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ABSTRACT

Dementia diagnosis often relies on expensive and invasive neuroimaging techniques that limit access to early screening. This study proposes an innovative approach for facilitating early dementia screening by estimating diffusion tensor imaging (DTI) measures using accessible lifestyle and brain imaging factors. Conventional DTI analysis, though effective, is often hindered by high costs and limited accessibility. To address this challenge, fuzzy subtractive clustering identified 14 influential variables from the Lifestyle for Brain Health and Brain Atrophy and Lesion Index frameworks, encompassing demographics, medical conditions, lifestyle factors, and structural brain markers. A multilayer perceptron (MLP) neural network was developed using these selected variables to predict fractional anisotropy (FA), a DTI metric reflecting white matter integrity and cognitive function. The MLP model achieved promising results, with a mean squared error of 0.000 878 on the test set for FA prediction, demonstrating its potential for accurate DTI estimation without costly neuroimaging techniques. The FA values in the dataset ranged from 0 to 1, with higher values indicating greater white matter integrity. Thus, a mean squared error of 0.000 878 suggests that the model's predictions were highly accurate compared to the observed FA values. This multifactorial approach aligns with the current understanding of dementia's complex etiology influenced by various biological, environmental, and lifestyle factors. By integrating readily available data into a predictive model, this method enables widespread, cost-effective screening for early dementia risk assessment. The proposed accessible screening tool could facilitate timely interventions, preventive strategies, and efficient resource allocation in public health programs, ultimately improving patient outcomes and caregiver burden.

INTRODUCTION

Dementia, a progressive neurodegenerative disorder, poses a significant challenge to individuals, healthcare systems, and societies worldwide.[1] As the global population ages, the prevalence of dementia continues to rise, with an estimated 66×10^6 cases projected by 2030 and 115×10^6 by 2050.[2] Early detection and diagnosis of dementia are crucial for timely intervention, symptom management, and improving the quality of life of affected individuals,[3] socioeconomic costs associated with dementia, and Alzheimer's disease alone imposing an annual cost exceeding $350 000 per patient in the United States.[4]

Current diagnostic methods often rely on invasive and costly techniques, such as positron emission tomography (PET) scans or cerebrospinal fluid analysis, which may not be readily accessible or affordable for many individuals.[5] In addition, the lack of accessible

and cost-effective methods for estimating diffusion tensor imaging (DTI) and diagnosing dementia at an early stage has hindered timely intervention and treatment.[6] Recently, computational approaches are effectively used in biomedical engineering for the treatment of different patients.[7,8]

The proposed approach in this study is an important step toward addressing this need. Using the synergy between lifestyle factors, structural brain markers, and machine learning techniques, we aimed to create a cost-effective and accessible tool for timely dementia screening. The integration of diverse data sources, including the More Effective Lifestyle Factors for Brain Health (LIBRA) and Brain Injury and Atrophy Index (BALI), reflects the multifaceted nature of dementia and its underlying drivers.[9,10] The potential impact of this effort extends beyond the realm of individual patient care, as it holds promise for enabling large-scale screening initiatives and targeted interventions in public health programs. By providing access to early diagnosis of dementia, this approach could pave the way for improved patient outcomes, reduced caregiver burden, and more efficient allocation of healthcare resources.[11]

Several studies have investigated the potential of machine learning algorithms to predict dementia risk based on health-related factors.[12,13] Studies using variables, such as age, education, high blood pressure, obesity, and physical inactivity, have shown the possibility of identifying people at high risk of cognitive impairment.[14,15] In other studies, using structural MRI data and machine learning algorithms to classify people with Alzheimer's disease, mild cognitive impairment, and healthy people, their approach showed improved diagnostic accuracy.[16–18] Although these studies have made significant progress, the reliance on less expensive neuroimaging techniques remains a barrier to widespread implementation. Consequently, researchers have explored alternative strategies for estimating neuroimaging markers using more accessible data sources.[19,20] In other studies, using demographic factors, a model was developed to predict diffusion tensor imaging (DTI) measurements sensitive to white matter integrity.[21–23]

