusually brief (e.g., one or two sentences), evaluators provided the scripted prompt, "Do you see anything else going on?" Only one prompt is given when necessary. Language samples had a mean duration of 54 seconds (SD = 24) including prompts from the examiner. All responses were recorded using an Olympus VN-6200 PC digital audio recorder placed flat on a table approximately six inches in front of the participant.

2.4 | Transcription and automated language analysis

Language samples were transcribed by trained speech-language pathology graduate students using Codes for the Human Analysis of Transcripts (CHAT).[27] Transcribers were blinded to the cognitive status and amyloid status of the participant. Utterances were manually segmented into C-units, defined as "an independent clause and all of its modifiers."[28] Transcripts were manually coded for automatic analyses using the Computerized Language Analysis (CLAN) program,[27] including codes for filled and unfilled pauses, repetitions, revisions, and semantic units. Twenty percent of all transcripts (n = 135) were assessed for inter-rater reliability. Agreement was 98% for transcription of total words and 92% for utterance segmentation (Cohen's Kappa was automatically calculated by the "RELY" command in CLAN). If reliability on any one transcript was lower than the Kappa ≥ .90 threshold, disagreements were discussed, consensus was reached, and coding decisions subsequently manualized. Two discourse measures of interest were automatically extracted by the CLAN software for these analyses based on previous literature of CSL in early cognitive decline[14,29] and probable AD dementia,[30] as well as by a previous study examining CSL in cognitively unimpaired participants with AD biomarker data[19]: type-token ratio and open-to-closed class words ratio (Table 1). The type-token ratio is automatically extracted using the "FREQ" command in CLAN, which calculates the total number of unique words by a speaker and divides that number by the total number of words used by that speaker; the open-to-closed class words ratio is calculated by first running the "MOR" command on all of the transcripts. MOR is an automatic computation of the morphosyntactic structure of transcripts, including both part-of-speech tagging of each

TABLE 1 Description connected speech/language variables obtained from transcribed digital recordings of picture description

Connected speech language variable	Description of variable
Total words	All spoken words in language sample
Unique words	Total # non-repeating words
Type-token ratio	# unique words / # total words
Open to closed class words ratio	Total # nouns, verbs, adverbs / total # function words (e.g., prepositions, determiners, conjunctions)

individual word as well as a complete syntactic dependency analysis. Then, the "EVAL" command was run for all transcripts, which automatically calculates the open-to-closed class ratio.

2.5 | Cognitive status

Participants did not have dementia at enrollment.[22] To determine cognitive status after each visit, algorithmic criteria based on a robust normative approach were applied to participants' neuropsychological test scores, and participants were "flagged" for review if scores fell below expected ranges (see Johnson et al.,[22] Koscik et al.,[31] and Clark et al.[32]). Clinical mild cognitive impairment (MCI) or dementia due to AD was determined in accordance with National Institute on Aging-Alzheimer's Association (NIA-AA) criteria,[33] and without reference to biomarkers.

2.6 | Standardized neuropsychological measures of language

In secondary analyses, we were interested in determining whether standardized language variables more commonly used in research studies were sensitive to amyloid status. The measures included: the Boston Naming Test (BNT)[26] (a 60-item test of confrontation naming), phonemic (letter) fluency from the Multilingual Aphasia Examination (letters C, F, L), and category (animal) fluency.

2.7 | Statistical methods

Linear mixed effects models were used to examine the effect of age, amyloid status (A+/−) and the interaction between them on CSL variables (type-token ratio, open-to-closed words ratio) and standardized measures of language (animal fluency, letter fluency [CFL], BNT) collected at the same study visit. To compare the effect of study predictors across outcomes, all CSL and standardized neuropsychological measures were converted to z-scores using the mean and standard deviation from the first CSL visit. Model selection began by evaluating the subject-level random structure, by fitting models with and without random intercepts and random slopes. We chose the best-fitting model using likelihood ratio tests for nested models. Random intercepts were retained in all models; a random slope for age was added only to the models with open-to-closed ratio as the outcome. In Model 1, age and amyloid status were entered as fixed effects. In Model 2, the interaction between age and amyloid status was added to the fixed effects in Model 1. We repeated the analyses including sex, apolipoprotein E (*APOE*) ε4 carrier status, and Wide Range Achievement Test-3 (WRAT3) reading scores (reflecting literacy) as covariates. The WRAT and CSL scores were negatively correlated, counter to expectations; we added both linear and quadratic WRAT scores to the models with covariates (Figure S1 in supporting information) to account for non-linear association between reading ability and CSL outcomes. To account for prac-

