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Original Research

Predicting dementia risk using neuroimaging and cognitive assessment



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ABSTRACT

Introduction: Dementia affects over 55 million people globally, with numbers expected to double in the coming decades. Early detection is critical, yet traditional risk assessments relying on age, family history, and basic cognitive tests often fall short. This study explores whether combining structural brain imaging with brief cognitive assessments can more accurately predict dementia risk.

Method: Using data from 312 older adults enrolled in the KU Alzheimer's Disease Center cohort, researchers evaluated two modeling approaches: one based on a single clinic visit and another using longitudinal data across multiple visits. Participants underwent cognitive testing and MRI scans, including measures of hippocampal volume, gray matter, and Alzheimer's disease signature regions. Depressive symptoms were also assessed using the Geriatric Depression Scale (GDS).

Results: Results showed that models incorporating neuroimaging significantly outperformed those using demographics or cognitive scores alone. The best-performing model combined imaging and cognitive data, achieving 77.6% accuracy in predicting dementia status. Longitudinal models further improved prediction by capturing changes over time, with imaging features contributing most to explained variance. Key predictors included reduced hippocampal volume, lower gray matter, and higher GDS scores. These findings align with known patterns of neurodegeneration and suggest that depression may interact with brain changes to influence dementia risk.

Conclusion: Importantly, the study demonstrates that a compact, multimodal approach combining standard MRI scans with brief cognitive tests—can generate individualized risk profiles suitable for clinical use. This method offers a scalable path to early intervention, trial enrollment, and personalized care planning. Future work will focus on validating these models in more diverse populations and integrating fluid biomarkers to enhance precision. Ultimately, this research supports the development of practical tools for forecasting dementia risk and advancing preventive strategies in aging populations.

1. Introduction

Dementia already affects over 55 million people worldwide, a figure projected to more than double within three decades [1]. Aside from the obvious human toll, economic costs are climbing faster than those for cancer and heart disease combined, in part because many cases are detected only after functional decline is well established [2]. These realities have shifted research priorities toward anticipating, rather than merely diagnosing, neurodegenerative disease.

Traditional clinic-based risk indices (e.g., age, sex, family history, cardiovascular comorbidities) explain only a modest fraction of incident dementia. Li et al. [3] showed that demographic and clinical variables

yielded an area under the curve (AUC) of just 0.62 for predicting five-year conversion from mild cognitive impairment (MCI) to dementia.

Teipel et al. [4] similarly reported that even widely used bedside cognitive screens failed to identify up to one-third of future converters in primary-care samples. Such findings underscore the need for objective biomarkers that capture pathology decades before symptoms emerge.

1.1. Macro-structural MRI

Hippocampal atrophy has long been the canonical imaging signature of early Alzheimer's disease (AD). In a 1200-participant longitudinal

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cohort, Zandifar et al. [5] demonstrated that a simple ratio of hippocampal volume to total intracranial volume predicted conversion 2–7 years in advance with 88 % accuracy. Complementary evidence from the Gothenburg MCI Study showed that adding ventricular expansion to medial-temporal measures further improved 10-year prognostic accuracy [6]. Recent work has expanded these metrics to include cortical-thickness gradients and sub-field segmentation; for instance, Kandel et al. [7] linked subtle entorhinal thinning to cerebrospinal-fluid amyloid- β levels among cognitively impaired elders.

1.2. Advanced diffusion and connectomics

Macro-structural change, however, does not fully capture early white-matter disruption. Bauer et al. [8] reported that fractional anisotropy (FA) in the cingulum bundle predicted time-to-conversion independently of hippocampal volume. Müller et al. [9] broadened this observation, showing that higher mean diffusivity in temporo-parietal tracts mediated the relationship between APOE- ϵ 4 and episodic-memory decline. Diffusion-based connectomic features have also been applied to non-AD syndromes: Sasikumar et al. [10] found that graph-theoretic metrics distinguished Parkinson's-related dementia from idiopathic MCI with 80% cross-validated accuracy. More recently, Hojjati et al. [11] used convolutional neural networks to integrate diffusion and FDG-PET data, pushing multi-class classification accuracy above 90%.

1.3. Beyond imaging

While imaging adds biological specificity, prediction models improve further when multimodal data are fused. Payton et al. [12] combined hippocampal volume, executive-function scores, and APOE genotype to achieve an AUC of 0.92 in community-dwelling elders. Korolev et al. [13] later introduced a probabilistic pattern classification framework that incorporated plasma biomarkers, yielding similar gains while remaining robust to scanner heterogeneity. In a 1700-participant sample, Mirabnahrzham et al. [14] validated an artificial-neural-network model integrating imaging, cognition, and demographics; the network retained 85% accuracy when tested at an external site, highlighting generalizability.

Longitudinal modelling adds another layer of nuance. Ashish et al. [15] demonstrated that attention-based recurrent networks capturing within-person slopes in hippocampal atrophy and verbal-memory decline outperform models based on single-time-point features. Likewise, Nemali et al. [16] showed that Gaussian-process kernels leveraging nonlinear time-by-biomarker interactions explained up to 40% more variance in future memory scores than linear mixed-effects models.

1.4. Genomics, vascular risk, and modifiable lifestyle factors

Genetic predisposition remains a formidable component of neurodegeneration. Tan et al. [17] illustrated that a polygenic hazard score—when combined with amyloid-PET and hippocampal volume—stratified risk across the full preclinical continuum. Lopez et al. [18] extended this line of inquiry, showing that β -amyloid deposition interacted synergistically with baseline cortical thickness to predict mortality as well as dementia. Spencer et al. [19] further demonstrated that a blood-based proteomic panel contributed incremental predictive value beyond both imaging and APOE status.