Conventional diagnostic methods for dementia rely heavily on neuroimaging techniques, particularly diffusion tensor imaging (DTI).[24] DTI measurements, derived from advanced magnetic resonance imaging (MRI) scans, have proven to be highly effective in detecting structural and functional changes in the brain associated with dementia.[25,26] However, the widespread implementation of DTI has been hindered by its substantial cost and the limited availability of specialized facilities and expertise required for image acquisition and analysis.[27] In response to this challenge, researchers have sought to develop alternative, cost-effective methods for estimating DTI measurements, thereby facilitating early dementia diagnosis without the financial burden associated with conventional neuroimaging techniques.[28]

Researchers have explored alternative approaches that use affordable and readily available factors as potential dementia risk indicators. Factors such as lifestyle for brain health (LIBRA) or brain atrophy and lesion indices (BALI) have been shown to be associated with brain health and cognitive function.[28–31]

The aim of this study was to develop an innovative system identification network using a multilayer perceptron (MLP) method to estimate DTI metrics based on a subset of the most influential factors of BALI and LIBRA. Using a data-driven approach, this study sought to identify effective variables from a combined set of BALI and LIBRA factors that can serve as input to the MLP network to predict DTI measures. The successful implementation of this approach could pave the way for an inexpensive and accessible dementia screening tool that enables early intervention and improved patient outcomes.

This challenge involves employing a data-driven approach to select the most salient LIBRA and BALI factors for estimating DTI measures. Specifically, we utilize fuzzy subtractive clustering, a powerful machine learning technique, to identify the factors that exhibit the greatest variation among patients referred to for dementia diagnosis. By focusing on these key variables, we sought to develop an MLP network capable of accurately estimating DTI measures, thereby enabling early dementia diagnosis through an inexpensive and accessible method.

The successful implementation of this approach has the potential to revolutionize dementia diagnosis by providing a cost-effective alternative to conventional neuroimaging techniques. By leveraging readily available lifestyle and brain imaging markers, healthcare systems could screen larger populations for cognitive impairment, facilitating timely interventions and improving patient outcomes. Moreover, the proposed methodology could serve as a foundation for further research and development, ultimately paving the way for a more equitable and accessible approach to dementia diagnosis worldwide.

PROBLEM STATEMENT

The lack of an accessible and cost-effective method for estimating DTI measurements and diagnosing dementia at an early stage has far-reaching implications. Delayed diagnosis often leads to a missed window of opportunity for therapeutic interventions, ultimately compromising patient outcomes and quality of life.[32] Furthermore, the absence of early screening perpetuates the substantial emotional, physical, and financial burdens imposed by caregivers and healthcare systems. Moreover, the absence of early intervention can accelerate the progression of dementia, leading to more severe cognitive impairments and functional limitations, ultimately diminishing individual's independence and quality of life.[33] The development of an accessible and cost-effective method for estimating DTI measurements and enabling early dementia diagnosis is imperative for mitigating the far-reaching consequences of this debilitating condition.

In light of the growing demand for early dementia diagnosis and the limitations of conventional methods, there is an urgent need for a cost-effective and accessible approach for estimating DTI measurements. By leveraging inexpensive and readily available factors, such as lifestyle and brain imaging markers, it may be possible to develop a reliable model for predicting DTI measurements and facilitating early dementia diagnosis. This approach could alleviate the financial burden on healthcare systems and improve patient outcomes by enabling timely interventions and treatment strategies.

MATERIALS AND METHODS

This study was conducted on a cohort of elderly individuals referred to the Memory Clinic of Roozbeh Hospital in Tehran, Iran. The initial pool consisted of 201 volunteers who met the eligibility criteria for participation. However, several subjects were

excluded due to their inability to undergo the required tests, lack of interest in continuing the assessments, or the practitioner's decision to withdraw them from the study. The final sample comprised 51 subjects from diverse regions of Iran. The study protocol adhered to the principles of the Ethics Committee of the Islamic Azad University Science and Research Branch (Approval No: IR.IAU.SRB.REC.1401.285). All participants provided informed consent prior to their inclusion in this study.