tice effects (see Table S1 in supporting information for descriptives by study visit), participant's CSL sample number (1–4) was added as a time-varying covariate.

We conducted three sensitivity analyses. To determine whether the participants (*n* = 8) who converted to cognitively impaired by their most recent study visit were driving the results, we repeated the analyses after excluding them. To determine whether amyloid burden was *prospectively* related to CSL outcomes, we repeated the analyses with a subset (*n* = 86) of participants with at least one PiB-PET scan prior to CSL collection. To determine whether the number of *APOE* ε4 alleles explained additional variance in CSL outcomes, we reran the models including the *APOE* risk score, or the *APOE* genotype log odds ratio.[34]

Statistical analyses were performed in R (R Core Team, 2013). A+/− group differences in baseline demographics were tested using chi-square (categorical variables) or *t*-tests (continuous variables). We examined correlations between the CSL variables and the standardized language measures using Pearson correlation coefficients. Linear mixed effects models were fit using lmerTest package v3.1-2.[35] Statistical tests for parameter estimates were based on *t*-tests with denominator degrees of freedom approximated by the Satterthwaite method.

2.8 | Data availability

Data from the WRAP cohort can be requested through an online submission process.

3 | RESULTS

Demographics are shown in Table 2. The A+ group was older at baseline and had more *APOE* ε4 carriers than the A− group. More A+ participants converted to cognitively impaired by their most recent study visit than A− participants (9% vs. 1.5%; *P* = .01). The two groups were comparable on baseline cognitive ability and language function. CSL outcomes were moderately intercorrelated (*r* = .29, *P* < .001). CSL outcomes were uncorrelated or only modestly correlated with standardized language measures (−.11 to .09; Table S2 in supporting information).

Results from linear mixed effects models are shown in Table 3. Modeling the type-token ratio, we saw no significant effect for age, A+ (Model 1), or the interaction between them (Model 2). However, carriage of at least one copy of *APOE* ε4 and greater numbers of CSL samples (numbers of exposures to the picture description task) were significantly associated with lower type-token ratio. Modeling the open-to-closed class ratio, we saw a marginal main effect for amyloid status such that A+ participants had lower open-to-closed class ratios than A− participants (Model 1; *est[SE]* = −0.26 [0.11], *P* = .05). The interaction between age and A+ was also significantly associated with open-to-closed class ratio (Model 2; Figure 1). The simple slopes for age were *est[SE]* = .004 [0.009], *P* = .67 among A− participants; *est[SE]*) = −0.04 [0.01], *P* = .006 among A+ participants. Among the covariates, only the linear and quadratic WRAT reading scores were significantly related

TABLE 2 Baseline[a] sample characteristics and study variables by amyloid (PiB PET) status

