AN INTERPRETABLE HYBRID STATISTICAL-FUZZY RISK MODELING FRAMEWORK FOR ALZHEIMER'S DISEASE

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Abstract:

Alzheimer's disease (AD) risk assessment involves complex interactions among heterogeneous demographic, metabolic, behavioral, nutritional, and cognitive factors. Existing approaches often face a trade-off between interpretability and modeling flexibility, particularly under small-sample conditions. To address these limitations, this study proposes a domain-level hybrid risk modeling framework. Logistic regression is first used to construct an interpretable baseline model. Random forest feature importance is then applied to calibrate adaptive domain weights, and fuzzy inference is introduced to model nonlinear interactions among risk domains. Questionnaire-based risk variables were organized into five domains, including baseline demographics, chronic disease and metabolic factors, lifestyle behaviors, nutrition and gastrointestinal conditions, and cognitive symptoms. Logistic regression was used to construct an interpretable baseline model, while random forest feature importance was applied to calibrate domain weights for global risk aggregation. A fuzzy inference module with triangular membership functions was further introduced to model nonlinear multi-domain interactions. Experimental results show that the domain logistic model achieved an AUC of 0.89, the RF-weighted global risk score achieved an AUC of 0.88, and the fuzzy-derived risk score achieved an AUC of 0.76. These results demonstrate that combining domain structuring, adaptive weighting, and fuzzy reasoning can support interpretable disease risk assessment under small-sample conditions.

Keywords:

Artificial intelligence (AI); Alzheimer's disease (AD); Risk analysis; Domain-level; Fuzzy

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and one of the leading causes of cognitive decline in older adults [1]. Because effective curative treatment remains unavailable, early risk assessment and stratified intervention are regarded as important strategies for delaying disease progression and reducing care burden [2]. Consequently, developing reliable and interpretable AD risk assessment models has become an important research topic in intelligent healthcare.

Disease risk assessment plays an important role in early intervention and prevention decision-making and has become a key component of intelligent healthcare and precision medicine [3]. With the rapid development of artificial intelligence (AI), machine learning and data-driven methods have been increasingly applied to disease risk prediction tasks [3]. However, in real-world medical scenarios, heterogeneous variables, limited sample sizes, and measurement uncertainty remain common challenges. In addition, black-box models often provide limited interpretability, which restricts their practical value in high-stakes clinical decision-making [4]. The risk factors of AD span multiple domains, including genetic predisposition, chronic diseases, lifestyle behaviors, nutritional status, and cognitive symptoms [5]. These variables are heterogeneous in type and often exhibit complex hierarchical structures, nonlinear relationships, and cross-domain interactions [6, 7]. Such characteristics make accurate and reliable risk modeling particularly challenging, especially under small-sample conditions.

Thus, there is a practical need for modeling frameworks that can support multi-dimensional risk assessment, offer structurally interpretable outputs, and remain robust when the available sample size is limited. In this study, we develop a hybrid modeling framework tailored for small-sample, multi-domain AD risk assessment scenarios. The framework integrates statistical modeling, machine-learning-based weight calibration, and fuzzy rule-based inference to simultaneously address interpretability, nonlinear interaction modeling, and robustness under limited data conditions.

2. Related works

Existing approaches relevant to multifactor disease risk modeling commonly include statistical models, machine-learning-based models, and rule-based reasoning methods [8]. Statistical models usually offer relatively clear parameter interpretability and have been widely used in medical risk analysis. However, they may be less flexible in representing nonlinear relationships and complex cross-domain interactions among heterogeneous risk factors [9]. Machine learning models are capable of learning complex patterns from data and have been increasingly applied in disease prediction tasks. Nevertheless, their performance may become unstable in small-sample settings, and their inference processes are often less transparent, which may limit their adoption in clinical decision-making scenarios [10]. Rule-based or knowledge-driven reasoning systems provide explicit reasoning structures and strong interpretability, making them attractive for medical applications that require explainable decision processes. However, such systems may lack adaptive data-driven calibration and can be sensitive to rule design or prior knowledge specification [11]. Consequently, achieving discriminative performance, structural transparency, and robustness simultaneously remains challenging in multifactor disease risk modeling under limited-data conditions. These limitations are especially prominent in AD risk assessment, where models are required to capture nonlinear relationships and cross-domain interactions among heterogeneous variables while maintaining interpretability [12, 13].