This study utilized a comprehensive set of 49 variables derived from two established frameworks: the Lifestyle for Brain Health (LIBRA), comprising 42 factors, and the Brain Atrophy and Lesion Index (BALI), comprising seven factors. The LIBRA factors encompass a wide range of demographic, physical health, lifestyle, and laboratory components known to influence brain health and cognitive function.[34] Specifically, the demographic components included age, sex, education level, occupation, marital status, and income level.[35] The physical health factors included the presence and duration of conditions, such as diabetes mellitus, hypertension, hypercholesterolemia, kidney dysfunction, coronary heart disease,[36] and the use of various medications, including benzodiazepines, antipsychotics, anticholinergics, antidepressants, antiplatelets, lipid-modulating drugs, and diabetes control drugs.[29,37] In addition, family history, stroke, psychiatric illness, sleep apnea, and sensory impairments (hearing and vision) were considered.[38] Lifestyle factors included physical activity levels, body mass index (BMI) as a measure of obesity, smoking habits, dietary patterns (including saturated fat intake, adherence to a dementia-preventive diet, and alcohol consumption), cognitive activity, sleep quality, and stress levels.[39] Furthermore, laboratory components, such as C-reactive protein (CRP), cobalamin (vitamin B12), folate, cholesterol, homocysteine, fasting blood sugar (FBS), glycated hemoglobin (HbA1C), and thyroid-stimulating hormone (TSH), were included in the LIBRA framework.[40]

Complementing the LIBRA factors, the BALI framework focused on brain structural changes and lesions. Specifically, the presence and severity of gray matter lesions and subcortical dilated perivascular spaces (GM-SV), deep white matter lesions (DWM), periventricular white matter lesions (PV), lesions in the basal ganglia and surrounding areas (BG), infratentorial lesions and atrophy (IT), global atrophy (GA), and microhemorrhages (MH) were evaluated.[41,42]

Diffusion tensor imaging (DTI) data were acquired from nine major white matter tracts known to be implicated in cognitive function and neurodegenerative disorders. Specifically, DTI measurements were obtained from the left and right arcuate fasciculi, the frontal–parietal portions of the left and right cingulum bundles, the left and right superior longitudinal fasciculi, and the genu, body, and splenium of the corpus callosum.[43]

From these DTI data, fractional anisotropy (FA) values were calculated as a measure of the directionality and coherence of water molecule diffusion within the white matter tracts.[44] FA is a widely used scalar metric derived from the diffusion tensor, which provides valuable insights into the microstructural organization and integrity of white matter fibers.[45] Lower FA values are generally associated with disruptions or disorganization of white matter pathways, which can occur in various neurological conditions, including dementia.[46]

To ensure the accuracy and consistency of the data collection, trained researchers conducted comprehensive in-person interviews with participants, gathering relevant demographic information, clinical assessments, lifestyle factors, and details regarding medication usage. These researchers underwent meticulous training on standardized data collection protocols, minimizing potential sources of variability and maximizing the reliability of the acquired data.

By integrating these comprehensive sets of factors from both the LIBRA and BALI frameworks, this study aimed to capture the multifaceted nature of dementia and its underlying contributors, encompassing demographic, lifestyle, physical health, laboratory, and brain structural markers.

Fuzzy subtractive clustering, a data-driven technique, was employed to identify the most influential variables among the LIBRA and BALI factors. The factors that exhibit the greatest number of distinct membership functions within the resulting clusters are considered the most influential variables for estimating DTI measures.[47,48]

MLP neural network was utilized to develop a predictive model for estimating DTI measures based on the identified more influential variables.[49] The MLP architecture consisted of an input layer, one or more hidden layers, and an output layer.[50] The number of nodes in the input layer corresponded to the number of selected influential variables, while the output layer had nodes representing the DTI measures to be estimated (e.g., fractional anisotropy). The hidden layers employed nonlinear activation functions to capture the complex relationships between the input variables and the DTI measures.[51] The network was trained using a backpropagation algorithm, which iteratively adjusted the connection weights to minimize the error between the predicted and actual DTI measurements.[52] To prevent overfitting and ensure model generalizability, techniques such as early stopping, regularization, and cross-validation were employed during the training process.[53]

Preprocessing steps were taken to normalize the input variables. Specifically, min–max normalization was applied to rescale the feature values to a common range, between 0 and 1. This step is crucial to ensure that no single variable dominates the learning process due to its larger numerical range. The pre-processed data were then divided into training, validation, and testing sets to evaluate the performance of the developed model.[54]

DTI is an advanced neuroimaging technique in which, using the principles of magnetic resonance imaging (MRI), DTI captures the anisotropic diffusion of water molecules, particularly in the white matter regions of the brain.[55] Through the use of a tensor model, DTI facilitates the estimation of the dominant direction and integrity of white matter fibers and provides valuable insights into the structural connectivity and architecture of neural pathways in the brain.[56] This noninvasive technique is valuable for studying various neurological disorders as well as cognitive processes.