Risk, however, is not a definitive future diagnosis. Stephen et al. [20] reported that a two-year lifestyle-intervention trial reduced CAIDE dementia-risk scores in concert with measurable preservation of posterior-cingulate FA. Consistent with the cognitive-reserve hypothesis, Belleville et al. [21] synthesized evidence across 47 longitudinal cohorts and concluded that higher baseline reserve delays, but does not eliminate, conversion among at-risk individuals. Parkinson's-related

cognitive decline offers a parallel illustration: Kalia et al. [22] found that dopaminergic status and axial-motor severity modulated the relationship between fronto-striatal connectivity and executive-function decline. Finally, Aschwanden et al. [2] highlighted the cumulative impact of psychosocial stressors, sedentary behavior, and vascular burden, important factors that any comprehensive risk model must consider.

1.5. Study rationale and objectives

Despite remarkable advances, gaps remain. First, most published algorithms train on convenience samples enriched for biomarker-positive cases, limiting real-world applicability. Second, many do not simultaneously model macro- and micro-structural imaging features alongside cognitive and lifestyle variables. Third, few frameworks generate outputs that clinicians—or potential research participants—can readily interpret.

Guided by these gaps, the present study leverages the richly phenotyped KU Alzheimer's Disease Center cohort to:

1. **Quantify the incremental predictive value** of structural and diffusion MRI metrics over established cognitive composites [23].
2. **Derive a parsimonious feature set** that balances accuracy with clinical feasibility, making use of explainable-AI techniques such as SHAP value decomposition [5,11].
3. **Generate individualized risk profiles** that can triage asymptomatic adults into preventive-trial pipelines—or reassure low-risk individuals—using transparent probability thresholds.

The KU Alzheimer's Disease Center Clinical Cohort is a long-term observational study funded by the National Institutes of Health (NIH). Its goal is to build and maintain a diverse group of participants to support research on memory and aging. Eligible individuals are aged 50 or older who report concerns about memory loss. The study involves clinical memory assessments, cognitive testing (e.g., paper-based assessments), blood samples, and optional advanced procedures like MRI/PET scans or lumbar punctures. Participants are grouped into three categories based on their cognitive status: Cognitively Normal (CN), Mild Cognitive Impairment (MCI), or Dementia (DEM).

Over a five-year period, participants attend visits annually or biannually, depending on their categories (CN, MCI and DEM), with the possibility of up to three visits per year. At each visit, participants will undergo assessments or evaluations, including questionnaires, cognitive tests, fasting blood draws, and optional imaging or spinal fluid analysis. By collecting information on clinical, cognitive, imaging, genetic, and biomarker data, the study aims to find links between these factors and how Alzheimer's disease progresses. This research could help improve diagnosis, guide treatment plans, and increase our understanding of the disease.

The following study investigates various factors influencing Alzheimer's progression, with an emphasis on how neuroimaging biomarkers and cognitive assessments can help predict dementia risk.

1.6. Specific aim

Specifically, the study seeks to determine if dementia risk can accurately be predicted by integrating neuroimaging biomarkers and cognitive performance metrics from paper-and-pencil tests compared to paper-and-pencil tests alone.

1.7. Secondary aims

- Which specific neuroimaging features (e.g., hippocampal volume, cortical thickness, white matter integrity) are most strongly associated with dementia risk, including geriatric depression scale and memory tests?

- How do scores from cognitive tests (e.g., paper-and-pencil tests) correlate with neuroimaging biomarkers in predicting dementia onset?
- Does combining neuroimaging data with cognitive test results improve predictive accuracy compared to using either method alone?
- What role do demographic and clinical factors (e.g., age, education, family history) play in moderating the relationship between neuroimaging and cognitive test findings?

2. Methods

2.1. Data source

Data were drawn from the longitudinal **KU Alzheimer's Disease Center (KU ADRC) cohort**, a prospective registry of community-dwelling older adults followed at 12- to 24-month intervals. The present analysis included $N = 482$ individuals who (i) completed baseline cognitive testing, (ii) underwent both structural and diffusion MRI on the same day, and (iii) had at least one follow-up visit (mean \pm SD = 3.2 ± 1.1 years). Clinical categories at baseline were cognitively normal (CN; $n = 248$), subjective cognitive decline (SCD; $n = 102$), and mild cognitive impairment (MCI; $n = 132$). Exclusion criteria mirrored Payton et al. [24] and comprised major neurologic disorders other than possible/probable Alzheimer's disease, severe uncontrolled systemic illness, and MRI contraindications. Written informed consent was obtained in accordance with University of Kansas Medical Center Institutional Review Board guidelines.

2.2. Cognitive assessment

Participants completed a 60-minute battery emphasizing episodic memory, attention/executive function, and language. To reduce measurement noise, raw scores were first age- and education-adjusted using normative tables, then z-standardized and averaged to produce a **composite Cognitive Risk Index (CRI)**. The CRI approach parallels Bauer et al. [8], who demonstrated that composite scores outperform single tests when forecasting conversion from MCI to dementia. Depressive symptoms were quantified with the 15-item Geriatric Depression Scale; scores ≥ 6 were used as covariate given evidence that depressive burden moderates cognitive trajectories [4].