Variable	Total sample	Amyloid+	Amyloid−	
Demographics	n (%) or mean (SD)	n (%) or mean (SD)	n (%) or mean (SD)	*P*
N	255	57 (22.3%)	198 (77.6%)	
Total number of longitudinal speech samples (1/2/3/4)	21/59/160/15	5/13/36/3	16/46/124/12	
Age at first speech sample[a]	62.7 (6.23)	64.9 (5.08)	62.1 (6.4)	.008
Female	175 (69%)	37 (65%)	138 (70%)	.60
APOE genotype				<.001
2/3	30 (12%)	2 (4%)	28 (14%)	
2/4	10 (4%)	2 (4%)	8 (4%)	
3/3	122 (48%)	17 (30%)	105 (53%)	
3/4	82 (32%)	31 (54%)	51 (26%)	
4/4	9 (3%)	5 (9%)	4 (2%)	
Race				.92
American Indian or Alaska Native	3 (1%)	1 (2%)	2 (1%)	
Asian	1 (0%)	0 (0%)	1 (1%)	
Black or African American	10 (4%)	3 (5%)	7 (4%)	
White	240 (94%)	53 (93%)	187 (94%)	
Other	1 (0%)	0 (0%)	1 (1%)	
Cognitively impaired[b]	10 (2.5%)	5 (9.0%)	3 (1.5%)	.01
Parent history of dementia	189 (74%)	48 (84%)	141 (71%)	.08
CES-D	6.03 (6.02)	5.6 (5.58)	6.16 (6.15)	.52
Years education	16.2 (2.59)	16.2 (2.27)	16.3 (2.68)	.79
WRAT-3 reading standard score	107.2 (9.01)	106.18 (8.78)	107.5 (9.07)	.31
Standardized neuropsychological tests				
Animal Fluency	22.5 (5.50)	22.9 (6.41)	22.3 (5.22)	.56
Boston Naming Task	57.6 (2.79)	57.2 (3.18)	57.7 (2.66)	.29
Letter Fluency (CFL)	46.4 (13.4)	46.2 (11.9)	46.4 (13.8)	.92
MMSE	29.3 (1.13)	29.0 (1.22)	29.4 (1.09)	.05
Trails-B	64.8 (23.9)	71.1 (31.1)	63.0 (21.2)	.07
R-AVLT total	50.4 (8.60)	50.6 (8.36)	49.6 (9.42)	.48
Logical Memory Delayed Total	25.8 (7.58)	24.2 (7.87)	26.2 (7.45)	.09
Digit Symbol Coding Total	55.2 (9.75)	53.6 (9.98)	55.6 (9.66)	.17
Connected speech language				
Type-token ratio	0.60 (0.08)	0.60 (0.09)	0.60 (0.08)	.52
Open-to-closed ratio	0.77 (0.13)	0.74 (0.13)	0.78 (0.13)	.06
Total words	108.8 (53.6)	116.7 (57.3)	106.5 (52.4)	.22
Duration (minutes)	0.89 (0.41)	0.91 (0.37)	0.88 (0.42)	.69

Abbreviations: *APOE*, apolipoprotein E; CES-D, Clinical Evaluation Scale of Depression; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; R-AVLT total, Rey Auditory Verbal Learning Test total; SD, standard deviation; WRAT-3 Reading Standard Score, Wide Range Achievement Test – Third Edition reading subtest standard score.

Notes: Boston Naming Task from the Boston Diagnostic Aphasia Examination; Logical Memory Delayed Total and Digital Symbol Coding from the Wechsler Memory Scale-R; Type-Token ratio, number of unique words/number of words; Open-to- Closed ratio, total # of open class word (nouns, verbs, adverbs) / total # of closed class words (function words, e.g., prepositions, determiners, conjunctions). Tests of group differences were not adjusted for age or sex.

[a]Baseline in these analyses is defined as the visit at which first speech sample was obtained; all cognitive measures were concurrent with speech samples except for the WRAT reading measure, which was obtained at study entry.

[b]Cognitive status at most recent study visit (N = 6 MCI and N = 2 AD) as determined by consensus conference following the National Institute on Aging-Alzheimer's Association (NIA-AA) criteria, without reference to biomarkers.