3. Methodology

This study proposes a hybrid risk modeling framework that integrates statistical modeling, machine-learning-based weight calibration, and fuzzy rule-based inference. First, questionnaire variables are grouped into semantically coherent risk domains to reduce feature heterogeneity. Then logistic regression and random forest models are used to estimate domain contributions and calibrate domain weights. Finally, fuzzy inference is used to model nonlinear interactions among risk domains and generate interpretable risk scores.

3.1. Domain-Level risk establishment

Questionnaire variables were organized according to commonly reported AD risk factor categories in prior epidemiological and clinical studies [15], together with variable-type semantics and assessment structure. Factors describing similar risk mechanisms or functional attributes were grouped into the same field to reduce cross-type feature interference. This grouping method follows established multi-factor risk modeling practice while remaining compatible with the structure of the collected questionnaire variables [15]. The five domains were presented in table 1.

TABLE 1. Five risk domains and their corresponding variables

Domain	Type	Variables
1	Baseline demographic domain	Age, education level, BMI indicators
2	Chronic disease and metabolic domain	Hypertension, diabetes, hyperlipidemia, cardiovascular disease history, neurological disease history
3	Lifestyle behavior domain	Sleep duration, physical activity level, smoking intensity, alcohol consumption, toxin exposure, social activity
4	Nutrition and gastrointestinal domain	Vitamin D status, dietary balance, supplements, periodontal disease, gastrointestinal disease, food intolerance
5	Cognitive and functional symptom domain	Memory decline, language difficulty, attention problems, daily function independence

All questionnaire variables were transformed into structured numerical formats prior to modeling. Binary variables were encoded as 0-1 indicators to preserve categorical presence information. Continuous variables such as age, body measurements, and behavioral duration measures were normalized when necessary to reduce scale imbalance across domains. Ordinal health and lifestyle variables were encoded as ordered scores (0, 1, and 2) to preserve severity or frequency ordering while maintaining compatibility with subsequent statistical and machine learning models.

3.2. Hybrid statistical-fuzzy analysis

A multi-method hybrid modeling analysis was adopted to balance structural interpretability, nonlinear interaction capture, and data-adaptive calibration under small-sample (60 samples) conditions. At the statistical modeling level, logistic regression was applied by domain-level risk scores as predictors to construct a baseline interpretable risk model and reference discriminative performance. This component showed transparent domain contribution structure and served as a comparison anchor for subsequent hybrid strategies. To introduce data-driven calibration, a random forest model was trained on domain-level risk features, and normalized feature importance values were used to derive adaptive domain weights. Feature importance values produced by the trained model were normalized and used to derive adaptive domain weights. These calibrated weights were then used to compute a weighted global risk score

through domain score aggregation [14]. This step enabled nonlinear contribution sensitivity to be reflected in the domain weighting scheme.

The weighted global risk score was computed as follows [14] :

$$R_{global}=\sum_{d=1}^{D} W_d R_d \quad (1)$$

W_d represents domain weight and R_d represents domain risk score.

In addition, a fuzzy inference module was constructed as a rule-based nonlinear mapping layer to model multi-domain interaction patterns and produce linguistically interpretable risk scores. Each normalized domain risk score was mapped to linguistic risk levels using predefined membership functions. Triangular membership functions were applied based on their simplicity, parameter parsimony, and stability under small-sample conditions. For each field input, three overlapping linguistic states-low, medium, and high-were defined on the interval **[0, 1]**. The medium-risk function was assigned a wider support range to improve transition smoothness and rule activation coverage [14], while low and high functions covered boundary regions (Figure 1). Overlapping supports were used to avoid hard threshold effects. The fuzzy rule base was constructed using a mechanism-guided design strategy [13]. Domain grouping and rule priority were defined according to commonly reported disease risk factor categories and domain relevance. Rules (R) were formulated in IF-THEN form to capture single-domain high-risk dominance and multi-domain moderate-risk aggregation patterns (2). Mamdani inference was used min-max operators [14], and centroid defuzzification was applied to obtain continuous fuzzy risk scores.

$$R_{fuzzy}=f(R_{baseline}, R_{vascular}, R_{lifestyle}, R_{nutrition}, R_{cognitive}) \quad (2)$$

To sum up, these components together form a hybrid framework combining statistical modeling, machine-learning-based weight calibration, and fuzzy rule-based inference.