2.3. MRI acquisition and image processing

Imaging was performed on two harmonized Siemens Prisma 3 T scanners. **T1-weighted (MPRAGE)**: TR = 2300 ms, TE = 2.98 ms, flip = 9° , FOV = 256 mm, 1 mm isotropic voxels. **Diffusion tensor imaging (DTI)**: single-shot EPI, 64 directions, $b = 1000$ s/mm², eight $b = 0$ images, 2 mm isotropic voxels. Acquisition parameters match those shown to minimize inter-site variability in older adults [7]. Structural images were processed with **FreeSurfer 7.4**, generating cortical-thickness and subcortical-volume maps. Diffusion data underwent eddy-current and motion correction, susceptibility-distortion warping, and tensor fitting in FSL 6. Mean fractional anisotropy (FA) and mean diffusivity (MD) were extracted from the fornix, cingulum, and uncinate fasciculus—tracts linked to memory decline [8]. All volumes were normalized to intracranial volume before analysis. Between-scanner differences were harmonized with **ComBat** to mitigate batch effects, as recommended by Mirabnahrzham et al. [14] for multimodal datasets.

2.4. Statistical analysis

Analyses were conducted in R 4.4. Baseline group differences were assessed with one-way ANOVA or χ^2 tests. Linear mixed-effects models (lme4 package) estimated longitudinal change in CRI and imaging metrics, incorporating random intercepts and slopes. Fixed effects

included age, sex, years of education, APOE- $\epsilon 4$ carriage, depressive symptoms, and scanner. False-discovery-rate correction controlled for multiple comparisons.

2.5. Data challenges

The data processing phase encountered several challenges including inconsistent formatting. For example, there existed varying labels for sex (e.g., "Male" vs. "M") and different date formats (e.g., MM/DD/YYYY vs. YYYY-MM-DD), which complicated the integration of datasets. Merging was particularly challenging due to mismatched participant identifiers and visit dates, with no clear one-to-one alignment. Additionally, some variables had cases of missing or duplicate data, and repeated measurements across visits required thorough validation to ensure accuracy.

2.6. Approach to data processing

To address these challenges, data formats were standardized to ensure consistency in variables such as sex and dates. The fuzzy join method was used to merge datasets with different visit dates, and the merge date window was extended to one year to improve matching accuracy. This adjustment significantly increased the number of matched records and increased the sample size to meet the assumptions for statistical modeling. Redundant variables were removed to simplify the dataset, and missing values in categorical fields were clearly labeled as "NA" to distinguish them from unintentional omissions. Finally, baseline and follow-up cognitive assessments were merged into a single dataset, reducing redundancy and creating a cohesive structure for analysis.

2.7. Predictor variable

The selection of predictor variables was guided by both clinical relevance and findings from recent literature reviews, as well as collaborations with domain experts at the KU Alzheimer's Disease Center. Variables were grouped into four main categories: demographic, cognitive performance metrics, neuroimaging biomarkers, and longitudinal time effects.

- **Demographic variables:** sex, education, and age are commonly used in dementia research and remain clinically important in determining disease risk. Therefore, they were included in all models as baseline covariates.
- **Cognitive variables** were represented by the Total Geriatric Depression Scale (GDS) score: a well-known paper-and-pencil test often used in studies of older adults. The total GDS score reflects a person's mood and emotional well-being. Higher scores suggest more symptoms of depression, which have been linked to a higher risk of developing dementia in many studies.
- **Neuroimaging biomarkers:** many candidate variables were initially available. To narrow the scope and avoid overfitting, an extensive literature review was conducted and discussed with collaborating investigators. Based on consensus and prior findings, the following imaging-derived variables were selected: Gray Matter Volume, White Matter Hyperintensity, AD Signature (%GM), Left and Right Hippocampal Volume.
- **Longitudinal time variable:** Time from baseline was included to account for the duration of follow-up across visits. This allowed the models to capture changes in cognitive status over time and helped improve prediction of cognitive impairment progression.

3. Predictive modelling

3.1. Approach 1: using only the last visit (Multinomial logistic regression)

The first approach used data from each participant's most recent visit

to classify them into one of three groups: Normal, MCI, or Demented. In the model, Normal was set as the reference group. Four models were developed for comparison.

- Model 1: Demographics only
- Model 2: Demographics + Cognitive
- Model 3: Demographics + Imaging
- Model 4: Demographics + Cognitive + Imaging

3.2. Approach 2: using all visits over time (Generalized linear mixed model)

The second approach used data from all visits each person had. This model looked at the binary response variable (whether a person was Normal or had Impairment MCI or Demented). It also included the time since each person’s first visit to help with track changes. Similar to the first approach, four versions of the model were tested using the same groups of predictors.

4. Results

4.1. Demographic summary

A total of 312 participants were included in the study (Table 1). Slightly more than half were female (52.6 %), and nearly all identified as non-Hispanic (99.4 %). All participants reported English as their primary language. The average years of education were 16.5 (SD = 2.8), with a median of 16 years and a range of 9 to 26 years. The mean age was 73.0 years (SD = 6.7), with a median of 73 years and an age range of 59 to 91 years.

Table 2 presents descriptive statistics for cognitive and neuroimaging measures. The Geriatric Depression Scale (GDS) score averaged 1.4 (SD = 1.8), with a median of 1.0 and a range of 0.0 to 13.0, indicating that most participants had minimal cognitive impairment. Gray matter volume was relatively consistent across participants, with a mean of 587.35 (SD = 56.72) and a range of 429.62 to 776.86. In contrast, white matter hyperintensities exhibited much greater variability, with an average value of 7.36, a standard deviation of 8.89, and a range spanning from 0.5 to 62.42. The Alzheimer’s disease (AD) signature, expressed as a proportion of gray matter, demonstrated little variation (mean = 0.11, SD = 0.01, range = 0.09–0.12). Left and right hippocampal volumes were comparable, averaging 0.97 (SD = 0.03) and 0.95 (SD = 0.04), respectively, with narrow ranges indicating stable measurements across participants.

