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Vocal acoustic biomarkers predict amyloid positivity in non-demented individuals

Hyunsun Ham
Seoul Metropolitan Government-Seoul National University (SMG-SNU) Boramae Medical Center
Alexander L. Han
University of Michigan Medical School
Minju Bae
University of Wisconsin–Madison
Hahyun Lee
Seoul Metropolitan Government-Seoul National University (SMG-SNU) Boramae Medical Center
Jiwon Son
Seoul Metropolitan Government-Seoul National University (SMG-SNU) Boramae Medical Center
Jiyoon Yeo
Seoul Metropolitan Government-Seoul National University (SMG-SNU) Boramae Medical Center
Eun Jin Yoon
Seoul Metropolitan Government-Seoul National University (SMG-SNU) Boramae Medical Center
Seok-Im Lee
Seoul Metropolitan Government-Seoul National University (SMG-SNU) Boramae Medical Center
Jung-In Lim
Seoul Metropolitan Government-Seoul National University (SMG-SNU) Boramae Medical Center
Keun You Kim
Institute of Behavioral Science in Medicine, Yonsei University College of Medicine
So Yeon Jeon
Seoul Metropolitan Government-Seoul National University (SMG-SNU) Boramae Medical Center
Yu Kyeong Kim
Seoul Metropolitan Government-Seoul National University (SMG-SNU) Boramae Medical Center
Jun-Young Lee
benji@snu.ac.kr

Seoul Metropolitan Government-Seoul National University (SMG-SNU) Boramae Medical Center

Article

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Abstract

Amyloid-β deposition begins in the earliest preclinical stages of Alzheimer's disease, long before cognitive decline is detectable by standard clinical assessments, which are often limited by ceiling effects and create a need for non-invasive, scalable markers. Speech production is a demanding motor skill requiring precise neuro-motor coordination, so the acoustics of motor speech may index early pathological burden that conventional cognitive testing overlooks. In this cross-sectional study, we analyzed acoustic features of motor speech from a sequential motion rate task in 64 non-demented participants (43 amyloid-negative, 21 amyloid-positive), spanning prosody, voice quality, and spectral domains. Using two complementary linear classifiers with repeated stratified five-fold cross-validation, we tested whether these motor-speech features improved classification of amyloid positivity beyond clinical baselines comprising demographics, white matter hyperintensity burden, and scores on the Korean version of the Mini-Mental State Examination (MMSE-KC). Adding acoustic features substantially improved classification across both classifiers, and acoustic-only models outperformed models using MMSE-KC scores alone. Features reflecting variability and consistency across repeated speech motor productions were the most informative. These results indicate that high-load motor speech can reveal subtle neuro-motor changes associated with early Alzheimer's pathology, supporting vocal acoustic markers as a sensitive, low-burden complement to established biomarkers.

Introduction

Aggregation of amyloid-β (Aβ) plaques, a pathological hallmark of Alzheimer's disease (AD), precedes the onset of overt clinical symptoms by decades, resulting in a long preclinical stage for early intervention. However, identifying individuals in this preclinical stage remains a significant challenge[1,2]. While positron emission tomography (PET) and cerebrospinal fluid (CSF) analysis are gold standards for confirming Aβ pathology, their widespread use is constrained by high costs, limited accessibility, and invasiveness[3,4]. Consequently, there is a critical need for non-invasive and scalable biomarkers capable of screening for early pathological burden. This is particularly crucial in the non-dementia stage, where conventional neuropsychological assessments such as the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) often fail to capture subtle deficits due to ceiling effects and individual heterogeneity in cognitive reserve[5,6]. Moreover, these assessments evaluate verbal response accuracy alone, thereby overlooking the pathophysiological changes in acoustic-motor functions.

Voice offers a unique window into cognitive health, functioning as a scalable digital biomarker that integrates complex cognitive processes with fine motor control into a single, remotely accessible measure[7–9]. Conventional analytic approaches to dementia speech have divided into two major domains: an acoustic-phonetic component involving respiration, phonation, prosody and articulation, and a linguistic component involving lexical-semantics and syntax. Deficits are evident across both domains in the clinical stage of dementia, manifesting as slower speech rates, monotonous tone, simplified syntax and word-finding difficulty. However, in the preclinical or early prodromal stages, linguistic markers often remain relatively preserved due to compensatory cognitive strategies, potentially masking subtle pathological changes[10,11]. Emerging evidence suggests that acoustic features, which rely on the integrity of subcortical–cortical networks, may be more vulnerable to early disruption than higher-level linguistic functions[9,12–14]. Recent studies indicate that acoustic features can differentiate individuals with amnestic mild cognitive impairment (aMCI) from healthy controls even when semantic performance is comparable[9,15,16], and subtle acoustic abnormalities have been shown to predict cognitive decline years before clinical diagnosis[7,17]. This suggests that the mechanism of speech production, particularly the acoustic features, may reveal latent signals of underlying pathology during the prodromal phase, before lexico-semantic deficits become measurable.