TABLE 3 Summary of mixed effects linear regression models showing the relationship between amyloid status and connected speech and language outcomes

| A. | Type-token ratio outcome | | | | | |
| | Model 1 | | | Model 2 | | |
	Estimate	t	P	Estimate	t	P
Intercept	−1.6			−1.5		
A+	−0.06	−0.45	.66	−0.04	−0.34	.74
Age at visit	0.001	0.13	.89	0.002	0.25	.80
Age at visit × A+/− status				−0.007	−0.38	.70
Covariates						
Male	−0.02	−0.22	.83	−0.02	−0.22	.82
WRAT-3	0.05	0.62	.54	0.05	0.58	.56
WRAT-3 quadratic	−0.0003	-0.78	.44	−0.0003	−0.74	.46
APOE risk	**−0.14**	**−1.92**	**.05**	**−0.14**	**−1.93**	**.05**
CSL number	**-0.08**	**-2.08**	**.04**	**−0.08**	**−2.05**	**.04**
Random effects						
Intercept	0.38			0.37		
Age slope	−			−		
Residual	0.58			0.58		
ICC	.39			.39		
Marginal/conditional R^2	0.03/0.41			0.03/0.41		
B.	Open-closed class ratio outcomes					
	Model 1			Model 2		
	Estimate	t	P	Estimate	t	P
Intercept	−8.9			−8.9		
A+	**−0.26**	**−2.39***	**.02**	−0.22	−1.95	.05
Age at visit	−0.001	−0.12	.90	0.005	0.59	.56
Age at visit × A(+/−) status				**−0.04**	**−1.98**	**.05**
Covariates						
Male	0.08	0.92	.36	0.08	0.91	.36
WRAT-3	**0.18**	**2.52**	**.01**	**.17**	**2.33**	**.02**
WRAT-3 quadratic	**−0.0008**	**−2.59**	**.01**	**−0.0008**	**−2.40**	**.02**
APOE risk	.03	0.52	.61	0.03	0.51	.61
CSL number	−0.07	−1.79	.07	−0.06	−1.67	.10
Random effects						
Intercept	0.18			0.18		
Age slope	0.002			0.002		
Residual	0.52			0.52		
ICC	.34			.34		
Marginal/conditional R^2	.04/.37			.05/.37		

Notes: Section A refers to models with Type-token ratio outcome; Section B refers to models with Open-Closed Class Ratio Outcomes. *Definitions:* Type-token ratio, number of unique words/number of words; open-closed ratio, total # of open class word (nouns, verbs, adverbs)/total # of closed class words (function words, e.g., prepositions, determiners, conjunctions). WRAT-3 Reading Standard Score, Wide Range Achievement Test–Third Edition reading subtest standard score; *APOE* risk, apolipoprotein E log odds risk based on genotype (see Darst et al.[34]); ICC, adjusted intraclass-correlation coefficient reflecting the uncertainty of all random effects; Adjusted/Marginal R^2, the proportion of variance explained by the fixed factors.[36] The best fitting random effects structure was tested via likelihood ratio test. CSL values > 3×SD over the mean were replaced with the mean + 3×SD. CSL outcomes were standardized to baseline values prior to analyses. Model 1, age and amyloid positivity and covariates were entered as fixed effects. Model 2, the interaction between age and amyloid positivity was added to Model 1. Items in bold indicate statistically significant difference at:$P < .05$.