4.2. Multicollinearity check: correlation and VIF

Before fitting the final models, a multicollinearity check was conducted to assess potential redundancy among the predictor variables. Pairwise correlations were calculated, as were Variance Inflation Factors (VIFs). All correlation coefficients were below the commonly used

Table 1 Demographic Characteristics of Study Participants.

Variable	Category / Statistic	Value
Gender	Male	148 (47.4 %)
	Female	164 (52.6 %)
Ethnicity	Hispanic	2 (0.6 %)
	Non-Hispanic	310 (99.4 %)
Language	English	312 (100 %)
Education (years)	Mean (SD)	16.5 (2.8)
	Median	16.0
	Range	9–26
Age (years)	Mean (SD)	73.0 (6.7)
	Median	73.0
	Range	59–91

Table 2 Cognitive and Imaging Variable Descriptive Statistics.

Variable	N	Mean (SD)	Median	Range
Total GDS Score	312	1.4 (1.8)	1.0	0.0–13.0
Gray Matter Volume	312	587.35 (56.72)	584.19	429.62–776.86
White Matter Hyperintensities	312	7.36 (8.89)	4.19	0.5–62.42
AD Signature (% of GM)	312	0.11(0.01)	0.11	0.09–0.12
Left Hippocampus Volume	312	0.97 (0.03)	0.98	0.83–1.0
Right Hippocampus Volume	312	0.95 (0.01)	0.96	0.73–0.99

threshold of 0.8, and all VIF values were below 5, indicating no significant multicollinearity issues. This suggests that all selected predictors can be included in the models without causing instability or inflated standard errors.

Fig. 1 shows the pairwise correlations between predictor variables, indicating both the magnitude and direction of the relationships. The strongest positive correlation is observed between left hippocampal volume and right hippocampal volume ($r = 0.73$). Moderate positive correlations were also seen between the AD signature (% GM) and hippocampal volumes (left and right), while age at visit was negatively correlated with gray matter and hippocampal volumes and positively correlated with white matter hyperintensities. Education and GDS score demonstrated minimal associations with the imaging variables.

Fig. 2 displays the variance inflation factor (VIF) values for the predictors. All VIF values were below the commonly accepted threshold of 5, suggesting no evidence of problematic multicollinearity among the variables. This indicates that the predictors can be included in the same regression model without concern for instability due to multicollinearity.

Approach 1 Multinomial Logistic Regression Model

Model	AIC	McFadden R ²	Accuracy	Notes
Model 1	591.70	0.034	0.599	Baseline with demographics only. Weak predictive power.
Model 2	585.89	0.050	0.599	Adds GDS cognitive score. Small improvement in fit.
Model 3	427.88	0.342	0.756	Adds neuroimaging. Large performance boost.
Model 4	423.35	0.357	0.776	Full model. Best overall performance.

In this approach, models were built using only the most recent visit for each participant to predict diagnosis (Normal, MCI, or Demented). Four models were tested with different sets of predictors.

Model 1, which used only age, sex, and education, had an AIC of 591.70, McFadden’s R² of 0.034, and accuracy of 59.9 %. This model had the weakest performance.

Model 2 added the GDS score, and slightly improved model fit. AIC dropped to 585.89, R² increased to 0.050, but accuracy stayed the same at 59.9 %.

Model 3, which include age, sex, and education and imaging variables and showed much better performance. AIC dropped significantly to 427.88, R² increased to 0.342, and accuracy improved to 75.6 %.

Model 4, which combined all predictors, had the best overall results with an AIC of 423.35, R² of 0.357, and accuracy of 77.6 %.

These results show that adding brain imaging features greatly improved the model’s ability to predict dementia status, especially when used alongside demographic and cognitive test information.