DTI uses a specialized MRI technique known as diffusion-weighted imaging (DWI) to quantify the diffusion tensor.[57] DWI uses the random movement of water molecules in tissues to assess MR signal attenuation, denoted by S. This signal attenuation is controlled by the diffusion coefficient (D), the value of b, and the direction of the gradient equation (1),[58,59]

$$S = f(D, b, g), \tag{1}$$

where f represents the functional relationship between MR signal intensity (S) and tissue diffusion properties, including the diffusion

coefficient (D), diffusion-weighted coefficient (b), and applied gradient direction (g). By systematically varying these parameters and obtaining multiple DWI measurements, the diffusion tensor can be calculated, enabling the description of the directional dependence of water molecule diffusion in tissue.[60]

The diffusion tensor, D, encapsulates the diffusion characteristics of water molecules in each unit volume, known as a voxel, of the biological tissue under investigation. This tensor can be expressed mathematically as follows:

$$D = \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{pmatrix}, \tag{2}$$

where D_{xx}, D_{yy}, and D_{zz} represent the axial, radial, and mean diffusion values, respectively, which quantify the degree of displacement of the water molecule along the main diffusion axes. The off-diagonal elements D_{xy}, D_{xz}, D_{yx}, D_{yz}, D_{zx}, and D_{zy} account for the oblique emission components in the voxel.[60]

Axial diffusion tensor imaging (DTI) metrics, such as fractional anisotropy (FA), are derived from the eigenvalues and eigenvectors of the diffusion tensor, D. These scalar and vector values provide valuable insight into the underlying tissue microstructure.[61]

Fractional anisotropy (FA) is obtained from DTI data, which characterizes the degree of anisotropic diffusion of water in biological tissues. In the context of brain imaging, FA provides valuable insights into the orientation and coherence of white matter tracts, reflecting the extent to which water molecule diffusion is restricted along the orientation of fiber bundles. The value of FA can be calculated from the eigenvalues of the diffusion tensor, D, using the following expression:

$$\mathrm{FA} = \sqrt{\frac{1}{2}\frac{(\lambda_1-\lambda_2)^2 + (\lambda_1-\lambda_3)^2 + (\lambda_2-\lambda_3)^2}{\lambda_1^2+\lambda_2^2+\lambda_3^2}}, \tag{3}$$

where λ_1, λ_2, and λ_3 represent three distinct eigenvalues of the diffusion tensor that correspond to the principal diffusion directions in the tissue voxel. The FA value ranges from 0 to 1, with higher values indicating a greater degree of anisotropic diffusion, which is typically associated with more coherent and organized white matter fiber tubules.[60]

After clinical assessments and neuroimaging acquisition, numerical values were assigned to each LIBRA and BALI factors, as specified in the Appendixes; however, the inherent variability in the ranges of these values presents a potential barrier to unbiased analysis. To address this challenge, a standardization procedure was implemented whereby data from LIBRA were converted into BALI factors using the following equation:

$$x_s = \frac{x - \min(X)}{\max(X) - \min(X)}, \tag{4}$$

where x represents the original numerical value assigned to a given factor, X represents the set that includes all values of x across the study population, and x_s is the resulting standardized value. Through this process, the range of all variables was rescaled to fit within the interval [0, 1], thereby facilitating a fair and unbiased comparative analysis among the various factors under investigation.[62]

In this research effort, a Sugeno-type fuzzy inference system (FIS), a class of fuzzy systems that are famous for their efficiency in data-driven modeling, was considered for the development of the target model. These fuzzy systems can be converted into fuzzy neural networks.[63]

In the context of this research, a significant challenge arises when all inputs are assigned an identical number of membership functions, as the resulting number of fuzzy rules would be equal to the number of n^m rules. For instance, if all 49 BALI and LIBRA factors were to be utilized as inputs to the fuzzy model, and three membership functions were assigned to each input, the model would have 3^{49} or nearly 2.39×10^{23} rules. Considering that each rule would encompass 49 membership functions and 98 parameters, namely, C_{ij} and Ω_{ij}, the model would possess an overwhelming 2.35×10^{23} parameters solely within the membership functions. To identify such an astronomical number of parameters, billions of datasets would be required, an evidently unrealistic and unavailable prospect. The pragmatic solution lies in identifying and removing less influential inputs from the list through the process of subtractive clustering.