Motor speech characteristics are particularly informative, as they depend on the precise coordination of articulation, sequencing, and temporal regulation supported by distributed subcortical–cortical networks[18–20]. These processes place

continuous demands on executive control and sensorimotor integration, making vocal production especially sensitive to subtle network-level inefficiencies that may arise in the earliest stages of Alzheimer's pathology. Early disruption may not simply result in slower speech; rather, it may first emerge as greater variability in timing or reduced consistency across repeated speech productions[16,21]. Growing evidence suggests that fine-grained alterations in vocal rhythm and intensity modulation can distinguish individuals with mild cognitive impairment (MCI) from healthy controls even when standard cognitive scores remain within normal range[16,22], and may precede clinically detectable decline by several years[17]. Extending this line of work, recent studies have begun to explore associations between speech features and amyloid status[9]. These preliminary findings motivate more systematic and targeted investigations, including classification-based approaches. Furthermore, it remains unclear whether these associations are primarily driven by higher-order linguistic processes or whether motor-specific processes contribute independently. Examining vocal acoustic features in tasks with minimal linguistic demands may clarify the relative contribution of these processes, helping establish the mechanistic basis and diagnostic utility of speech-based biomarkers of amyloid pathology.

This study examines whether vocal acoustic features provide incremental value for identifying amyloid PET positivity in a non-dementia cohort. By systematically comparing models with and without acoustic features, we evaluate the extent to which vocal acoustic characteristics capture pathology-relevant information not adequately explained by standard neuropsychological or neuroimaging measures. We find that acoustic features substantially improve classification of amyloid positivity beyond clinical baselines, with variability-related speech features emerging as the most informative predictors, positioning voice biomarkers as complementary, low-burden functional markers for early AD risk screening.

Methods

Participants

We analyzed data from 64 non-demented participants. Among the total cohort, 78.1% had mild cognitive impairment (MCI). Demographic variables (age, sex, years of education) and scores on the Korean version of the Mini-Mental State Examination (MMSE-KC), a component of the Korean version of the Consortium to Establish a Registry for Alzheimer’s Disease assessment packet (CERAD-K)[23], were obtained from clinical records. For brevity, MMSE-KC scores are denoted as MMSE in model names, tables, and figures.

Eligible participants were those who spoke standard Korean, as determined by interview. The mean duration of residence in the Seoul metropolitan area was 52.17 ± 17.73 years. All participants were non-smokers at the time of assessment; 15 participants were former smokers and had maintained smoking cessation for an extended period (mean cessation duration of 35.80 ± 13.66 years).

Participants with marked regional dialects were excluded, as dialect differences may affect acoustic feature extraction. Individuals reporting alcohol consumption four or more times per month were excluded due to potential effects on vocal quality. Those with clinically significant hearing impairment were excluded to minimize disruption of auditory–motor feedback relevant to speech motor performance. Participants with a history of major neurological or psychiatric disorders affecting speech production, including stroke, parkinsonism, or other neurodegenerative or motor speech conditions, were also excluded. The study was approved by the Institutional Review Board of Seoul Metropolitan Government–Seoul National University Boramae Medical Center (IRB No. 20-2022-63), and all participants provided written informed consent. All methods were carried out in accordance with relevant guidelines and regulations and with the principles of the Declaration of Helsinki.

Amyloid PET assessment

Amyloid status was determined from ^{18}F-florbetaben amyloid PET imaging. Regional cortical tracer uptake (RCTU) and brain amyloid plaque load (BAPL) scores were obtained by visual semi-quantitative assessment, and participants were classified as amyloid-negative (n = 43) or amyloid-positive (n = 21).

MRI acquisition and WMH quantification

White matter hyperintensity (WMH) burden was quantified from MRI and included in all analyses, as cerebrovascular pathology may affect speech production and motor control, thereby confounding speech-based markers[24–26]. Brain MRI was acquired using a 3T scanner (Ingenia 3T CX, Philips Medical Systems). WMH volumes were automatically segmented from FLAIR images using AQUA software (Automatic Quantification of White Matter Hyperintensities and Brain Volumes)[27], yielding deep and periventricular WMH volumes for use as covariates.