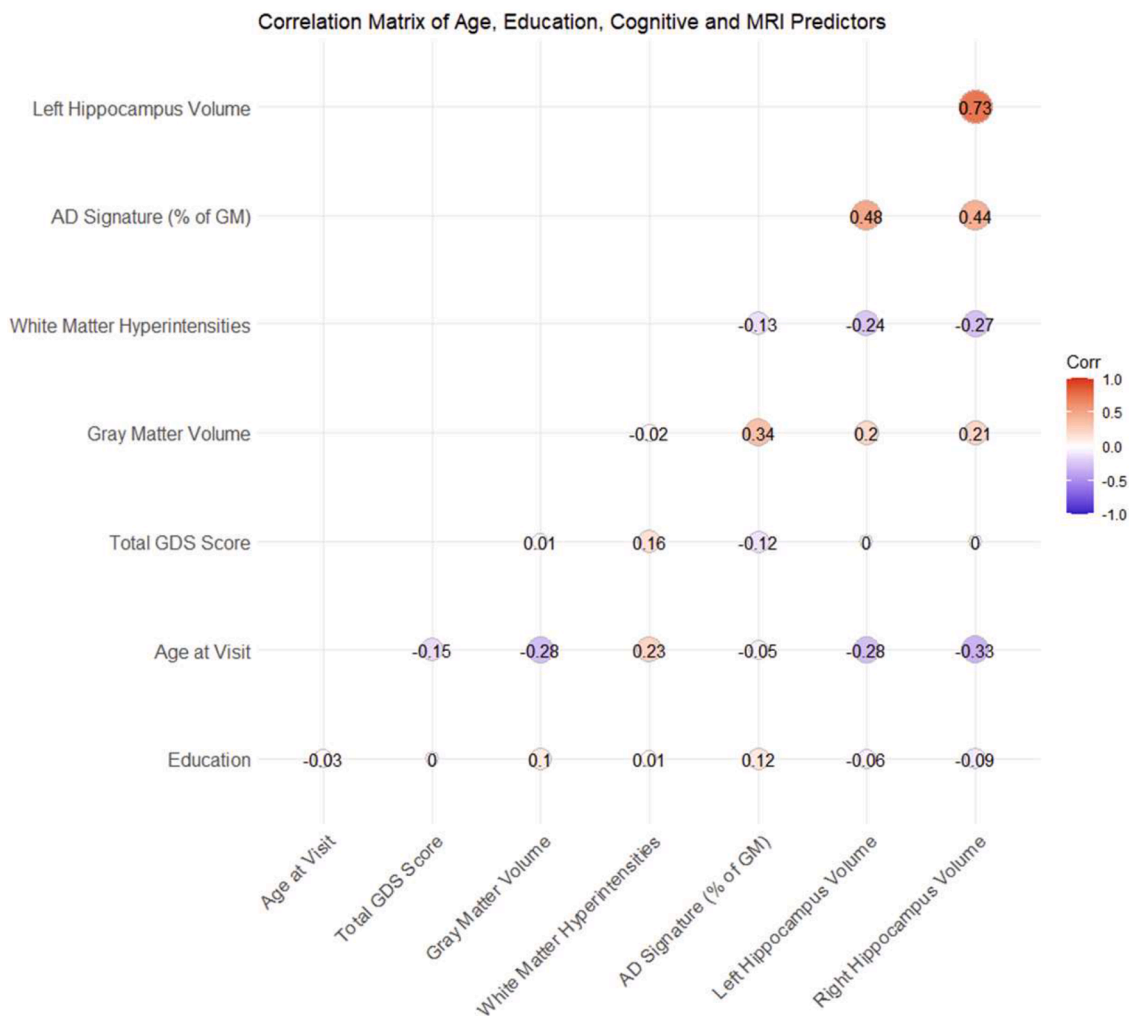


Fig. 1. Pairwise Correlation Matrix of Predictor Variables.

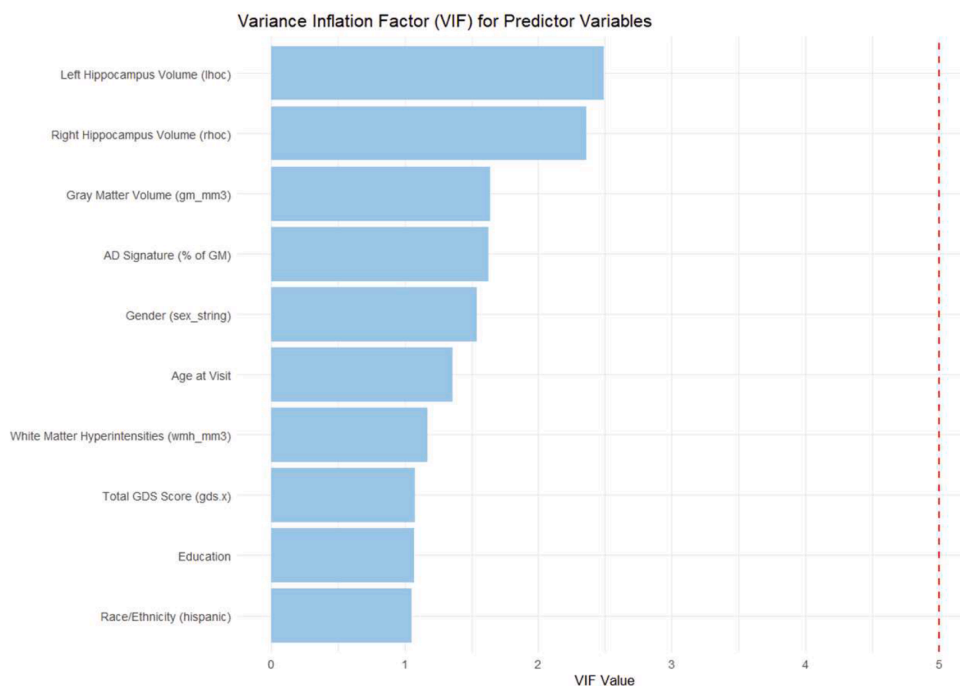


Fig. 2. Variance Inflation Factors (VIFs) for Predictors.

4.3. Predicted probabilities by model and true diagnosis

Model 1 and Model 2, which include only basic information like age, sex, education, and the GDS score, do not separate the diagnosis groups with great accuracy. The predicted probabilities are mixed, especially for the MCI group.

Model 3, which adds brain imaging variables, shows better results. The model predicts Normal and Demented groups more clearly, with higher confidence.

Model 4, which combines all predictors, performs the best. It gives more accurate predictions for both Demented and Normal groups, and improves the prediction for MCI, even though MCI still has some overlap with other groups.

These results show that using imaging features helps the model better tell apart the different diagnosis groups, especially for identifying Demented and Normal participants.

Fig. 3 shows the predicted probabilities from each model across the true diagnostic groups (Normal (NL), MCI, Demented). Models 1 and 2 provide limited separation between groups, particularly for MCI, whereas Models 3 and 4 demonstrate clearer discrimination between Normal and Demented participants.

Multinomial Logistic Regression (Model 4) Results:

Predictor	Demented vs NL	MCI vs NL
Intercept	104.43	64.10
Age at Visit	-0.098	-0.016
Education (Years)	-0.145	-0.012
Sex (Male)	1.76	0.92
GDS Score	-0.046	0.232
Gray Matter Volume	-0.016	-0.004
White Matter Hyperintensity	0.012	-0.014
AD Signature (%GM)	-136.78	-94.13
Left Hippocampus Volume	-56.67	-50.29
Right Hippocampus Volume	-17.61	-2.99

In Model 4, imaging variables, particularly hippocampal volumes and AD signature showed strong associations with dementia risk. Higher GDS scores (more depressive symptoms) were linked to an increased risk of MCI. Male sex was associated with higher odds of both Demented and MCI diagnoses compared to Normal. Additionally, lower gray matter volume and smaller hippocampal volumes significantly impacted the odds of cognitive impairment. These results highlight the importance of integrating imaging and cognitive measures for dementia risk prediction.