Subtractive clustering commences by calculating the density value of each set of input data or $\mathbf{u}^k$ from pre-processed data, where k refers to a subject or patient, and $\mathbf{u}^k$ encompasses the 49 BALI and LIBRA factors. This density value can be expressed as follows:

$$D_k = \sum_{l=1}^{51} \exp\left(-\frac{\sum_{i=1}^{49}(\mathbf{u}_i^k - \mathbf{u}_i^l)^2}{(r_a/2)^2}\right), \tag{5}$$

where r_a represents the range of influence, which is a positive number, and 51 denotes the total number of data points.

The point with the highest density is designated the center of the first cluster, and data points with a density value smaller than the reject ratio are eliminated from the process. Subsequently, the density of the remaining points is redefined as follows:

$$D_k' = D_k - D_{C1}\exp\left(-\frac{\left\|\mathbf{u}^k - \mathbf{u}^{C1}\right\|^2}{(r_b/2)^2}\right), \tag{6}$$

where r_b is referred to as the squash factor, and $\mathbf{u}^{C1}$ represents the center of the identified cluster. If the redefined density of any data point falls below the reject ratio, it is eliminated; conversely, if it exceeds the accept ratio, it is defined as the center of a new cluster. The density of the remaining points is then redefined via the following equation:

$$D_k'' = D_k' - \sum_{i=1}^{\substack{number\ of \\ exisiting\ clusters}} D_{Ci}\exp\left(-\frac{\left\|\mathbf{u}^k - \mathbf{u}^{Ci}\right\|^2}{(r_b/2)^2}\right), \tag{7}$$

and this iterative process continues until the clusters remain unchanged between two consecutive stages. These clusters can be conceptualized as spheres with a diameter of r_a in a 49-dimensional space. Each of these clusters contributes to the formation of membership functions for a fuzzy rule. The center of the jth cluster in the

dimension of the ith input will become C_{ij} in the previous equation, while $\Omega_{ij} = r_a$.

The process of developing a fuzzy inference system (FIS) can be outlined through the following pseudocode:

1. The density of each data point, $\mathbf{u}^k$, was calculated using the equations and r_a = Range of Influence, where k ∈ ℕ ⋂,[1,51] and 51 is the number of subjects (patients).
2. Identify the data point with the highest density value that exceeds the accept ratio threshold and designate it as the center of a new cluster.
3. Assign the current number of clusters to NC (Number of Clusters).
4. If NC is equal to ONC (Old Number of Clusters), proceed to step 2.
5. Update ONC with the current value of NC.
6. Eliminate data points (subjects) with a density value less than the reject ratio from the process.
7. Subtract the influence of the existing clusters using the generalized equation D_k'', where r_b is the squash factor, and Ct represents the center of the identified cluster.
8. Go back to step 2.

In fuzzy subtractive clustering, each rule is associated with a membership function for every input (BALI or LIBRA factor). However, some membership functions of an input may be nearly identical due to their close proximity. By considering these similar membership functions as one, each input ends up with a distinct number of membership functions. A greater number of distinct membership functions for an input indicates that the clusters may cover a wider range of that input, suggesting that the input is more influential in estimating DTI measures (or any other output).[64] Theoretically, if an input has only one distinct membership function, it implies that, in the centers of all the data clusters, the input has the same value. Such an input plays an identical role across all fuzzy rules and can be ignored in modeling; however, it does not necessarily diminish its importance as a factor in the disease itself.

In the subtractive clustering process, several key parameters were defined to control the formation and characteristics of the resulting clusters. The aspect ratio, set to 0.5, specifies the ratio of the longest and shortest dimensions of the cluster, allowing for the identification of elongated or irregular cluster shapes. The reject ratio, set to 0.15, establishes a threshold for discarding data points with low density values, effectively removing outliers or noise from the clustering process. The squash factor, set to 1.25, governs the extent to which the potential of a data point to become a new cluster center is reduced by the influence of existing clusters in its vicinity. Finally, the range of influence, set to 0.5, determines the radius or spread of the cluster's neighborhood, ensuring that data points within this range contribute to the cluster's formation. With these parameter settings, the subtractive clustering process resulted in 40 clusters, which corresponded to 40 fuzzy rules.

It was reasonably assumed that membership functions in which the distance between their centers is equal to or less than 0.02 (2% of the inputs' range) are not distinct. This assumption helped simplify the model by considering closely spaced membership functions as a single entity, reducing redundancy and improving computational efficiency.