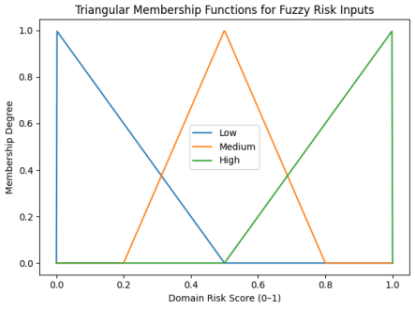

FIGURE 1. The membership function of this fuzzy analysis

4. Experiments

4.1. Dataset used

The data was collected by Sichuan Taikang Hospital and the Taikang Shuyuan Senior Care Community. We have the permission to use them for our analysis. They collected the data by questionnaire-based risk assessment tool from elderly participants. **A total of 60 subjects aged 60-90 years were included in the dataset**, consisting of 30 individuals clinically identified as having AD (AD group) and 30 cognitively normal elderly individuals (control group). Domain-level risk scores were successfully constructed for all participants across the five predefined fields. All variables were encoded into structured numerical formats for downstream domain-level risk modeling, and defined based on participants' conditions prior to AD onset whenever applicable, in order to decrease potential reverse-causality effects. For example, hypertension history was encoded as 0 = no and 1 = yes, and education level was converted into ordered categories according to attained schooling level.

4.2. Logistic regression analysis

Employing the five domain-level risk scores as predictors, the logistic regression model achieved a stratified 5-fold cross-validated AUC of 0.89 (Figure 3), representing the highest discrimination performance among all evaluated strategies. This result indicates that domain-level structured feature fusion preserves substantial disease-related information and enables strong separability between AD and control groups under small-sample conditions. Logistic regression coefficient analysis revealed heterogeneous domain contributions. The cognitive domain demonstrated the strongest association with AD status, with an odds ratio (OR) of 12.21, indicating dominant discriminative influence. The baseline demographic domain showed moderate association (OR = 2.48), while nutrition (OR = 1.69) and vascular (OR = 1.38) domains exhibited smaller but positive effects. The lifestyle domain showed an OR of 0.44, suggesting a negative association under the linear modeling assumption (Table 2).

TABLE 2. The OR values of each domain

Domain	OddsRatio
CognitiveRisk	12.21088254

BaselineRisk	**2.475092499**
NutritionRisk	**1.688243564**
Chronic diseaseRiskRisk	**1.378873573**
LifestyleRisk	**0.438723116**

4.3. Global risk aggregation and weight

Under a predefined heuristic weighting scheme guided by general disease risk factor relevance and domain importance, domain contributions were set as Baseline 0.15, Vascular 0.20, Lifestyle 0.20, Nutrition 0.15, and Cognitive 0.30 (Table 3) [15]. Employing this weighting strategy, the aggregated global risk score achieved a 5-fold cross-validated AUC of 0.82 (Figure 3, 4). After replacing prior weights with random forest-derived feature importance (Cognitive 0.398, Baseline 0.270, Lifestyle 0.149, Nutrition 0.110, Vascular 0.074) (Figure 2), the RF-weighted global risk score improved to an AUC of 0.88 (Figure 4), approaching the performance of the logistic regression model. The consistent ranking between feature importance and logistic odds ratios supports the structural validity of domain grouping, while the performance gain indicates that adaptive weighting enhances discrimination by emphasizing high-impact domains and down-weighting weaker contributors.

TABLE 3. The vaules of domain weights

Domain	Weight
CognitiveRisk	**0.30**
BaselineRisk	**0.15**
NutritionRisk	**0.15**
Chronic diseaseRisk	**0.20**
LifestyleRisk	**0.20**

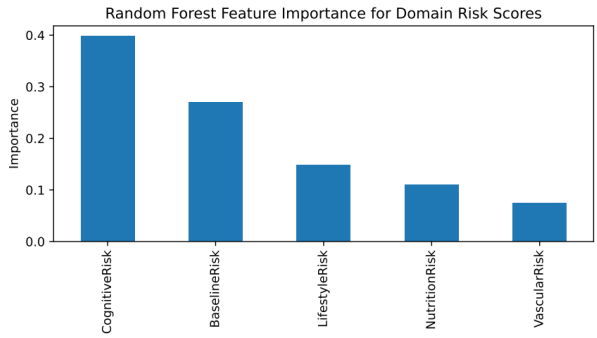

FIGURE 2. The RF feature importance score of each risk group

4.4. Fuzzy reasoning

The fuzzy inference-derived risk score achieved a 5-fold cross-validated AUC of 0.76 (Figure 3). While lower than both logistic regression and RF-weighted aggregation models, the fuzzy approach provided nonlinear rule-based mapping and interpretable linguistic transitions between risk levels. The moderate performance suggests that rule-based modeling captures structured interactions but does not fully exploit linear separability under small-sample conditions.