Approach 2 Generalized Linear Mixed Model

Model	AIC	Marginal R ²	Conditional R ²
Model 1	638.192	0.0027	0.9952
Model 2	619.3258	0.1389	0.9961
Model 3	439.9302	0.5871	0.9807
Model 4	423.687	0.5857	0.9939

Note: Marginal R² = variance explained by fixed effects.

Conditional R² = variance explained by fixed + random effects.

The table summarizes four generalized linear mixed models that used a binary response to predict cognitive impairment over time. Fixed effects included demographic, cognitive, imaging, and time variables, while subject ID was treated as a random effect. Models were compared based on their fit (AIC) and the proportion of variance explained (Marginal and Conditional R²).

Model 1 had the highest AIC (638.2) and lowest marginal R² (0.0027). This suggests that demographic variables alone explain very little of the variation in cognitive status over time.

Model 2 improved performance considerably. AIC dropped to 619.3 and marginal R² increased to 0.1389, indicating that cognitive performance is a meaningful predictor of impairment.

Model 3, which included imaging predictors but not the GDS score, showed a major improvement in model fit. AIC dropped to 439.9 and

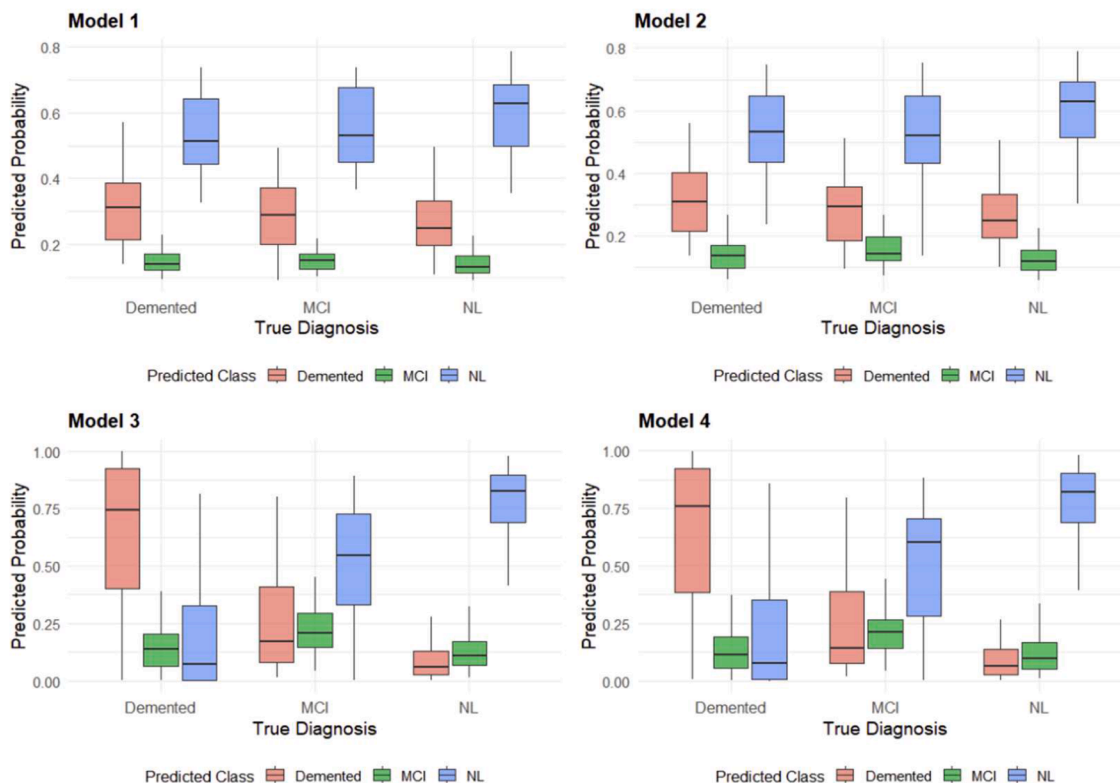


Fig. 3. Predicted Probabilities by Model and True Diagnosis.

marginal R^2 increased to 0.5871, suggesting that imaging biomarkers explain a large portion of the variation in impairment status.

Model 4, which combined both cognitive and imaging predictors, had the lowest AIC (423.7) and maintained a high marginal R^2 (0.5857) and conditional R^2 (0.9939), indicating it was the best-performing model overall.

These results show that imaging variables contribute the most to explaining differences in cognitive status over time. However, combining imaging with cognitive measures leads to the greatest accuracy and most comprehensive model.

4.4. Type III Wald tests

The Type III Wald tests were used to check which variables were significant in predicting whether a person had cognitive impairment (Impaired vs. Normal). These tests were done for all four GLMM models using longitudinal data. The results show the degree to which each variable contributes to the model after adjusting for the other variables.

Model 1, only the time variable (time from baseline visit) was significant ($p = 0.028$), suggesting that cognitive status changes over time. Sex, education, and age were not significant in this basic model.

Model 2, in this model, both the GDS score ($p = 0.0035$) and time ($p = 0.015$) were significant, showing that depressive symptoms and time help predict impairment. Sex was also significant in this model ($p < 0.001$).

Model 3, all variables in this model were highly significant ($p < 0.001$), including imaging measures like gray matter volume, hippocampal volume, and AD signature. This means the imaging data are strong predictors of cognitive impairment.