Speech task

Participants completed a sequential motion rate (SMR) task requiring rapid repetition of /pa-ta-ka/ ten times, as quickly and accurately as possible[28,29]. The task consisted of four blocks, each with three repetitions, yielding up to 12 recording files per participant. Audio was recorded in a quiet laboratory using a directional microphone connected to a tablet PC (Samsung Galaxy Tab S7+, SM-T970), with consistent microphone distance and room conditions across participants. Audio segmentation was performed manually by three trained research coordinators using a standardized guideline and verified by two clinical researchers. Each segment contained only participant speech, with examiner speech excluded. The four blocks were part of a larger speech battery administered in a fixed order across all participants.

Acoustic feature extraction

Acoustic features were extracted at the recording level using a custom pipeline[30]. Prosodic features included fundamental frequency (F0), intensity, duration, and measures of articulatory rate and rhythmic stability. F0 was estimated using Praat[31] with sex-specific pitch ranges[32], retaining only voiced frames (F0 > 0). Mean F0 was computed from voiced frames, and voiced fraction was calculated as the proportion of voiced frames relative to the total number of frames. Mean intensity and recording duration were derived from the Praat intensity and sound objects, respectively. Articulatory rate and rhythmic stability were quantified using an automated syllable detection algorithm based on the root-mean-square (RMS) energy envelope[33,34]. Syllable nuclei were identified as local maxima exceeding an adaptive threshold (20th percentile of signal energy), with a minimum inter-peak interval of 80 ms enforced to prevent spurious detection of stop bursts. These parameters were empirically determined based on the acoustic characteristics of the SMR task. Peak rate (syllables per second) and the coefficient of variation of inter-peak intervals (speech rhythm variability) were derived from these detected events. Inactivity ratio was calculated as the proportion of frames falling below the energy threshold, serving as a proxy for pausing or reduced articulatory activity. Voice quality features (local jitter, local shimmer, and harmonics-to-noise ratio (HNR)) were extracted using Praat. Spectral features such as Mel-frequency cepstral coefficients (MFCCs) were extracted using librosa[35].

Recording-level features were summarized at the participant level to capture overall performance and variability across repeated trials. The median for each feature was computed across all recordings. For prosodic features, between-block standard deviation (SD) was additionally calculated to reflect variability across the four blocks. For voice quality and rhythm features, within-block repetition consistency was defined as the mean SD across repetitions within each block. For inactivity ratio, a block slope was also computed as the linear trend across successive blocks, capturing changes in articulatory activity over the course of the task.

Statistical analysis

Group differences in continuous variables (age, years of education, and MMSE-KC score) were assessed using independent samples t-tests, and sex distribution was compared using the chi-square test. Descriptive statistics are reported as mean ± standard deviation or frequency (percentage).

We assessed whether vocal acoustic features elicited from a sequential motion rate task improve classification of amyloid positivity beyond standard clinical variables of demographics (Demo), WMH, and MMSE-KC. Analyses were conducted at the participant level with amyloid status as a binary outcome. We evaluated seven prespecified feature combinations: (i) acoustic features only, (ii) MMSE only, (iii) acoustic + MMSE, (iv) demographic variables with WMH burden (Demo + WMH), (v) Demo + WMH+MMSE, (vi) Demo + WMH+acoustic, and (vii) Demo + WMH+MMSE+acoustic (Fig. 1).

Two supervised classifiers were implemented. First, ridge-regularized logistic regression was applied, with the regularization parameter selected by inner cross-validation optimizing area under the receiver operating characteristic curve (AUC). Second, a linear support vector machine (SVM) was trained, with probabilistic outputs obtained by Platt scaling.

Model performance was estimated using repeated stratified 5-fold cross-validation with 100 iterations, preserving class balance across folds. For each iteration, we generated out-of-fold predicted probabilities for all participants, resulting in 100 probabilities per participant. These out-of-fold probabilities were averaged to obtain a stable, subject-level probability estimate, which served as the primary prediction for downstream ROC/AUC analyses. Discrimination was quantified using AUC, with 95% confidence intervals (CIs) estimated via stratified subject-level bootstrap (2,000 resamples). DeLong's test was used to assess differences in predictive performance between models. All analyses were performed in Python. The study was conducted in a single cohort of 64 participants; all reported results reflect out-of-fold performance across 100 repeated cross-validation iterations.