Abbreviations: A=, amyloid positive; A−, amyloid negative; CSL, connected speech and language; SD, standard deviation.
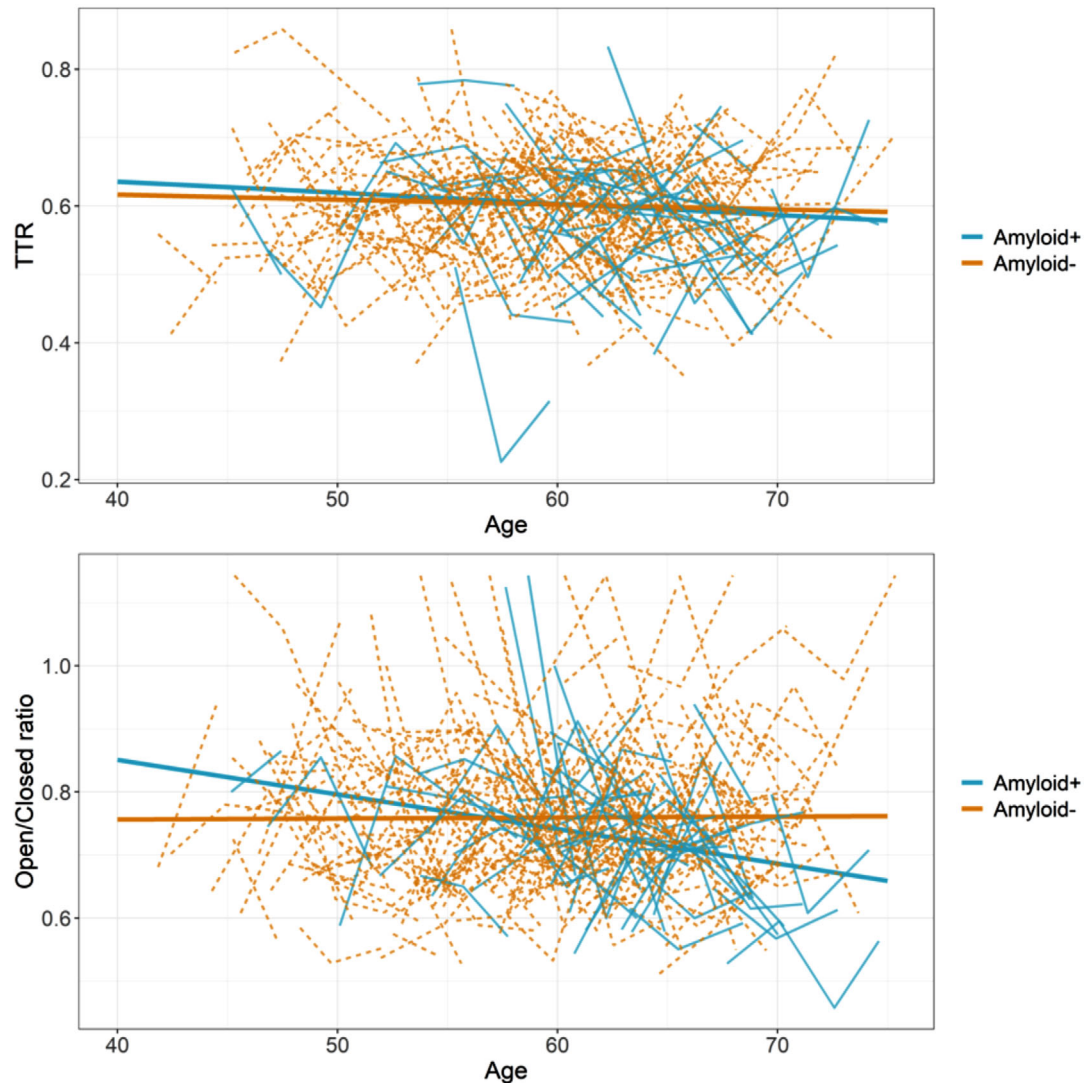
FIGURE 1 Change in type-token ratio (top panel) and open-closed ratio (bottom panel) by age and amyloid status (N = 255). *TTR* = type-token ratio, a measure of unique words to total words capturing lexical diversity; *Open/Closed Class Ratio* = measure of specific to non-specific content words capturing semantic content. Connected speech and language (CSL) outcomes are shown in their original scale to aid interpretation. Simple slopes (thick lines) for CSL outcomes regressed on age for amyloid positive (blue) and amyloid negative (tan) participants. Thin lines indicate raw data. Dashed = amyloid negative and solid = amyloid positive. Values > 3×SD over the mean were replaced with the mean + 3×SD