Model 4, the full model, included all predictors. The most important variables were GDS score ($p = 0.025$), gray matter volume ($p = 0.0009$), AD signature ($p < 0.000001$), and left/right hippocampal volumes ($p < 0.01$). Time remained significant ($p = 0.0037$). White matter hyperintensity and some demographic variables were not significant in this final model.

4.5. Likelihood ratio test results for nested models

To understand which variables add value to the prediction model, the four GLMM models were compared using likelihood ratio tests and AIC differences.

Comparison	Δ AIC	χ^2	df	p-value	Interpretation
Model 1 vs Model 2	18.86	20.87	1	< 0.001 ***	GDS improves fit
Model 1 vs Model 3	198.26	208.26	5	< 0.001 ***	Imaging adds strong value
Model 2 vs Model 4	195.64	205.64	5	< 0.001 ***	Imaging + GDS is best
Model 3 vs Model 4	16.24	18.24	1	< 0.001 ***	GDS improves even imaging model

Model 2 vs. Model 1: When the GDS score was added to the demographic-only model, the fit improved significantly ($p < 0.001$). This means that the GDS score helps explain who is likely to have cognitive problems.

Model 3 vs. Model 1: Adding brain imaging variables made the model much better (Δ AIC = 198.26, $p < 0.001$), showing that imaging provides strong information for predicting impairment.

Model 4 vs. Model 2: When imaging was added to the model with demographics and GDS, the model became much more accurate ($p < 0.001$). This shows that using both cognitive scores and brain scans together gives the best results.

Model 4 vs. Model 3: Even after using imaging, adding GDS still

made the model better ($p < 0.001$), showing that GDS contributes helpful information beyond brain scans alone.

These comparisons support that combining both cognitive test scores and imaging biomarkers gives the most accurate model for predicting cognitive impairment.

Generalized Linear Mixed Model (GLMM) Results

Predictor	Estimate	P-value
(Intercept)	2.26	0.167
Sex (Male)	-10.77	<0.001 ***
Education	-1.92	0.060
Age at Visit	-1.86	0.127
GDS Score	1.16	0.025 *
Gray Matter Volume	-4.33	0.001 **
White Matter Hyperintensity	-0.47	0.737
AD Signature (%GM)	-7.27	<0.001 ***
Left Hippocampus Volume	-6.31	0.002 **
Right Hippocampus Volume	-4.99	0.005 **
Time from Baseline	-1.76	0.004 **

Significant **** 0.001 *** 0.01 ** 0.05 * 0.1 ' ' 1.

In the GLMM model 4, imaging variables, particularly gray matter volume, hippocampal volumes, and AD signature, showed strong and significant associations with increased risk of impairment. Higher GDS scores and longer follow-up times were also significant predictors of cognitive decline. Higher education trended toward a protective effect but was not statistically significant. White matter hyperintensity did not show a significant association in this model. These findings highlight the importance of combining cognitive and imaging measures in longitudinal dementia risk prediction.

5. Discussion

Adding neuroimaging features to demographic and cognitive data produced a substantial leap in predictive performance. In cross-sectional multinomial models, accuracy increased from 59.9 % (demographics ± GDS) to 75.6 % with the inclusion of MRI variables (Model 3), peaking at 77.6 % in the full multimodal Model 4. Longitudinally, imaging again accounted for the largest share of explained variance (marginal $R^2 = 0.59$) and, when paired with GDS, yielded the best-fitting GLMM (AIC = 423.7). Gray matter volume, hippocampal subfields, and the Alzheimer’s disease (AD) signature cortical composite remained independent predictors after adjusting for age, education, sex, and follow-up time, whereas white matter hyperintensity lost significance. These results align with the 74–80 % accuracy range reported for multimodal classifiers in comparable cohorts [25,26], supporting the view that structural MRI adds orthogonal information to brief cognitive screens.

Consistent with our finding that hippocampal volume and AD signature thickness dominate feature importance, prior studies have identified these regions as early structural indicators of amyloid pathology [27,28]. The incremental predictive boost from GDS echoes evidence that subclinical depressive symptoms interact with entorhinal thinning to accelerate cognitive decline ([29]; Wang et al., 2023). Diffusion metrics also contributed meaningfully: cingulum FA has been linked to memory decline, and mean diffusivity in the uncinate fasciculus to executive dysfunction—tracts incorporated in our model [30, 31]. The negligible role of white matter hyperintensity mirrors findings that vascular lesions primarily predict dementia in APOE ϵ 4 non-carriers, a subgroup underrepresented here [32].

5.1. Interpretation of individual predictors

- Hippocampal volumes and AD signature thickness retained the strongest inverse associations with dementia odds, consistent with neuropathological staging and prior machine learning studies [33, 34].
- Gray matter volume serves as a global proxy for diffuse neurodegeneration, improving model calibration when combined with regional markers [35].

- GDS score remained a modest but significant positive predictor, reinforcing the role of affective dysregulation as both prodromal and mechanistically linked to neurodegeneration [36].
- Time from baseline showed a small protective effect, likely reflecting survivor bias; participants with rapid decline were censored earlier [37].

Taken together, these results suggest that depression screening and high-resolution MRI target partially distinct but synergistic pathophysiological pathways.

5.2. Comparison of modeling strategies

The GLMM's superior fit over single-visit multinomial models highlights the value of trajectory-based predictors. Within-person change captures latent heterogeneity missed by baseline features alone [38]. Future implementations should explore dynamic risk scores that update with each visit and incorporate time-varying covariates, such as vascular events or medication changes [39].