Results

Demographic characteristics

Table 1 shows the demographic and clinical characteristics of the study participants. No significant group differences were observed for age (p = 0.725), sex distribution (p = 0.971), years of education (p = 0.655), or MMSE-KC score (p = 0.160). The amyloid-negative group had a mean age of 76.06 years (SD = 5.15), comparable to the amyloid-positive group (mean = 75.61 years, SD = 5.72). Years of education were similar between groups (amyloid-negative: mean = 9.65, SD = 4.77; amyloid-positive: mean = 10.00, SD = 3.60). Sex distribution was balanced, with females comprising 67.4% of the amyloid-negative group and 71.4% of the amyloid-positive group. MMSE-KC scores did not differ significantly, with the amyloid-negative and amyloid-positive groups scoring 25.00 (SD = 3.42) and 24.19 (SD = 2.82), respectively.

	Total (N = 64)	Amyloid Negative (N = 43)	Amyloid Positive (N = 21)	p-value
Demographics				
Age	75.92 ± 5.30	76.06 ± 5.15	75.61 ± 5.72	0.725
Years of education	9.76 ± 4.39	9.65 ± 4.77	10.00 ± 3.60	0.655
Female sex, n (%)	44 (68.8)	29 (67.4)	15 (71.4)	0.971
MMSE-KC score	24.70 ± 3.23	25.00 ± 3.42	24.19 ± 2.82	0.160
Clinical diagnosis (MCI, %)	50 (78.1)	32 (74.4)	18 (85.7)	

Table 1. Demographic information. Continuous variables are presented as mean ± standard deviation; categorical variables as n (%). Group differences in continuous variables were assessed by independent samples t-tests; sex distribution was compared using a chi-square test. MCI, mild cognitive impairment; MMSE-KC, Korean version of the Mini-Mental State Examination included in the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease assessment packet; SD, standard deviation.

Amyloid status prediction improves with acoustic features

Acoustic features provided improvements in amyloid classification beyond standard clinical variables across both classifiers (Fig. 2A,B). Adding acoustic features to the Demo+WMH model yielded a marked increase in AUC for both Ridge (0.41 → 0.70) and Linear SVM (0.48 → 0.71), with DeLong's test confirming significance for both models (Ridge: p = 0.003; Linear SVM: p = 0.038; Table 2). A similar pattern was observed when acoustic features were added to the Demo+WMH+MMSE baseline (Ridge: 0.50 → 0.69, p = 0.039; Linear SVM: 0.49 → 0.71, p = 0.039).

When evaluated without clinical covariates, acoustic-only models achieved higher AUC than MMSE-only models in both classifiers (Ridge: 0.74 vs 0.56, p = 0.049; Linear SVM: 0.71 vs 0.56), and performed comparably to MMSE+acoustic models. These findings suggest that acoustic features may capture amyloid-related signals beyond those reflected in global cognitive assessment scores (Fig. 2C). Ridge and Linear SVM models showed comparable performance across all matching feature sets, indicating that the improvements are driven primarily by feature information rather than the specific classifier (Fig. 3A,B).

Model	Feature set A	Feature set B	AUC (Feature set A)	AUC (Feature set B)	ΔAUC	z	p-value
Ridge	Acoustic only	MMSE only	0.738	0.559	0.178	1.971	**0.049**
Ridge	Acoustic only	MMSE+Acoustic	0.738	0.718	0.020	2.098	**0.036**
Ridge	MMSE only	MMSE+Acoustic	0.559	0.718	−0.158	−1.755	0.079
Ridge	Demo+WMH	Demo+WMH+Acoustic	0.405	0.702	−0.297	−2.939	**0.003**
Ridge	Demo+WMH+MMSE	Demo+WMH+MMSE+Acoustic	0.495	0.688	−0.193	−2.059	**0.039**
Linear SVM	Acoustic only	MMSE only	0.711	0.563	0.148	1.665	0.096
Linear SVM	Acoustic only	MMSE+Acoustic	0.711	0.707	0.004	0.292	0.771
Linear SVM	MMSE only	MMSE+Acoustic	0.563	0.707	−0.144	−1.5	0.134
Linear SVM	Demo+WMH	Demo+WMH+Acoustic	0.476	0.709	−0.233	−2.072	**0.038**
Linear SVM	Demo+WMH+MMSE	Demo+WMH+MMSE+Acoustic	0.487	0.705	−0.218	−2.065	**0.039**

Table 2. DeLong's test results. ΔAUC = AUC of feature set B - AUC of feature set A. Bold p-values indicate statistical significance ($p < 0.05$).