to open-to-closed class ratio. For the sensitivity analyses, we first fit Model 2 with covariates after removing participants who converted to cognitive impairment ($n = 8$) by their last study visit. The results were unchanged; the interaction between age and amyloid status did not predict type-token ratio (*est[SE]* = −0.007 [0.02], *P* = .70), but did predict the open-closed class ratio (*est[SE]* = −.04 [0.02], *P* = .03). Second, we fit Model 2 with covariates including only participants who had prospective PET scans. Nineteen participants were A+ prior to CSL collection (3/16 people had an ambiguous PET scan prior to baseline CSL, which resolved to A+ at second PET scan during the CSL study period); $n = 67$ participants were A− prior to CSL collection and remained A− (3/67 had an ambiguous PET scan at baseline which resolved to A− at a second PET scan during the CSL study period). The pattern of results was unchanged. The association between open-to-closed ratio and the interaction of age and amyloid status was non-significant in this smaller

sample (*est[SE]* = −.06 [04], *P* = .12), but followed the same overall pattern (Figure S2 in supporting information). To determine whether the *APOE* genotype log odds ratio explained additional variance in type-token ratio and open-closed ratio, we re-fit models using the *APOE* log-odds ratio instead of the binary *APOE* variable (no ε4 vs. at least one ε4), and results were unchanged.

To compare CSL outcomes to standardized language tests, we fit Models 1 and 2 with covariates to the standardized tests. The interaction between amyloid status and age was not significantly associated with letter fluency (CFL) or the BNT; the interaction between age and amyloid status was significantly associated with animal fluency (Table S1). The simple slope for age was significant regardless of amyloid status; however, A+ individuals experienced a steeper decline per year in animal fluency (*est[SE]* = −0.12[0.02], *P* < .001) than A− individuals (*est[SE]* = −0.03[0.01], *P* < .001).

4 | DISCUSSION

This study examined associations between longitudinal CSL trajectories and cortical Aβ plaques (PiB-PET) in a group of late-middle-aged adults who were cognitively unimpaired at baseline. The main study finding was that Aβ positivity (A+) was associated with more rapid decline in the use of specific content words (open-to-closed class ratio) in a picture description task, but amyloid status was not associated with longitudinal change in lexical diversity. There were no main effects of amyloid on lexical diversity (as measured by unique/total words, or "type-token ratio"), but there was a significant association between lexical diversity and *APOE ε*4 carrier status, which remained when the interaction between age and amyloid status was included in the model. We also examined standardized language measures (animal fluency, letter fluency and naming); A+ was associated with a more rapid decline in animal fluency, but not with any of the other language variables. We found similar effect sizes between longitudinal change in animal fluency (simple slope for A+ = −.044) and open-to-closed class ratio (simple slope for A+ = −.067).

To date, Verfaille et al.[19] is one of the only other studies to investigate CSL in cognitively unimpaired individuals with evidence of Aβ accumulation, and in their cross-sectional investigation the authors found a similar connection between individuals who had elevated levels of CSF-Aβ or increased amyloid deposition on [18F]florbetaben or [18F]florbetapir PET scans and use of specific words (as measured by total "content words" and total "abstract nouns"). In our study, we were able to address some of the limitations listed by Verfaille et al.,[19] particularly by the longitudinal design of our study (vs. cross-sectional).

There is considerable between-subject variability on measures of connected speech due to a variety of reasons, including speaking style,[37] mood,[38] and regional or cultural dialectal differences[39]; a longitudinal, within-person design controls for problematic individual variability issues such as these (i.e., both fixed and random effects). That said, the results between our findings and that of Verfaille et al.[19] are strikingly similar, in that we found differences between A+ and A– individuals with specific word content (both main effects and interactions with age), but not with lexical diversity as measured by type-to-token ratio. These similarities are interesting due to the differences in study design, population, and measures, most notably: (1) the Verfaille et al.[19] study was a cross-sectional design that included several different measures of amyloid positivity (CSF Aβ1-42, Florbetapir or Florbetaben PET) while ours was a longitudinal design with only PiB-PET as the Aβ measure of interest; (2) the Verfaille et al.[19] study included Dutch-speaking individuals with subjective cognitive complaints, while our study was of English-speaking individuals recruited for a family-history cohort study. Of notable interest is the fact that both studies included individuals who are in late-middle-age: mean age at baseline speech sample for our study was 62 years for those who were A– and 64 for A+, while for Verfaille et al.[19] the mean age was 62 for A– and 68 for A+. An important future direction would be to determine whether the degree of subjective cognitive complaints moderates the longitudinal relationship between amyloid burden and CSL. If so, CSL plus cognitive complaints may provide valuable information for selecting those individuals who may be most likely to show clinical benefit in clinical trials.