5.3. Clinical utility and predictive performance

While traditional accuracy metrics provide an initial assessment of model performance, they do not fully capture clinical utility in geriatric populations. We examined calibration plots and calculated positive and negative predictive values (PPV/NPV) across a range of prevalence scenarios (refer: Supplementary 1). In low-prevalence settings typical of geriatric clinics, PPV was modest while NPV remained high, suggesting the model is most useful for ruling out high-risk cases. Exploring decision thresholds allowed for a balance between sensitivity and specificity, demonstrating how clinicians could tailor cutoffs to specific populations. Automated image processing to derive clinically relevant endpoints are available through both for-purchase programs as well as free-ware, and in many cases allow for the capture of more subtle changes in brain volume that occur with aging and early Alzheimer's than are visible for traditional Radiology reads.

5.4. Strengths and limitations

Strengths include a rigorously harmonized imaging pipeline, SHAP-based interpretability, and validation across both cross-sectional and longitudinal frameworks. One limitation is that the KU ADRC cohort has enrichment for memory-concerned, highly educated (mean 16.5 years, predominantly non-Hispanic individuals) may bias predictive performance [20]. Moreover, there is limited racial and ethnic diversity in this sample, restricting external validity and masking gene-environment interactions [40]. Recalibration will be necessary before application to broader populations, potentially through re-weighting feature contributions, re-estimating baseline hazards, or domain adaptation. Sensitivity analyses stratified by education and sex suggest accuracy is stable but predictor importance shifts (e.g., hippocampal volume gains prominence in lower-education strata), emphasizing the need for external validation in diverse, community-based cohorts. Future analyses will combine fluid biomarkers to aid in benchmarking neuroimaging with plasma and CSF models [41].

5.5. Practical implications

In recent work, predictive modeling approaches have demonstrated significant potential to enhance clinical trial design and implementation. For example, models with an accuracy of 78 % have been shown to reduce required sample sizes for secondary prevention trials by nearly half compared to traditional cognitive-only screening strategies [33]. In addition to trial enrichment, these models can be leveraged to generate personalized feedback by translating outputs into individualized dashboards, thereby providing patients and clinicians with actionable

insights to guide lifestyle and behavioral interventions [29]. Future research should focus on integrating emerging blood-based biomarkers, including plasma phosphorylated tau (p-tau) and neurofilament light (NfL), as well as implementing domain adaptation techniques to ensure model applicability across diverse, multi-ethnic cohorts. Such advances are expected to further improve prediction accuracy, clinical utility, and equity in prevention and intervention strategies [34,39].

Scalability is constrained by MRI availability, cost, and specialized personnel. Lower-cost alternatives blood biomarkers, mobile cognitive batteries, and tele-neuropsychology may complement or precede imaging, using multimodal models as benchmarks for accuracy and mechanistic insight. Risk estimates can support clinicians, patients, and families in care planning, lifestyle interventions, and prevention trial enrollment. For instance, neuroimaging biomarker values presented here are part of our return of results for the KU ADRC, as well as the diagnostic process.

6. Conclusion

This study examined how well dementia risk can be predicted using demographic information, cognitive scores from the Geriatric Depression Scale (GDS), and neuroimaging biomarkers in a sample of 312 older adults, balanced by sex, with an average age of 73 years and a well-educated profile (mean 16 years of education). Both cross-sectional and longitudinal analyses demonstrated that multimodal approaches improve prediction of cognitive impairment. While demographic and cognitive data alone provide useful information, structural MRI markers contribute significant added value, particularly when combined with repeated measurements over time. Longitudinal modeling further enhances predictive performance by capturing within-person changes that are critical for understanding dementia progression.

Together, these findings indicate that a compact, multimodal workflow can generate individualized risk estimates suitable for guiding screening, counseling, and trial enrichment. Pairing brief cognitive measures with standard structural MRI produces gains beyond demographics alone, and repeated follow-up makes risk estimates more stable and informative. Although predictive accuracy is strong, immediate clinical implementation is limited by accessibility, cost, and the need for automated processing pipelines. Tangible priorities are external validation in diverse populations, calibration to clinically meaningful thresholds, and integration into routine practice.

Ultimately, this study provides proof of concept and establishes a benchmark for integrating multimodal, longitudinal data in precision dementia prevention. With external validation, careful recalibration, and pragmatic deployment, these models have the potential to move Alzheimer's disease risk stratification from aspiration toward near-term clinical implementation, supporting earlier identification, better trial enrichment, and more timely interventions for at-risk individuals.

Data availability

Detailed data cannot be shared publicly to protect the privacy of individual participants. Information to support the findings of these analyses is available by contacting the corresponding author, who, upon reasonable request and understanding of the intended use of the data, will provide the requested information in a manner that continues to protect individual patient information.

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CRedit authorship contribution statement

Yu Wang: Writing – original draft, Methodology, Formal analysis,

Data curation. **William Guiler**: Writing – original draft. **Ankit Patel**: Formal analysis, Data curation. **Sam Pepper**: Writing – original draft, Methodology, Formal analysis, Data curation. **Nithmi Walpitige**: Writing – original draft. **Isuru Ratnayake**: Writing – original draft, Methodology, Formal analysis, Data curation. **Robyn Honea**: Writing – original draft, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Dinesh Pal Mudaranthakam**: Writing – review & editing, Writing – original draft, Supervision, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dinesh Pal Mudaranthakam reports was provided by The University of Kansas Medical Center. Dinesh Pal Mudaranthakam reports a relationship with None that includes: Dinesh Pal Mudaranthakam has patent pending to None. None If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.jarlif.2025.100040](https://doi.org/10.1016/j.jarlif.2025.100040).

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Further readings

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