Feature contribution across models

In both Ridge and Linear SVM models, the five highest-ranked features by absolute coefficient or weight were exclusively acoustic features (Fig. 4). F0 mean (between-block SD) and inactivity ratio (block slope) appeared consistently among the top-ranked features across both models. Acoustic features reflecting variability and consistency across blocks and repetitions within blocks were prominently represented in the upper ranks of both models. Across all 30 features, the percentile ranks of coefficients and weights were moderately correlated between the two models (Pearson's $r = 0.443$, $p = 0.014$). These results indicate that acoustic features are the key drivers of the observed improvement in amyloid classification across modeling approaches.

Discussion

Vocal acoustic markers derived from an SMR task improved classification of amyloid status in non-demented individuals beyond conventional clinical variables, including demographic factors, WMH burden, and MMSE-KC scores. Furthermore, in this non-dementia cohort, where standard cognitive tests often show a ceiling effect, acoustic-only models outperformed MMSE-only models. These findings suggest that vocal acoustic features capture amyloid-related information not fully reflected in conventional clinical measures. Such pathology-related vocal signals were detected in a simple speech task that required rapid and precise syllable repetition without linguistic demands, highlighting that acoustic-motor execution of speech carries clinically relevant information independent of lexico-semantic content[8,16].

The improved predictive performance after incorporating acoustic features may reflect the complex motor demands and coordination required for speech production. While conventional clinical profiles including demographic factors, structural imaging, and cognitive tests provide broad clinical indicators, they may be less sensitive to subtle pathophysiological changes. In contrast, vocal acoustic markers may better capture these subtle changes[11,32] because speech production

relies on tightly coordinated articulatory, temporal, and phonatory processes[18,19]. Consequently, in the preclinical or non-demented stage, acoustic features may reveal underlying amyloid burden even in the absence of overt cognitive decline[16,21].

The most informative vocal predictors in both classifiers were measures related to variability and consistency across repeated trials — between-block standard deviation, repetition consistency, and block slope. This suggests that amyloid-positive individuals did not differ markedly in average performance levels but exhibited reduced stability across repeated speech productions compared to amyloid-negative individuals. These findings may reflect early inefficiency in neural circuits supporting rapid speech sequencing, articulatory timing, and sensorimotor coordination[18,19]. Because the SMR task places sustained demands on stable speech planning and execution, reduced consistency across repetitions may index network-level dysfunction emerging before overt structural atrophy or measurable cognitive decline[21,41]. Similar observations have been reported in other neurodegenerative conditions, where reduced motor speech stability can manifest as an early indicator before clear motor symptoms appear[36,37]. Overall, these findings raise the possibility that reduced stability in speech motor performance may emerge during the earliest stages of amyloid accumulation, potentially preceding overt cognitive decline, and highlight the need for further investigation of variability-related acoustic metrics in preclinical AD.

Previous studies in clinical speech research have primarily focused on connected speech analysis, which provides rich information about lexical retrieval, semantic organization, and syntactic processing[38–40]. Recent work has demonstrated the feasibility of remote speech assessment and explored associations with amyloid pathology[9], primarily using connected speech paradigms. Although such linguistic features are clinically informative, aspects of linguistic performance may remain relatively preserved in preclinical stages due to cognitive reserve and compensatory strategies[42,43]. In contrast, the SMR task minimizes linguistic demands and emphasizes the motor-acoustic components of speech production. This approach is particularly useful for isolating pathology-related signals that are less influenced by compensatory language strategies, thereby capturing subtle neuromotor disruptions.

Several limitations should be considered when interpreting these findings. The sample size was modest, the cohort was drawn from a single centre, and the analysis was cross-sectional without external validation. The robust performance observed across repeated cross-validation and bootstrapping supports the validity of this proof-of-concept study. Longitudinal studies will be necessary to validate the robustness of the proposed acoustic feature set and to determine whether acoustic features can predict future cognitive decline or progression to clinical dementia in currently non-demented individuals.