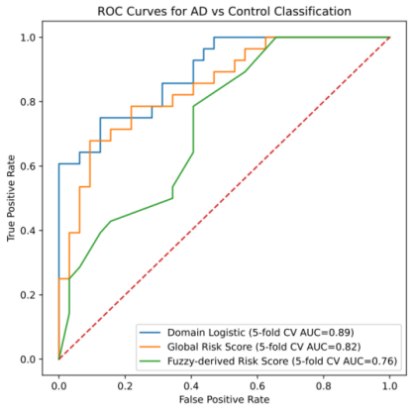

FIGURE 3. ROC curves of different risk modeling strategies for AD vs control classifications

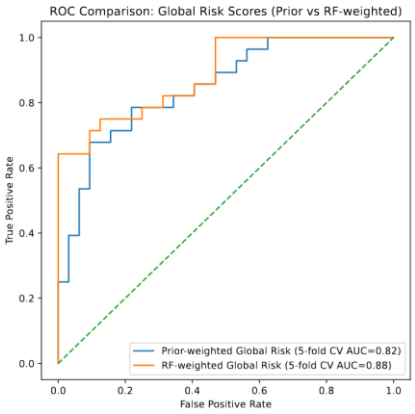

FIGURE 4. ROC comparison of prior-weighted and RF-weighted global risk scores

5. Discussion

This study proposes a domain-level hybrid risk modeling framework for AD under small-sample conditions and evaluates the contributions of statistical modeling, data-driven weighting, and fuzzy inference. The results demonstrate that domain-based feature structuring provides

a stable foundation for risk discrimination, while different modeling strategies exhibit distinct strengths and trade-offs.

The domain-level logistic regression model achieved the highest discrimination performance (AUC = 0.89), indicating that structured aggregation of heterogeneous variables into semantically coherent domains effectively preserves disease-related signal and enables robust separation between AD and control groups. This suggests that domain-level representation is more stable than direct high-dimensional variable modeling in small-sample settings. The comparison between prior-weighted and RF-weighted global risk scores highlights the importance of adaptive calibration. While the predefined weighting scheme provides a mechanism-consistent and interpretable structure, replacing it with random forest-derived importance improves performance (AUC: 0.82 → 0.88). This improvement indicates that data-driven weighting can better capture relative domain contributions and adjust for dataset-specific characteristics. At the same time, the consistency between feature importance ranking and logistic regression odds ratios supports the structural validity of the domain grouping strategy.

The fuzzy inference model achieved moderate discrimination performance (AUC = 0.76), lower than both statistical and machine learning-based approaches. However, this result should be interpreted in the context of model purpose. Unlike logistic regression and random forest models, the fuzzy module is not optimized purely for classification accuracy but is designed to provide rule-based nonlinear risk mapping and interpretable inference pathways [17]. The performance gap suggests that rule-based systems may not fully exploit linear separability in small datasets [18], but they offer advantages in transparency and interpretability, particularly for modeling multi-domain interaction patterns [18]. There are some differences in the lifestyle domain between logistic regression (negative association) and random forest importance (non-negligible contribution), which may reflect nonlinear or interaction effects that are not fully captured by linear models. Logistic regression estimates independent linear contributions, whereas random forest importance can reflect nonlinear sensitivity and cross-domain interactions. This further supports the inclusion of hybrid modeling strategies.

Overall, the results show that domain-level structuring, adaptive weighting, and rule-based inference each contribute complementary strengths. The proposed framework demonstrates that combining these approaches can balance discrimination performance and structural interpretability in small-sample disease risk assessment scenarios.

However, there are also some limitations in this research. First, the sample size is relatively small, which may affect model stability and generalizability. Thus, the current study should be interpreted as an exploratory framework-oriented investigation under limited-data conditions. Second, the prior weighting scheme is heuristic rather than statistically derived, although it is partially validated through consistency with data-driven importance. Third, the fuzzy rule base is manually constructed and not optimized using data-driven rule learning, which may limit its predictive performance. Future work will focus on expanding sample size, incorporating multimodal data, and exploring data-driven optimization of both weighting and fuzzy rule structures.

6. Conclusions

This study presents a domain-level hybrid risk modeling framework for AD under small-sample conditions, integrating statistical modeling, data-driven weight calibration, and fuzzy inference. Results show that domain-based feature structuring offers a stable foundation for risk discrimination, while adaptive weighting improves aggregation performance. Although the fuzzy component yields lower accuracy, it enables interpretable nonlinear modeling of multi-domain interactions. Overall, the framework demonstrates the value of combining complementary methods to balance performance and interpretability in multi-factor disease risk assessment and provides a flexible foundation for future extensions to larger and multimodal datasets.

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