The input to each neuron in a multilayer perceptron (MLP) is calculated by summing the products of the input values and their corresponding weights, followed by a bias term,[65,66] such that each neuron receives a weighted sum of the inputs, allowing it to process the information efficiently.[67] The input equation of a neuron is represented by v and is calculated as follows:

$$v = \left(\sum_{i=1}^{n} w_{ij} x_i + b_i \right). \tag{8}$$

This equation shows the linear combination of inputs x_i, weights w_i, and a bias term b.

After computing the input, the result v is passed through an activation function, enabling the network to learn complex patterns. The activation function is shown in ϕ (v), where ϕ is the chosen activation function.[68]

The final output of the MLP is calculated by summing the outputs of the hidden neurons and their corresponding weights, adding bias, and passing the result through the activation function. This process enables the MLP to approximate complex functions and model complex relationships between inputs and outputs. The output equation y is expressed as follows:

$$y = \sum_{j=1}^{m} \phi \left(\sum_{i=1}^{n} w_{ij} x_i + b_i \right), \tag{9}$$

where m represents the number of neurons in the output layer, and w_{ij} represents the weight associated with the connection between the input neuron i and the output neuron j.

These equations form the basic components of an MLP model, allowing it to process input data, and generate meaningful output predictions through interconnected layers of neurons.[69]

The MLP network was initialized using the Levenberg–Marquardt backpropagation algorithm, as detailed in Appendix 4 of the study by Mohammadzaheri *et al.*[70] This initialization method assigns initial values to the connection weights and biases prior to the training process, ensuring that the network starts from a suitable point in the weight space for efficient convergence.

The MLP network was trained using the Levenberg–Marquardt backpropagation algorithm, as described in Appendix B of the study by Mohammadzaheri *et al.*[71] This supervised learning algorithm iteratively adjusts the connection weights and biases to minimize the error between the predicted and actual DTI measurements, leveraging second-order optimization techniques for efficient convergence.

Data-driven model development requires avoiding overfitting, where a model is overfitted to the complexities of the training data, hindering its ability to effectively generalize to new and unseen examples. A powerful technique to circumvent overfitting involves continuously evaluating the model's performance on a separate validation dataset during the training phase. While the training data drive the optimization of the model parameters, the validation data remain intact. If the model error on the validation set starts to increase while the training error continues to decrease, this is a clear signal that overfitting is occurring. At this point, the training process can be terminated to preserve the generalization capabilities of the model.[72]

To verify the robustness and reliability of a data-driven model, it is necessary to perform cross-validation, which involves evaluating the model's performance on an independent test dataset that has undergone both training and validation processes. The estimation error of the model in this test set should be reasonably small to verify its ability to generalize effectively and cross-validate its predictive accuracy. It is important to distinguish between validation data used to avoid overfitting and the test data used for cross-validation.[73]

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At each iteration of training, both modeling and validation errors were calculated. The validation error is the error calculated with the validation datasets (the data used to prevent overfitting, not the test data used for cross-validation). The coincidence of a decrease in the modeling error and an increase in the validation error is a sign of overfitting and triggers the termination of parameter identification.[74]

The available dataset, consisting of 51 subjects, was divided into three subsets: modeling, validation, and testing. The modeling subset was used to train the MLP network and optimize its parameters. The validation subset, separate from the modeling data, was employed to monitor the network's performance during training and prevent overfitting. Finally, the testing subset, which remained unseen during the training process, served as an independent dataset for cross-validating the MLP model's predictive accuracy.

Specifically, the dataset was divided as follows: 70% of the data (35 subjects) was allocated to the modeling (training) subset, 15% (8 subjects) constituted the validation subset, and the remaining 15% (8 subjects) formed the testing subset. This division ensured that the model was trained on a sufficiently large portion of the data, while reserving separate subsets for overfitting prevention and final cross-validation, respectively.

RESULTS

The fuzzy subtractive clustering analysis revealed that among the 49 LIBRA and BALI factors, a subset of 14 variables emerged as the most influential for estimating diffusion tensor imaging (DTI) measures. These factors exhibited a greater number of distinct membership functions within the resulting clusters, indicating their potential to capture the variability in the data and contribute significantly to the prediction of DTI measures. The identified influential variables are as follows: age, level of education, job status, history of blood pressure, coronary heart disease, antidepressant drug usage, diabetes control drug usage, physical activity, obesity (BMI), high cognitive activity, and adherence to a dementia preventive diet from the LIBRA factors, as well as gray matter lesions and subcortical dilated perivascular spaces (GM-SV), deep white matter lesions (DWM), and periventricular white matter lesions (PV) from the BALI factors as shown in Fig. 1.