This study demonstrates that a low-linguistic-demand speech task can reveal underlying amyloid pathology in non-demented individuals. The findings underscore the importance of task selection in clinical speech research, suggesting that acoustic features derived from sequential motion rate tasks may be more sensitive to early pathological burden than conventional cognitive assessments alone. Variability-related acoustic features emerged as particularly informative, raising the possibility that stability of speech production may serve as a sensitive and scalable indicator even during the non-demented stages of amyloid accumulation. More broadly, voice biomarkers hold promise as scalable, low-burden tools that may complement established biomarkers for early detection of preclinical AD.

Declarations

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request. Restrictions apply to the availability of these data, which were used under approval from the Institutional Review Board of Seoul Metropolitan Government–Seoul National University Boramae Medical Center.

Code availability

The custom analysis code used in this study is available from the corresponding author upon reasonable request.

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Author contributions

H.H. and A.L.H. contributed equally to this work. H.H.: conceptualization, data collection, methodology, formal analysis, data curation, visualization, writing (original draft). A.L.H.: methodology, formal analysis, data curation, visualization, writing (original draft). M.B.: study design, conceptualization, data collection. H.L.: data collection, data curation. J.S.: data curation, formal analysis. J.Y.: data collection, data curation. EJ.Y.: data collection, data curation. SI.L.: data preprocessing, data curation. JI.L.: data collection, data curation. KY.K.: investigation, project administration, writing (review and editing). S.Y.J.: investigation, project administration, writing (review and editing). YK.K.: supervision, investigation, project administration, writing (review and editing). JY.L.: supervision, writing (review and editing), funding acquisition, project administration. All authors read and approved the final manuscript.

Additional Information

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Figures

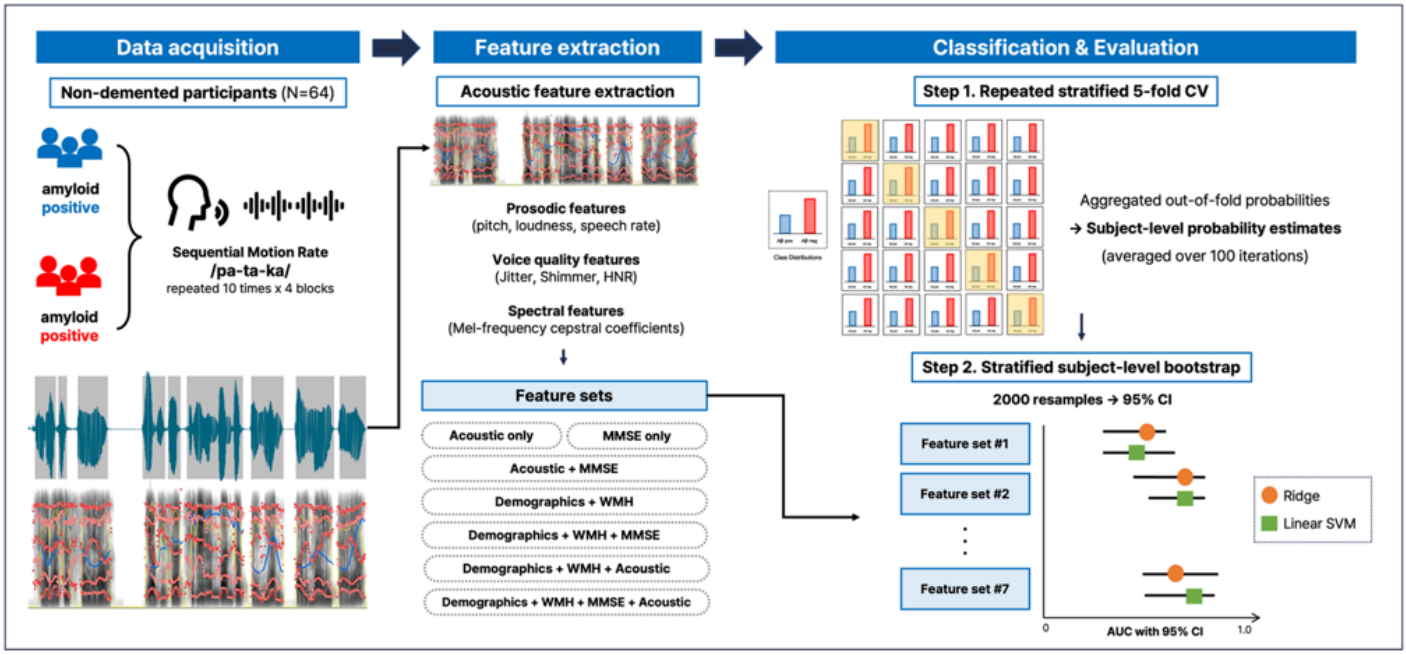


Figure 1

Modeling Framework. AUC, area under the receiver operating characteristic curve; Demo, demographic variables (age, sex, years of education); MMSE, Korean version of the Mini-Mental State Examination (MMSE-KC); SVM, support vector machine; WMH, white matter hyperintensity burden.