Other studies have shown that individuals with AD dementia show *both* reduced lexical diversity and a reduction in content words.[40,41] Here we did not find significant differences between amyloid groups and longitudinal change in lexical diversity over time. Interestingly, we found a significant association with *APOE ε*4 carriers and lower lexical diversity. To our knowledge, there is limited research investigating *APOE* carrier status and its relationships with lexical diversity or other CSL measures in cognitively unimpaired adults. Retrospective analysis of writing samples of participants from the Nun Study from their early 20s showed that low idea density and low grammatical complexity in early life were predictors of both late-life cognitive decline and autopsy-confirmed AD; however, the *APOE ε*4 status of the participants was not included in the study.[42] Future directions should include replicating this finding in other samples with connected speech and *APOE ε*4 genotyping, as well as determining the joint effects of *APOE ε*4, amyloid, and tau on connected speech measures.

When we examined standardized language assessments, we found that A+ was associated with more rapid decline in animal fluency, but there were no associations between amyloid status and BNT or letter fluency. This association with animal fluency has been reported previously in samples of cognitively unimpaired adults, both from our group and others.[43,44] The animal fluency measure and the open-closed class ratio measure were not correlated with one another, indicating that the measure of specific to nonspecific words captures a different process of word retrieval than category fluency, which is highly contextual. Although the picture description task also provides a constrained context, the participant has the increased demand of word retrieval while at the same time managing the grammatical and pragmatic (social) requirements for communication. Future directions include analyzing the open-to-closed class ratio from speech samples that were elicited from open-ended questions, which even more closely approximates everyday communication. Understanding early changes to everyday communication can provide valuable insight for developing effective cognitive-communication interventions for individuals living with cognitive decline.

Strengths of this study include our relatively large sample size, the longitudinal design of the study, and the well-characterized method of analysis of speech-language samples. There are also important study limitations that must be considered. First, the study sample presented here is 94% non-Hispanic White and comprised of participants largely residing in the upper Midwest, thus limiting generalizability to the larger population. Strong community engagement methods are underway to increase representation from Black, Native American, and other underrepresented groups;[45] therefore, important future directions include focusing these analyses within these groups to understand risk of communication impairment in preclinical AD. An additional limitation includes the fact that we only examined semantic content and lexical diversity from the speech-language samples and did not examine other measures that may be affected by preclinical AD, including speech fluency, syntactic complexity, and acoustic measures from the audio signal.[14,46] We chose only these two measures based on the

limited findings in the current literature regarding relationships between amyloid and CSL trajectories[19] to reduce multiple comparisons and the likelihood of Type I error. Perhaps as a result, the amount of variance explainable by CSL measures was fairly small. Future work will include additional characterization of CSL, including both computational linguistic measures and acoustic parameters in persons with and without amyloid, tau, and neurodegeneration (ATN). Furthermore, we plan to examine the associations between ATN in language-specific brain regions and longitudinal CSL to further elucidate the relationships between AD pathology and language decline.

5 | CONCLUSION

In this younger and cognitively unimpaired group of persons with increased AD risk, open-closed class ratios prospectively worsened more rapidly in the A+ versus A– group, although effects were small. Reductions in open-closed class ratios indicate a longitudinal decrease in content words relative to function words, a finding that has been shown multiple times in individuals with dementia, but not in a longitudinal, relatively young preclinical sample. Speech samples were ≈1 minute in length and were relatively quick and inexpensive to analyze. Further characterization of CSL trajectories in persons with preclinical AD is necessary to determine whether speech may be an early-appearing effective disease-monitoring measure of functional cognition.

CONFLICTS OF INTEREST

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