The MLP neural network, trained on the selected 14 most influential variables, demonstrated promising performance in estimating DTI measurements. Specifically, the network achieved a mean squared error (MSE) of 0.000 878 for predicting fractional anisotropy (FA) on the test set. These results indicate a strong correlation between the predicted and actual DTI measures, suggesting

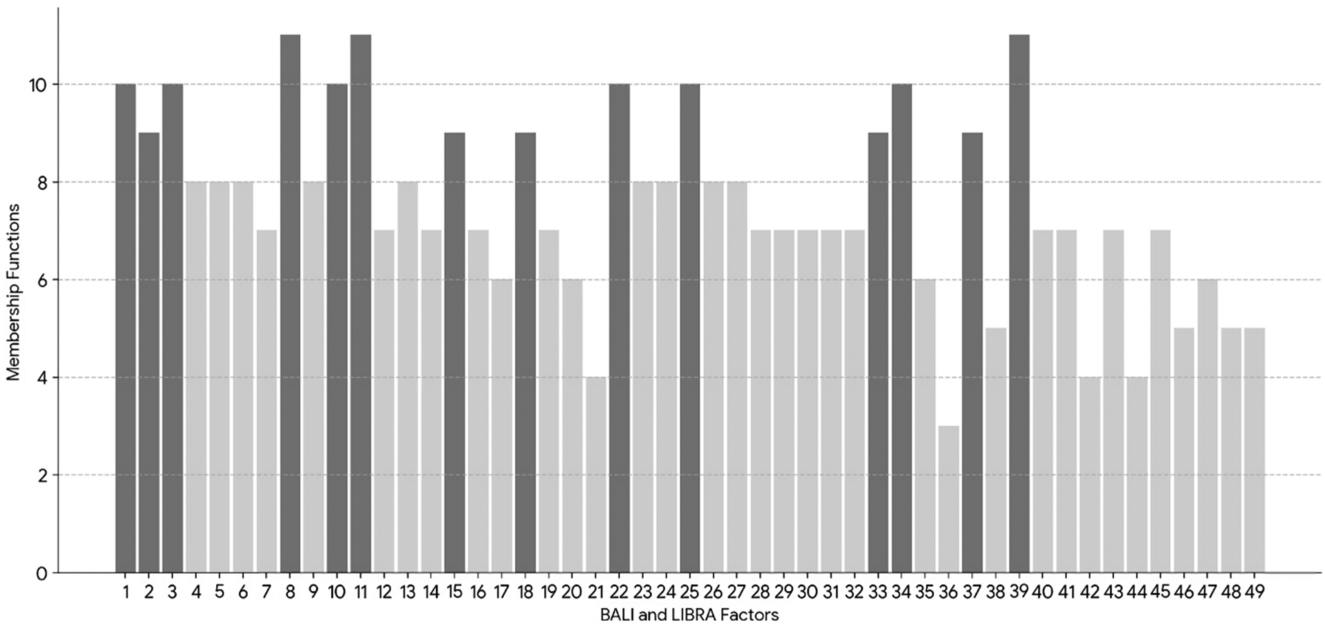

FIG. 1. Membership functions diagram of fuzzy subtractive clustering analysis for the BALI and LIBRA factors.

the effectiveness of the proposed approach in leveraging the identified influential variables for early dementia diagnosis. Specifically, the network achieved a performance metric of 0.298, representing the mean squared error between the predicted and actual DTI values. In addition, the gradient that indicates the rate of change in the error function during the training process converged to a value of 0.423. These results highlight the efficacy of the MLP network in learning the complex relationship between the identified influential variables, including demographic characteristics, lifestyle factors, medical conditions, and structural brain markers, and the DTI measures known to be reliable indicators of dementia.

DISCUSSION

The identification of the 14 most influential variables from the LIBRA and BALI factors has significant implications for the early diagnosis of dementia and the understanding of brain health. This multifaceted approach aligns with the current understanding that dementia is a complex condition influenced by various demographic, lifestyle, and biological factors.