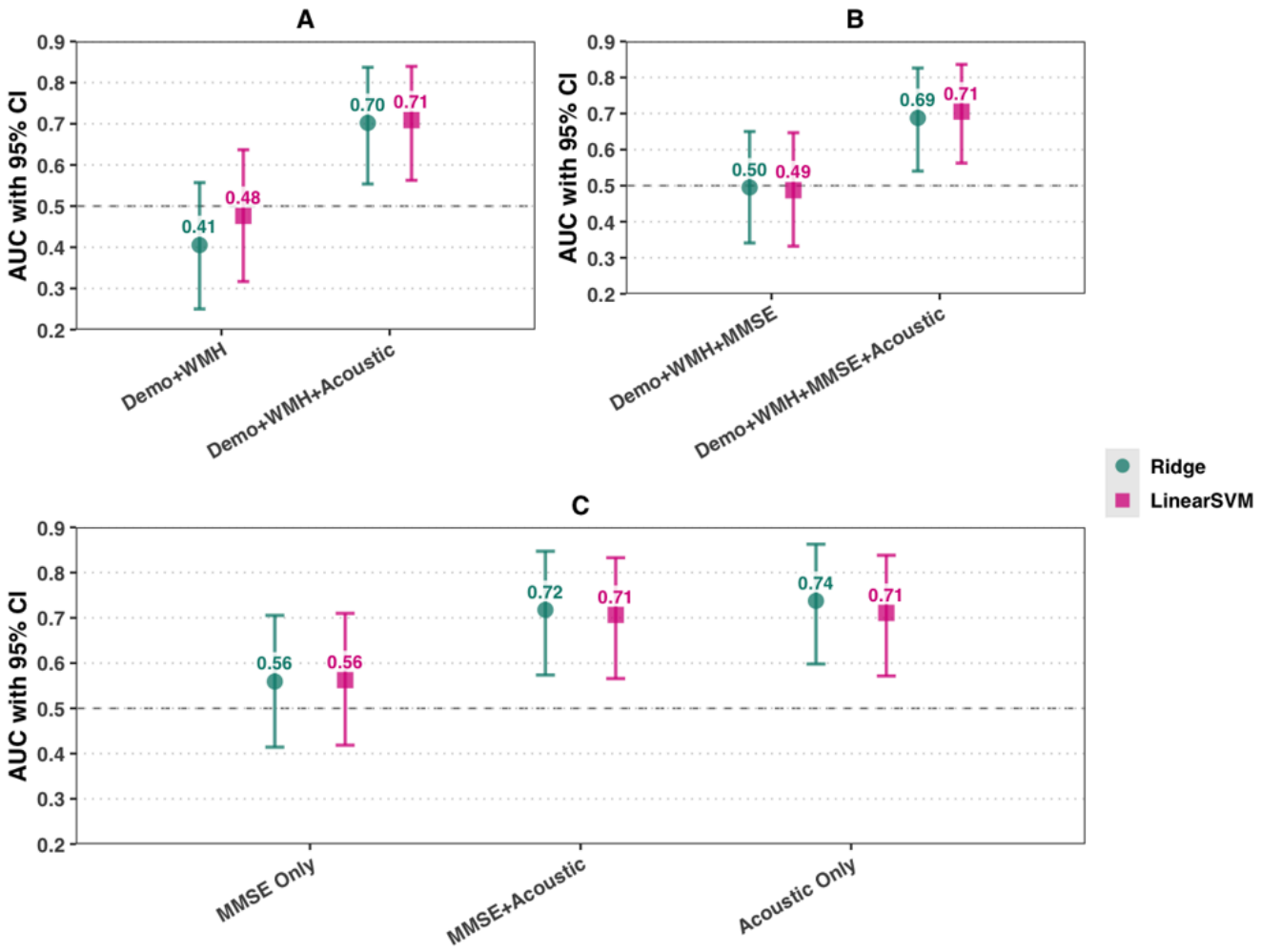


Figure 2

Performance of seven feature sets for amyloid status classification A) Incremental value of acoustic features beyond demographic and WMH baseline B) Incremental value of acoustic features beyond demographic, WMH, and MMSE C) Performance comparison of acoustic-only, MMSE-only, and combined feature sets

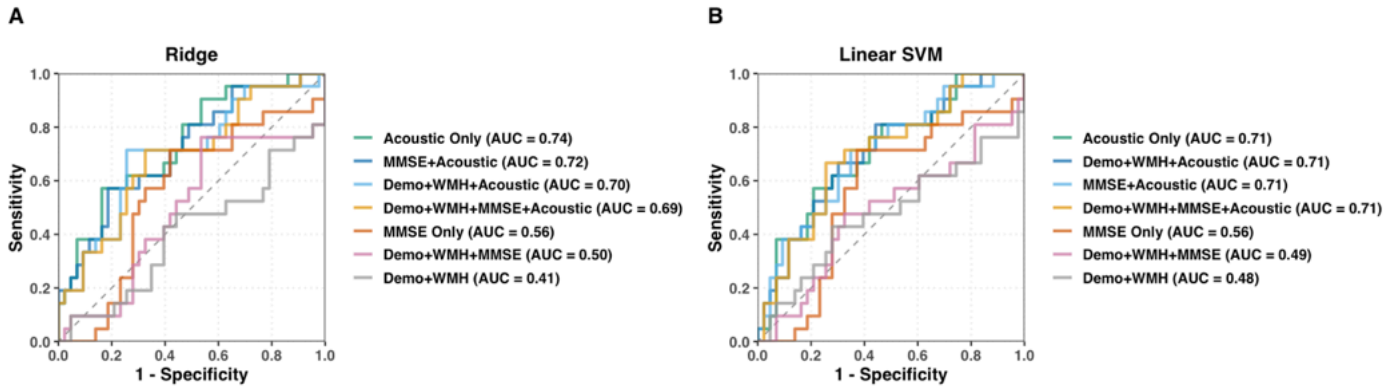


Figure 3

Cross-validated ROC curves for amyloid status classification across seven feature sets. A) Ridge regression model. B) Linear SVM model.

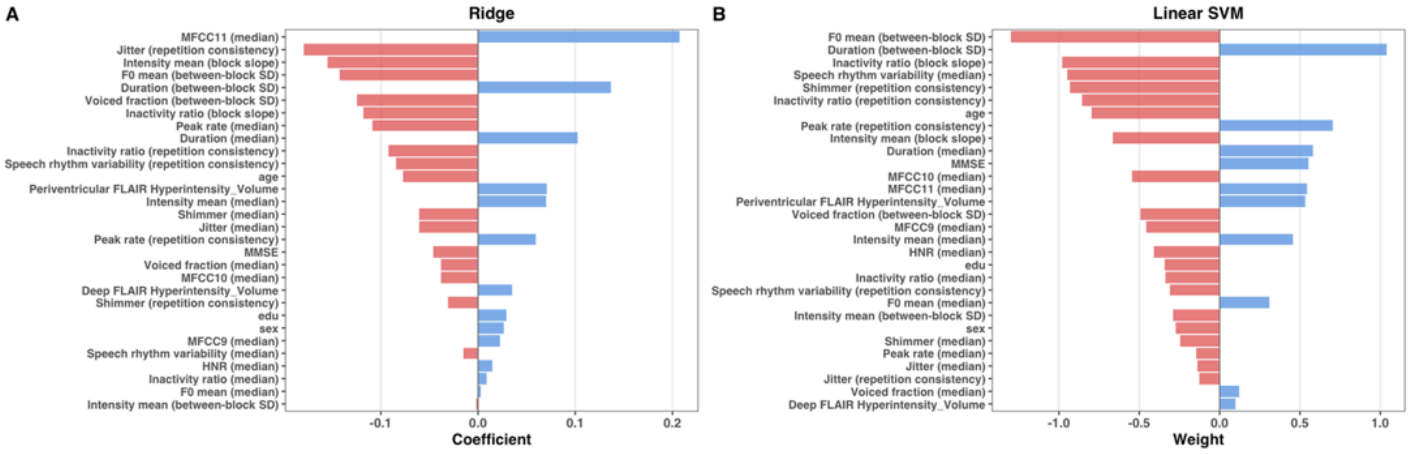


Figure 4

Feature coefficients and weights from ridge regression and linear SVM models using the Demo+WMH+MMSE+Acoustic feature set. A) Ridge regression model. B) Linear SVM model.