Notably, the inclusion of variables, such as age, education level, and job status, resonates with existing literature highlighting the association between cognitive reserve and dementia risk. Individuals with higher educational attainment and mentally stimulating occupations have been shown to exhibit increased resilience against cognitive decline, potentially due to the formation of more efficient neural networks and the recruitment of alternative brain regions to compensate for deteriorating function. Similarly, the influence of factors, such as antidepressants and diabetes control drug usage, underscores the intricate interplay between mental health, metabolic conditions, and brain health.

In comparison to traditional diagnostic methods relying solely on neuroimaging or cognitive assessment, the proposed MLP network leverages a comprehensive set of influential variables, potentially enhancing the accuracy and sensitivity of early dementia detection. Furthermore, the incorporation of lifestyle factors and brain lesion indices offers a holistic perspective, aligning with the current emphasis on multimodal approaches in dementia research.

The proposed approach holds promising potential for applications in clinical practice and public health initiatives. By identifying individuals at heightened risk of dementia based on the 14 influential variables, targeted interventions and preventive strategies can be implemented. Lifestyle modifications, such as dietary adjustments, increased physical activity, and cognitive stimulation, may be recommended to mitigate risk factors. In addition, early detection could facilitate timely treatment initiation, potentially slowing disease progression and improving the quality of life for patients and their caregivers.

CONCLUSION

This study presents a novel approach to facilitating early dementia diagnosis by leveraging a combination of lifestyle factors and brain structural imaging markers. Through the application of fuzzy subtractive clustering, a subset of 14 influential variables was identified from the LIBRA and BALI factors. The MLP neural network, trained on these selected variables, demonstrated promising performance in estimating DTI measures, which are widely recognized as reliable indicators of dementia.

The proposed approach contributes to the field of dementia research by addressing the need for accessible and cost-effective screening methods. By circumventing the reliance on resource-intensive techniques, such as MRI and DTI analysis, the identified influential variables offer a more feasible alternative for assessing dementia risk in large populations. The integration of lifestyle factors and brain structural markers into a unified predictive model represents a comprehensive and holistic approach, aligning with the current understanding of dementia as a multifactorial condition influenced by various biological, environmental, and behavioral factors.

The potential impact of this study lies in its capacity to improve dementia screening and early diagnosis, ultimately paving the way for timely interventions and improved patient outcomes. By identifying individuals at heightened risk based on influential variables, targeted preventive strategies, such as lifestyle modifications and cognitive stimulation, can be implemented. In addition, early detection could facilitate the initiation of appropriate treatments, potentially slowing disease progression and improving the quality of life for patients and their caregivers. Furthermore, the proposed approach holds promise for application in public health initiatives, enabling the efficient allocation of resources and targeted interventions for at-risk populations.

SUPPLEMENTARY MATERIAL

This manuscript contains the supplementary material providing additional details and supporting information for the research presented. The supplementary material consists of two Appendixes: Appendix A provides a detailed description of the factors included in the Lifestyle for Brain Health (LIBRA) framework, including the rating schemes used to assess each factor's severity or duration. Appendix B outlines the factors considered in the Brain Atrophy and Lesion Index (BALI), along with the rating schemes used to evaluate the presence and extent of various brain lesions and atrophy patterns. These Appendixes offer a comprehensive overview of the variables explored in this study, facilitating a deeper understanding of the multifaceted nature of dementia risk assessment and the potential contributors to cognitive decline. The supplementary material aims to enhance the transparency and reproducibility of the research findings reported in this manuscript.

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AUTHOR DECLARATIONS

Conflict of Interest

The authors have no conflicts to disclose.

Ethics Approval

The study protocol adhered to the principles of the Ethics Committee of the Islamic Azad University Science and Research Branch (Approval No: IR.IAU.SRB.REC.1401.285). All participants provided informed consent prior to their inclusion in the study.

Author Contributions

Ahmad Akbarifar: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Software (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing – original draft (equal); Writing – review & editing (equal). **Adel Maghsoudpour**: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Software (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing – original draft (equal); Writing – review & editing (equal). **Fatemeh Mohammadian**: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Software (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing – original draft (equal); Writing – review & editing (equal). **Morteza Mohammadzaheri**: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Software (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing – original draft (equal); Writing – review & editing (equal). **Omid Ghaemi**: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Software (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing – original draft (equal); Writing – review & editing (equal).

DATA AVAILABILITY

The datasets generated during and analyzed during the current study are available from the corresponding author upon reasonable request.

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